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DIAGNOSTICS



**World Health
Organization**

Technical Guidance Series (TGS) for WHO Prequalification – Diagnostic Assessment

**Designing instructions for
use for in vitro diagnostic
medical devices**

TGS-5

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Preface

WHO Prequalification – Diagnostic Assessment: Technical Guidance Series

WHO prequalification of IVDs	WHO prequalification is coordinated through the Department of Essential Medicines and Health Products. Prequalification of in vitro diagnostic medical devices (IVDs) is intended to promote and facilitate access to safe, appropriate and affordable IVDs of good quality in an equitable manner. The focus is on IVDs for priority diseases and their suitability for use in resource-limited settings. For prequalification, WHO undertakes a comprehensive assessment of individual IVDs through a standardized procedure that is aligned with international best regulatory practice. It also undertakes post-qualification activities for IVDs to ensure their ongoing compliance with prequalification requirements.
Procurement of prequalified IVDs	Products that are prequalified by WHO are eligible for procurement by United Nations agencies. The products are then commonly purchased for use in low- and middle-income countries.
Prequalification requirements	IVDs prequalified by WHO are expected to be accurate, reliable and able to perform as intended for the lifetime of the IVD under conditions likely to be experienced by a typical user in resource-limited settings. The countries where WHO prequalified IVDs are procured often have minimal regulatory requirements, and the use of IVDs in these countries presents specific challenges. For instance, IVDs are often used by health-care workers who do not have extensive training in laboratory techniques, in harsh environmental conditions, in the absence of extensive pre- and post-test quality assurance capacity, and for patients with a disease profile that differs from the profiles encountered in high-income countries. Therefore, the requirements of WHO prequalification may differ from the requirements of high-income countries, or those of the regulatory authority in the country of manufacture.
About the Technical Guidance Series	The Technical Guidance Series (TGS) was developed following a consultation held on 10–13 March 2015 in Geneva, Switzerland. The consultation was attended by experts from national regulatory authorities, national reference laboratories and WHO prequalification dossier reviewers and inspectors. The guidance series is a result of the efforts of this and other international working groups.
Audience and scope	<p>This guidance is intended for manufacturers interested in WHO prequalification of their IVD. It applies in principle to all IVDs that are eligible for WHO prequalification for use in WHO Member States. This guidance should be read in conjunction with relevant international and national standards and guidance.</p> <p>The TGS guidance documents are freely available on the WHO website.</p>

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The draft technical specifications document was posted on the WHO website for public consultation on 19 May 2017 for a 2-month response period. Various stakeholders – including manufacturers submitting to WHO prequalification of IVDs, IVD manufacturing industry associations, various national and international regulatory bodies, and IVD standards organizations – were informed of the consultation in order to solicit feedback. Comments were received from AdvaMedDx (a division of Advanced Medical Technology Association), Washington DC, USA; Alere (now Abbott Rapid Diagnostics (multiple sites)); and J. Budd, Immunoassay R&D, Beckman Coulter, Chaska, Minnesota, USA.

1 Abbreviations

CLSI	Clinical and Laboratory Standards Institute
EIA	enzyme immunoassay
GHTF	Global Harmonization Task Force
GMP	WHO Global Malaria Programme
HCV	hepatitis C virus
IFU	instructions for use
IVD	in vitro diagnostic medical device
mHarT	Roll Back Malaria “mRDT Harmonization Taskforce”
MHRA	Medicines and Healthcare products Regulatory Agency, United Kingdom
NAT	nucleic acid test
RDT	rapid diagnostic test
TGS	Technical Guidance Series
US FDA	Food and Drug Administration, United States of America
WHO	World Health Organization

2 Definitions

Accessories: Article intended explicitly by its manufacturer to be used together with an IVD medical device to enable the IVD medical device to achieve its intended purpose or to augment or extend the capabilities of the IVD medical device in the fulfilment of its intended purpose (1).

WHO comment: Accessories should be validated by the manufacturer for use with the IVD.

Calibrator: Measurement standard used in calibration of an IVD or system (1).

Control material: Substance, material or article used to verify the performance characteristics of an in vitro diagnostic medical device (1).

Test run: For the purpose of this document, a test run may involve a single specimen (as in a single-use rapid diagnostic test) or multiple specimens tested in the same run (as in a blood screening nucleic acid test).

Component: Part of a finished, packaged and labelled IVD medical device.

Note: Typical kit components include antibody solutions, buffer solutions, calibrators and/or control materials (1).

WHO comment: The component should be dedicated, specific to and necessary for using the IVD. WHO considers the instructions for use to be a component.

Configuration: A combination of items of equipment, as specified by the manufacturer, that operate together to provide an intended use or purpose as a medical device. The combination of items may be modified, adjusted or customized to meet a customer need (2).

Instructions for use (IFU): Information supplied by the manufacturer to enable the safe and proper use of an IVD.

Note: Includes the directions supplied by the manufacturer for the use, maintenance, troubleshooting and disposal of an IVD, as well as warnings and precautions (1).

Intended use: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer (3).

In vitro diagnostic medical device (IVD): 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 diagnostic, monitoring or compatibility purposes.

Note: IVDs include reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles. They are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status (4).

Kit: Set of components that are packaged together and intended to be used to perform a specific IVD examination.

Note. Kit components can include reagents (such as antibodies, enzymes, buffer and diluents), calibrators, controls and other articles and materials (1).

WHO comment: For rapid diagnostic tests this may include the IVD buffer bottle, specimen transfer device, lancet, alcohol swab and IFU (5).

Job aid: Information excerpted from an approved procedure that is presented in a more readily viewable format; job aids are subject to document control (6).

Lay person: Individual who does not have formal training in a relevant field or discipline (3).

Labelling: Written, printed or graphic information provided upon the medical device itself or on the packaging of each unit, or on the packaging of multiple devices (3).

Limitations of the procedure: Specific situation in which an IVD examination procedure might not perform as intended (1).

Note: This also may include a situation where the IVD was not evaluated in a specific patient population or under certain circumstances, or has not been evaluated for particular subtypes, species or genotypes of the organism being tested.

Lot/batch: Defined amount of material that is uniform in its properties and has been produced in one process or series of processes (1).

Point-of-care testing: Near-patient testing that is performed near or at the site of a patient, with the result leading to possible change in the care of the patient (7).

Device for near-patient testing: Means any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to or at the side of, the patient by a health professional (8).

Product code: The value given by the regulated entity (manufacturer) to identify the specific medical device as it relates to its form/fit, function and process (i.e., manufacturing processes requiring differentiation for distribution control (for example, sterilization, component material, reprocessing, etc.)) (9).

Precaution: A statement that alerts users to special care or activities necessary for safe and effective use of an IVD medical device, or to avoid damage to the IVD medical device that could occur as a result of use, including misuse (1).

Self-testing: Examination performed by a layperson to evaluate an individual's health status.
Note: Typically performed in a home or other environment outside a health-care institution without supervision by a health-care professional (1)

User: The person, either formally trained or lay, who uses a medical device. The patient may be the user (in the case of the user being a lay user). Adapted from (3).

Warning: A statement that alerts users about a situation that, if not avoided, could result in hazards or other serious adverse consequences from the use of an IVD medical device.

Note 1. the designation of a hazard alert as a warning is reserved for the most significant consequences.

Note 2. the distinction between a warning and a precaution is a matter of degree, considering the likelihood and seriousness of the hazard.

Note 3. use includes use errors and reasonably foreseeable misuse (1).

3 Purpose of this document

3.1 About the instructions for use

The instructions for use (IFU) is a critical part of an in vitro diagnostic medical device (IVD); it is expected to effectively communicate the product information to the intended user and ensure the safe use of the IVD. The IFU communicates the purpose for which the IVD should be used, who should use it, how the IVD works, what types of specimens it should be used with, what materials and reagents are needed to perform the IVD, how to perform the test, how to interpret the test result, the limitations of the test, warnings and precautions that need to be considered when using the IVD, and evidence to support IVD performance claims. It therefore communicates all that the user needs to know to make good clinical use of the IVD.

Any information that the manufacturer includes in the IFU should be supported by documentation; for example, the results of well-controlled studies to substantiate performance claims, and manufacturing specifications for the stated composition of test kit components. Manufacturers have a regulatory responsibility to ensure the safe use of their product.

WHO reviews the IFU as part of the WHO prequalification assessment.¹ The IFU is reviewed for clarity, correctness, consistency with the information submitted in the product dossier and with international guidance (1), requirements and suitability for the target user group for WHO prequalified IVDs. This document draws on documents developed as part of the Roll Back Malaria “mRDT Harmonization Taskforce” (mHarT) initiative to harmonize aspects of testing using malaria rapid diagnostic tests (RDTs), and suggests ways to make tests more user-friendly (5).

3.2 Scope of this guidance

This document provides guidance on the approaches to be taken by manufacturers in designing IFU for products that are eligible for WHO prequalification.² The general principles in this document can be applied to both paper and electronic IFUs; however, specific requirements relating to data security, file format and accessibility for electronic IFUs available on the Internet or on media (e.g. IFUs for IVDs intended for professional use that require regular software updates and self-test IVDs) are outside the scope of this document. In addition, labelling other than the IFU (e.g. primary and secondary package labels, and instrumentation manual requirements) are outside the scope of this document. Specific requirements can be found in the International Organization for

¹ See Section 8.2. Instructions for use in (11)

² See (12)

Standardization (ISO) 18113 standard series regarding package labelling and instrumentation manual requirements. WHO expects these standards to be used to demonstrate conformity.

4 Basic principles

4.1 Suitability of IFU for the end user

The IFU gives the manufacturer the opportunity to directly interact with the end user and inform the user about the product. The manufacturer needs to carefully consider the intended audience of the IFU to ensure that the information is clear and unambiguous to all users. The IFU should be in a language that is understood by intended users. This audience includes IVD users who may or may not have formal laboratory training and who need to use the IFU to conduct the assay procedure correctly (including those using IVDs for self-testing). The audience also includes procurers and testing managers who will use the IFU to aid in the choice and procurement of the IVD, or are responsible for the appropriate use, safe operation and storage of the IVD.

The IFU should be developed and evaluated with reference to a manufacturer's risk management process.

4.2 Readability

The IFU is expected to be easily readable for all intended users, and the level of detail should be commensurate with the complexity of the IVD. Technical language is often necessary in the IFU, but the material can still be readable if the writer uses short sentences and explains difficult words (e.g. desiccant and in vitro) for users who do not have formal laboratory training. Readability tests and calculators can be used to indicate how difficult the IFU is to understand for diverse users. For example, a readability level no higher than Flesch-Kincaid grade six is recommended for users who do not have formal laboratory training (13-15).

Some specific recommendations to improve readability given in Table 1 are taken from guidance documents from the Clinical and Laboratory Standards Institute (CLSI) (6), the US Food and Drug Administration (US FDA) (15, 16), the Medicines & Healthcare products Regulatory Agency, United Kingdom (MHRA) (17) and the European Commission (18). If feasible, these recommendations should be considered in the language of the document.

Table 1. List of recommendations for readability

✓	Use simple words with few syllables (three or fewer) as much as possible (15).
✓	Explain difficult words (e.g. desiccant and in vitro) in lay terms.
✓	Use short sentences and terms (e.g. 25 words or fewer per sentence) (15) and easy to understand. Vary the length of sentences.
✓	Use consistent terms and words throughout the IFU (see Section 2 for examples). Avoid using synonyms or alternative phrases.

- ✓ Avoid using abbreviations and acronyms, but if these need to be used, spell them out in full when first used in the text, and use them consistently throughout the text (15).
- ✓ For instructions and procedures, use active verbs (imperative) rather than passive voice (“should”) to reduce the risk of ambiguity or confusion.
Example: “Open the cassette packaging ...” (rather than: “The cassette packaging should be opened ...”)
- ✓ Use positive rather than negative statements when possible.
- ✓ Highlight important information using boldface, capitals, italics, text boxes, contrasting colour.
- ✓ When listing information points, use one line per action. Use bullets for nonspecific order (e.g. listing of materials) and numbering for chronological sequences (e.g. the steps in a procedure) (15).
- ✓ A flowchart or diagram can be useful to guide the user through an order of operations or multiple decisions (e.g. interpretation of results). Step-action tables and if-then tables can be used to guide instructions and actions (15).
- ✓ Indicate warnings clearly and write them early in the text before the action step in the procedure. It should be clear to the user when an action should be taken. For example: “If the colour indicator is pink, **discard** the test”.
- ✓ For IVDs intended for self-testing, use personal pronouns (e.g. “you” rather than “the user”).
- ✓ Use type size of a minimum of nine points. If elderly or visually impaired users are potential users, use a type size of at least 14 points.
- ✓ Do not use a narrow font. Make the spacing between lines at least 3 mm (18).
- ✓ For printed IFUs, avoid glossy paper. Use paper that is thick enough that print and graphics do not show through (15).
- ✓ If required for printed IFUs (e.g. for job aids), use waterproof pages.

4.3 Formats to use in an IFU

Different formats can be used to ensure that information and instructions are clear. Suggested formats are texts, flowcharts and lists. Regardless of the format used, the manufacturer must ensure that all regulatory requirements are met, that the critical details are supplied, and that the IFUs are subject to document control.

4.4 Pictorial representations, graphics and job aids

When appropriate, provide pictorial representations and illustrations next to the corresponding text. Drawings are often more informative than photographs. Some considerations for the illustrations used are given in Table 2.

Table 2. Considerations for illustrations and graphics

- ✓ Ensure that graphics (e.g. drawings and symbols) are large enough to be easily visible.
- ✓ Ensure that the figures used are consistent and accurate.

- ✓ Place pictorial representations and figures to the left of the text, and refer to them in the text. Match pictorial representations to the real-life situation (e.g. the colour of test lines, hands wearing gloves and right-handed user).
- ✓ Depict timing instructions by simple pictures of clocks showing start and end times.
- ✓ Match the pictures to the instructions. For example, if the kit content is labelled “alcohol swab”, show the same label in the image. If one drop of reagent is to be used, show one drop being used in the image.
- ✓ For illustrations, be consistent in terms of format and placement of headings.
- ✓ Include an image or schematic diagram of the IVD in the IFU.

Include a clear and simple job aid, either as a separate leaflet, or printed on the IVD packaging or on the box. The job aid should specify any major limitations regarding the IVDs use and be written at a level consistent with the education, training and any special needs of its intended readers. Also, it should instruct the IVD user to read the entire IFU because the job aid is a quick guide only. The information provided by the job aid must agree with that of the IFU. The job aid should contain the information on the required specimen types and materials, the essential steps of the procedure and the interpretation of results. Clear graphics with little text, and the use of flowcharts or decision tables are recommended. The sample generic job aids for malaria RDTs published by WHO and the Foundation for Innovative New Diagnostics (FIND) (19) provide clear drawings. The job aid should include the product code of the IVD and the address of the manufacturer or an authorized representative of the manufacturer where required.

4.5 IFU version numbers and changes control

Provide the IFU version number, including an indication of language and date of issue, with each updated IFU submitted for assessment. A job aid should also have a version number and date of issue. If a job aid is provided separately to the IFU, the IFU must clearly state the version of the job aid that is to be used. Updates to the IFU may also result in changes to the job aid. Where applicable, make clear to the user any changes that have been made since the previous version. This can be done by highlighting the relevant text and changing the version number of the IFU to reflect the update, or by drawing attention to the new IFU by an indication on the IVD box (e.g. using a sticker).

4.6 Pre-testing the IFU by the manufacturer

Before issuing an IFU, it is important to assess whether key messages and instructions from packaging and labelling will be understood and easily followed by the intended users, and to check that users can safely and effectively operate the IVD following the IFU instructions.

The first step is for the manufacturer to validate the information in the IFU. The author should re-read the IFU and check it for accuracy. Another person who is familiar with the IVD should then validate the information (15).

The second step is to pretest the IFU. Pre-testing is the systematic and formal gathering of target audience reactions to the content and format of the IFU before the IFU is issued in its final form (Appendix F of (16)). Pre-testing can take many forms, such as individual in-depth interviews, focus group interviews and questionnaires. A useful form of pre-testing is the user performance study, where potential users are asked to operate the IVD while following a draft of the IFU. Observers and users can then look for problems with the instructions (15). The study group should comprise intended users whose age, gender, level of education, literacy and other skills can challenge the usability of the IVD. Also, the test should be done in unfavourable operational settings (e.g. poor lighting).

Pre-testing the IFU may show that the IVD must be redesigned. This may lead to a need to revalidate the device or to perform additional specific performance studies and to update the risk analysis.

4.7 Accessing the IFU

IFUs for IVDs to be used principally by those who do not have formal laboratory training should always be provided in a paper format with the IVD (20). In addition, the use of electronic labelling, video guides and detailed information available on the Internet can help to simplify IVD labelling and increase access.

Manufacturers should consider situations where the IVD may be separated from the labelling and what the user needs to do to access the labelling; for example, clear instructions on the packaging on where to readily locate the IFU on a dedicated area of the website, or a telephone number that users can call for advice (21). If the manufacturer has a website, the IFU should be available on that website. Where multiple devices are available in a kit that comes with a single copy of the IFU, the manufacturer should provide further copies upon request.

5 Content of the instructions for use

WHO recommends that, where feasible and in the absence of formatting requirements (e.g. required by national regulatory agencies), manufacturers organize the IFU for the IVD according to the information given in Sections 5.1 to 5.22 below. A harmonized format provides several benefits – it facilitates ease of use of IFUs between products by users and facilitates the review during the prequalification process.

5.1 Table of contents

A table of content is strongly advisable when the IFU is five pages or longer.

5.2 Definition of terms and abbreviations (if required)

Keep the number of abbreviations to a minimum and avoid using any that may be confusing.

5.3 Product identification

5.3.1 Product name

State the name that identifies the IVD. The name could be a brand, a trade or proprietary name, or a common name. The product name should not conflict with the intended use.

5.3.2 Product code and configuration

State the manufacturer's product code. State the configuration(s) and kit size(s); for example, the number of tests per kit.

If the IFU covers a number of product codes, the configurations and contents should be fully described for each product code, including the number of tests and the contents of each kit. Each product code shall have only one defined product specification.

5.4 Intended use statement

The intended use statement needs to provide the user with a clear understanding of the purpose of the IVD (see [Annex 1](#) for an example). The intended use statement is generally understood to be a formal statement of the claims made by the manufacturer for the capabilities of its product. The language of the intended use statement may be simplified in an IFU for an IVD used for self-testing, provided key messages remain. In addition, IFUs for self-testing devices may omit some of the recommended elements, provided this does not affect safety or performance. Justification for any omission should be described in the manufacturer's risk assessment for the product. The main elements of an intended use statement are described below (3).

5.4.1 What is detected

Specify what the IVD is designed to detect. Examples include antibodies, antigens and nucleic acid. As appropriate, identify the specific variants, types and subtypes of a microorganism that the IVD can detect, but only if the claim is based on data from studies conducted to support it.

Specify limitations to the intended use. These may include variants, types and subtypes of a microorganism the IVD might be expected to detect but will not, and uses of the IVD that are not validated. For example:

- a hepatitis C virus (HCV) nucleic acid test (NAT) may not detect a particular genotype (or may not have been validated for that particular genotype by the manufacturer) or could have reduced sensitivity for one or more genotypes;
- an HIV RDT may have been validated as an aid to diagnosis but not for testing blood donations; and
- there may be limitations to the sensitivity of a test for HIV-1 subtype O, or variations in sensitivity between the different malaria species (e.g. sensitivity for *Plasmodium falciparum* is greater than for *P. vivax*, which is again more sensitive than for *P. ovale* or *P. malariae*).³

Specify any interfering substances (as identified in analytical specificity studies) that may affect the test result. For example:

- malaria RDTs may produce false-reactive results in specimens with positive rheumatoid factor; and
- HIV oral fluid RDTs may produce false-nonreactive results for patients under antiretroviral therapy.

5.4.2 The function of the IVD

Identify the role that the IVD plays in clinical use; that is, describe the circumstances under which an individual or patient would be tested. Examples include:

- screening (e.g. for surveillance or safety of blood supply);
- aiding the diagnosis and determination of a patient's disease course and prognosis;
- monitoring patient therapy or following their progress after treatment;
- staging or aid to determining the stage of a disease; and
- disease differentiation or prediction.

³ Further information on the limitations of malaria RDTs is available in (22)

5.4.3 The clinical indication for the IVD

Identify the specific disorder, condition or risk factor that the IVD is intended to detect, define or differentiate. For example, for a disease state caused by an infectious agent this would be the name of the infectious agent or the clinical condition caused by that infectious agent.

5.4.4 Whether the IVD is qualitative, semiquantitative or quantitative

A simple statement of whether the IVD is qualitative, semiquantitative or quantitative is sufficient.

5.4.5 Whether the IVD is automated or not

If the IVD is intended to be performed without any automated steps, identify it as a manually performed IVD. If the IVD is automated, identify the specific automated system or systems on which the IVD must be run.

If only a part of the testing process is automated, it would be considered semiautomated. Identify the steps that are automated and the instrument or instruments to be used.

5.4.6 The type of specimen required

Identify the validated specimen types in the intended use statement. More detailed information may be provided later in the IFU, as described in Section 5.12.

5.4.7 The intended testing population

Identify the characteristics of individuals that would be tested. This may include individuals with signs and symptoms of a clinical state (symptomatic), individuals who are at elevated risk for a clinical state but who are not showing signs and symptoms (asymptomatic), or individuals being treated for a clinical condition. There may also be identification or restrictions regarding age groups (e.g. for IVDs to be used in paediatric populations) or other limiting characteristics (e.g. pregnancy). Provide this information in sufficient detail to make clear for whom the IVD should be used.

5.4.8 The intended user

State who should use the device and any qualification they require. Also state the setting in which the IVD should be operated⁴; for example, “The assay is intended to be performed by a laboratory professional in a clinical laboratory”. Other examples may be a laboratory professional at the point-of-care, a health-care worker or an untrained lay user for self-testing.

Identify the level of training needed to operate the IVD, for example:

- training by the manufacturer;

⁴ For WHO Prequalification purposes, an RDT that uses capillary blood must be able to be operated by a lay user.

- knowledge of basic good clinical laboratory practices; or
- no specific training needed, other than following the IFU.

5.5 Statement that the product is for in vitro diagnostic use

Include a simple statement in the IFU, such as “for in vitro diagnostic use”, or include the international symbol (23).

5.6 Test principle summary and explanation

Briefly describe the general biological, chemical, microbiological, immunochemical and other principles on which the IVD is based. Proprietary information need not be disclosed, but provide enough detail to allow the user to understand how the IVD is able to carry out its function. This would include, for example, identifying the antibody (e.g. hepatitis B surface antibody), antigen (e.g. recombinant gp41), or nucleic acid primer and probe targets, and giving information on the chemical principles used to detect the analyte. If an instrument is required to perform the IVD test, then include a brief description of the instrument’s principles of operation.

5.7 Warnings and precautions

The risks and benefits the user needs to know about before using the IVD should be addressed in the warnings and precautions section, which should also explain how to avoid the hazards. A warning is warranted if there is increased likelihood or seriousness of a hazard. Designation as a warning is reserved for the most serious problems. The term “precaution” is used for hazards that are less significant and, if not avoided, may result in minor or moderate injury to the user, patient or equipment. For the sake of clarity, it is best to list warnings and precautions separately.

International symbols and signal words such as **WARNING** and **CAUTION** are effective in alerting the user to a hazard (24). When listing warnings and precautions, it is recommended to:

- use a signal word (e.g. **WARNING** or **CAUTION**);
- use bullet points and concise, clear language;
- clearly state the action to avoid and the nature of the hazard in a way that informs the user of the severity and likelihood of the hazard; and
- specify the likely consequences of the action to be avoided (if it occurs), to provide a clear idea of the risk (16).

5.7.1 Location of warnings and precautions in the IFU

General warnings and precautions should be placed near the beginning of the IFU. Procedure-related warnings and precautions should be integrated into the procedure instructions, where users will read the information at the relevant time. For example,

warnings about specimens are best placed before the associated instructional step relating to specimen manipulation.

5.7.2 List of warnings and precautions

The list of warnings and precautions should be presented in a logical order and should address issues related to the use of the IVD. The list should include the issues listed in Table 3.

Table 3. Examples of classification of warnings and precautions (when applicable)

IVD use	<ul style="list-style-type: none"> • How to read and interpret the results (e.g. minimum and maximum reading time, and how to avoid overlooking or over-reading faint test lines). • The need to add the specimen or reagents in the correct order. • A warning that the control line only controls for addition of specimen, and not for whether sufficient volume of specimen has been added. • The need to bring all reagents to room temperature before commencing IVD.
Safety and handling	<ul style="list-style-type: none"> • The correct user handling of specimens (e.g. how to avoid incorrect storage, incubation time or specimen type; and the effect of heat inactivation) and other potentially infectious materials (of human or animal origin), according to universal precautions. • The need to avoid exchanging components from different lots or reagent kits, or pooling reagents (e.g. buffer bottles from different lots should not be exchanged across lots). • The need for correct disposal of the IVD and its accessories (e.g. lancets), any consumables used with it (e.g. reagents) and any potentially infectious materials or hazardous materials. • In relation to disposal issues, identify the precise hazard, and reference specific internationally recognized standards, or recommend compliance with national and local requirements.
Storage instructions	<ul style="list-style-type: none"> • The need to avoid exposure of the IVD to certain environmental (e.g. excessive temperature or humidity) and the need to ensure that it is stored on a flat surface.
Contamination and inhibition	<ul style="list-style-type: none"> • Precautions regarding contamination of reagents and inadequate washing of microwells.
Any other warnings and or precautions	<ul style="list-style-type: none"> • An indication of instability or deterioration (e.g. when the control value is outside the expected range). • A warning that testing another person using a self-test IVD without their consent is illegal. • A warning that the IVD should not be used for testing once it is past its shelf-life.

5.7.3 Residual risks

Identify risks associated with the use of the IVD (e.g. note that a faint test line should be interpreted as a reactive result), including risks associated with calibrating or servicing an IVD (e.g. from contaminated equipment) (25).

5.7.4 Biological hazards

If the IVD contains material of human or animal origin, it should have a statement warning the user to handle with care. All materials of biological origin (whether inactivated or not) should be treated as potentially hazardous and disposed of accordingly.

5.8 Materials provided (test device, reagents, calibrators, controls and accessories)

5.8.1 Description of the reagents, calibrators, controls and accessories

List all components of the IVD and the quantity supplied for the given kit size and configuration (e.g. volume per box, number of boxes and number of specimen transfer devices).

- For easy reference, assign identification colours, numbers or letters to illustrations of the test kit components and their descriptions, so that they correspond to each other (and explain this coding where necessary).
- Instruct users to familiarize themselves with the components before they begin testing.
- Provide sufficient detail for users on the composition of critical components (e.g. antibodies).
- Provide detail on the concentration of hazardous component (e.g. preservatives).
- Identify any accessories intended to be used in combination with the IVD in as much detail as necessary to assure that the accessories will be used appropriately.
- Identify any test kit component or accessory that is sterile, and provide instructions on what the user should do if the sterile packaging is damaged.
- Identify any test kit device or accessory that is specified as single-use only and identify as “do not reuse”.
- If desiccant is included in the test kit, identify it, and provide instructions on what the desiccant is for, and what actions the user should take in the event of a colour change.
- Identify the maximum time that can elapse between calibrations.
- Describe control materials (e.g. positive and negative controls) and how often these controls should be run (e.g. with every IVD run, or at the start and end of testing, or with each new kit or kit lot).

- If internal controls are used as part of the assay procedure, indicate at what stage of the test procedure the internal control is added to the specimen (e.g. for NAT IVDs, specimen preparation, nucleic acid extraction and analytical phases such as amplification).
- Describe calibrators (if used) and the calculation for determining cut-offs or validity.
- Specify methods for the disposal of left-over, non-biological kit components (e.g. for normal laboratory waste, such as left-over buffer, flush down the sink with copious volumes of water).

5.9 Materials required but not provided

If applicable, identify specific materials that are required for testing but not provided in the kit (e.g. gloves, specimen collection materials, timer, additional reagents, equipment, software, pipettes, sharps disposal container, non-sharps disposal container, biohazard container and centrifuge). Give as much detail as necessary to assure that the appropriate materials will be used.

5.10 Instrumentation (if applicable)

For automated and semiautomated IVDs that can be used on different instrument systems (e.g. open systems), describe:

- the combination of reagents, consumables and equipment that has been validated; and
- the types of instruments or specific instruments needed in as much detail as necessary to assure that the appropriate instruments will be used.

5.11 Troubleshooting

Identify issues that would prompt the user to take specific actions, such as a change in performance or a malfunction of the IVD. Provide detailed instructions on what actions to take in such situations. This would apply to an IVD that is not performing as expected (e.g. no background clearing due to excessive amount of specimen or buffer addition, or no control line appearing) or to an IVD that identifies a deficiency (e.g. error messages). Actions to take may involve a user intervention or the user contacting the manufacturer using the detailed contact information provided in the IFU.

5.12 Collecting and preparing specimens

5.12.1 Types of specimens to be used and specimen collection and preparation

Identify the specimen types that may be used with the IVD (e.g. serum, plasma, venous whole blood, capillary (finger- or heel-prick) whole blood, dried blood-spot specimens, sputum, oral mucosal transudate or urine). Only specimens that are indicated in the

intended use and have been validated can be recommended for use with the IVD (see [Section 5.4.6](#)).

Indicate the specimen volume required, collection device to be used and method to be followed (the collection device and collection method for infants or young children may differ to those used for adults).

Illustrations should be included where applicable and useful; for example, showing the angle at which to deposit capillary blood collected on a specimen transfer loop into an RDT specimen well, or demonstrating capillary blood collection from an infant.

Clearly identify steps to minimize the risk to the user when handling specimens. The steps should be appropriate to the expected level of experience of the intended user; for example, for dried blood-spot specimens, the filter-paper should be stored in a bag with desiccant labelled with a biohazard symbol, to alert users that the contents may be infectious.

5.12.2 Specimen exclusion criteria

State any restrictions on specimens that can be used with the IVD. These restrictions may be based on the results of performance studies (e.g. specimens with visual evidence of hyperlipidaemia or haemolysis, excessive specimen age or excessive number of freeze–thaw cycles) or by risk assessment.

5.12.3 Specimen storage and transport conditions

Identify under what conditions the specimens can be stored and transported, and the recommended storage and handling instructions. Define the storage temperature and the maximum delay between specimen collection, processing and analysis. Give as much detail as possible for any specimen collection and transport material that must be provided by the user, to assure that specimen integrity is not compromised.

For specimens that are to be transported (e.g. dried blood-spot specimens), provide clear instructions on how to label stored specimens with patient identification information to avoid loss of specimen or patient traceability.

For specimens that can be frozen, validate and identify the maximum acceptable number of freeze–thaw cycles.

5.13 IVD storage, operating conditions and stability

Identify specific storage conditions (e.g. storage temperature, light, humidity and other relevant factors) and shelf-life for the opened kit and working solutions, such as reconstituted reagents, if they differ from the labelled shelf-life.

Include information on the recommended operating temperatures if they differ from the storage conditions.

WHO prequalification requires units of measurement to be International System of Units (SI). Storage temperatures should be indicated in degrees Celsius (°C).

5.14 Test procedure

Follow the basic principles described in Section 4 to maximize readability. Use clear and simple language, with numbered lists to identify each step. Provide drawings of steps and flow diagrams when possible, to simplify and clarify the test procedure for the user. Highlight critical steps or parameters using visual cues such as bolded words, boxed messages or standardized symbols.

5.14.1 Instructions on test procedure

The instructions or directions for using the IVD need to clearly describe how to use the IVD properly to get the correct result in terms that the intended user can understand. To minimize user error, the instructions should address all the areas of risk for incorrect use identified in the manufacturer's risk assessment.

Advise the user (including self-test users) to read the information in the IFU before using the IVD. This information should be displayed prominently on the IFU (e.g. boldface type and capital letters). In addition, include a statement (warning) to the effect that not following the test procedure exactly as described in the IFU could cause improper functioning of the IVD and inaccurate test results (including, as applicable, foreseeable misuse and potential outcomes).

Describe and number all steps, including the use of assay calibrators, internal or external controls (or both) and calculations. Indicate the time needed to carry out each of the various steps. For example, with microplate enzyme immunoassays (EIAs) performed manually, indicate the maximum acceptable time within which all specimens, conjugates, chromogen and acid should be delivered to the microwells.

5.14.2 Quality control procedures

Each type of IVD should have a quality control procedure that is clearly explained in the IFU.

In general, control procedures for RDTs will include the presence of a control line. In some cases, they will recommend use of quality control material (e.g. reactive and nonreactive specimens), either supplied with the IVD, or available for use as a separate product code.

Control procedures for EIAs will include control material (e.g. reactive and nonreactive specimens), either supplied with the IVD, or available for use as a separate product code, and may incorporate control wells, specimen addition controls and other measures within the kit.

Control procedures for NAT will consist of internal controls that are added to each specimen to ensure the overall validity of the individual test result. In addition, control material (with nucleic acid present or not present) will either be supplied with the IVD or available for use as a separate product code.

The IFU should include the following:

- The procedure for using the available controls (e.g. following the same instructions as for patient specimens, or a different procedure).

- Instructions recommending the frequency of use; for example:
 - control material for an RDT recommended for use when a new lot is received, when environmental conditions change or when a user has not previously conducted the test; and
 - control material for a NAT IVD recommended for use in every test run (a single test run, which can include one or more test specimens) or batch (which consists of one or more test runs using a single kit lot).
- The principles of how the quality control procedure achieves its intended purpose.
- The limitations of the quality control procedure, clearly delineated; for example:
 - **limitations of the control line of an RDT** – if the control line only indicates flow of diluent but does not specifically indicate that specimen has been successfully applied to the IVD, this limitation should be noted; and
 - **limitations of the internal control for a NAT IVD** – if the internal control is added after the extraction process, the user is unable to use this internal control to judge the effectiveness of the extraction procedure, and this limitation should be noted.
- An interpretation of the quality control procedure results. information should be clearly provided as to whether test results can or cannot be accepted when a quality control procedure fails.
- The actions to be taken if there is a failure of any of the controls; for example:
 - **Failure of an internal control in a NAT IVD** (a negative result for the internal control). This would invalidate the test specimen that included the failed internal control. For a run that includes multiple specimens, only the specimen with the failed internal control is invalidated; all other specimens in the run are valid provided the external controls (if used) for that run are valid (i.e. the positive external control is positive and the negative external control is negative). Only the specimen with the failed internal control needs to be retested.
 - **Failure of one or more of the control materials** (if used) will invalidate the results of all the specimens in the respective run or batch, irrespective of the results of the internal controls. In this case, all the specimens need to be retested.
 - **Failure of the control line to appear for an RDT** indicates that the test has not worked, and it must be repeated with a fresh IVD.

If quality control material is not provided with the kit for the user, the user should be alerted that it is available separately and where it can be obtained (if known).

5.15 Reading test results

For tests where the final reaction or result, or their accessibility, may change over time, indicate the amount of time for which the final reaction or result remains stable. Include a statement directing the user to compare results to the appropriate controls before interpreting the test results (e.g. on an RDT, reading the control line before interpreting the test results). For example:

“Read results 10–30 minutes after adding buffer. Reading results before 10 minutes or after 30 minutes may not give accurate results. Check control line is present before interpreting the result.”

5.16 Interpretation of test results

Provide an interpretation of all possible result outcomes. State when further testing (e.g. confirmatory or supplemental testing) is required; for example, with an initial HIV antibody reactive result.

5.16.1 Interpretation of quantitative IVD test results

For quantitative assays, provide an interpretation of the result outcomes, and the range over which measurements can be made. In addition, provide guidance for results that fall outside this range. If required to obtain the final result, define appropriate formulae or algorithms (e.g. a correction factor may be needed to obtain the final result, depending on the specimen type used). In addition, include an example of a calculation using the formulae or algorithms to obtain the final result.

5.16.2 Results interpretation for IVDs by users without formal laboratory training

For IVDs intended for users without formal laboratory training, include pictorial representations of all possible test results for IVDs that give a visual readout, where possible. If the results are indicated by a colour change, the colour should be shown on the pictorial representations (high-quality photograph or a reproduction of results). The colour shown should match the real-life condition. When red and green are used, they should be accompanied by some other indication of positive or negative, such as a word or symbol. Explain the meaning of each possible test outcome (including faint test lines and invalid results). Provide information on what should be done in the event of an invalid test result.

5.16.3 Results interpretation for self-test IVDs

Information on the interpretation and understanding of the result for a self-testing IVD should be provided in an easily understandable way; for example, “A reactive result indicates possible HIV infection”. Provide clear and concise information on where to seek advice and follow-up in the event of a reactive or invalid result; for example, “Consult with a health facility for additional testing or repeat testing”. Explain the meaning of a false-reactive or false-nonreactive test result.

5.17 Limitations of the procedure

Identify, in a list, issues or conditions that would affect IVD performance (i.e. false-reactive results, false-nonreactive results and invalid results), based on the results of the analytical performance studies and clinical performance studies.

Limitations may be related to the user or the conditions during transport and storage. Issues may occur despite correct storage and procedure, and could be related to:

- the general design of the IVD (e.g. limit of detection, limit of quantification, high dose hook effect (when the measured levels of the measurand displays a significantly lower response than the actual level present in a specimen) or assigning the cut-off);
- the impact of a serological window period on detection of antibodies (e.g. nonreactive results in early HIV infection, and possible in very late HIV infection); and
- the measurand (e.g. absence of a histidine-rich protein 2 (HRP2) gene in certain populations may give a false-nonreactive malaria result, or persistence of HRP2 following resolved malaria infection may cause a false-reactive result).

5.18 Performance characteristics

Studies presented in the IFU should be relevant to the final and qualified version of the IFU.

Provide a summary of analytical performance studies and clinical performance studies that support the performance claims for the IVD, including at least the following specifications, where applicable:⁵

- analytical sensitivity (e.g. limit of detection, limit of the blank, and upper and lower limits of quantitation);
- analytical specificity (e.g. rheumatoid factor; antinuclear antibody; influence of lipaemic, icteric or haemolysed specimens; and cross-reacting organisms);
- diagnostic or clinical sensitivity and specificity;⁶
- repeatability (IVD-related, within-run variability in setting of intended use);

⁵ See Section 7 of (11) and WHO Prequalification product specific technical specifications for studies that are expected for a given product.

⁶ For any self-test device, the results of diagnostic or clinical specificity and sensitivity studies should be reported for both professional and self-use.

- reproducibility (user-related, inter-day variability, inter-run variability, inter-site variability, inter-lot variability, inter-user variability and inter-instrument variability in setting of intended use);
- reference intervals;
- measurement interval; and
- accuracy (if quantitative).

Identify one section of the performance characteristics as “Analytical performance studies” and another as “Clinical performance studies”, with subsections of each to describe individual studies.

For each study, include a brief description of the purpose and design of the study, the manner and location in which the study was conducted, the number and type of specimens studied, the reference methods used, the results and the conclusions. Results from each different subset represented (e.g. population, specimen type), should be presented separately. In addition to the narrative of the results, include appropriately numbered and titled figures and tables that summarize the study results (see [Annex 2](#)).

For IVDs for self-testing, manufacturers may modify the amount of detail provided on the clinical and analytical performance characteristics when designing the IFU. However, key performance characteristics (e.g. sensitivity and specificity) should be included in clear and readily understood language.

Where IVDs are intended for use by both users with formal laboratory training and users without such training, the diversity of the needs of these different users must be addressed (e.g. additional information for professional users provided in a separate section) (17).

5.19 List of references

Include a numbered list of references used in the IFU. Select relevant and recent publications that are practical and relevant to the product.

5.20 Contact information

Provide the name and contact details of the manufacturer (or an authorized representative of the manufacturer where necessary) and, if possible, the distributor whom the user can contact to obtain assistance. The IFU should ideally provide a mailing address, telephone number, email address and website address.

The IFU should instruct the user to contact both the manufacturer and the local regulatory authority when a serious incident has occurred (e.g. repeated failure of the assay or increased rate of invalid test results).

For IVDs for self-testing, a toll-free (free-phone) telephone number is a preferred means of providing direct health-related support to the user.

5.21 Document control

Include a document version number and date of issue for the IFU, and an indication of the language of the IFU (e.g. English or EN, French or FR).

5.22 Symbol key

Using internationally recognized symbols simplifies communication. Symbols can save space, spare costs of translation and improve clarity. They may be used instead of statements to convey information. There are a number of internationally recognized symbols for certain IVD characteristics (e.g. storage temperature limits, identification of in vitro diagnostic use and manufacturer information) (23, 26). These symbols are especially useful when printed materials are generated in multiple languages or users are not familiar with the language in which the IFU is written. Symbols quickly communicate a concept to the user in a way that, if used properly, can transcend language differences. The symbols should be explained in a symbol key in the IFU and should appear on the last page of the IFU.

6 References

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Annex 1: Template layout for intended use statements

The following text is intended as a starting-point when preparing an intended use statement. It lists the critical points that are required as part of WHO Prequalification assessment. The italic text in brackets denotes the text that should relate to the specific IVD. Product specific information should be added.

Description of the IVD	The assay is <i>a [single-use]</i> in vitro diagnostic medical device, in the format of <i>[immunochromatographic/immunofiltration rapid diagnostic test] [enzyme immunoassay] [nucleic acid test] [flow cytometer]</i> .
What is detected by the IVD	<p>It is intended for the <i>[qualitative/quantitative]</i> detection of <i>[antibodies/antigen/surface antigen/nucleic acid/enzymes]</i> to/of <i>[human immunodeficiency virus types 1 (Group M/N/O) and 2/hepatitis C/hepatitis B/malaria parasites/Human papillomavirus/Vibrio cholerae/glucose-6-phosphate dehydrogenase/add]</i>.</p> <p>The assay <i>[does/does not]</i> differentiate between different <i>[types/genotypes/parasites]</i> of <i>[human immunodeficiency virus types 1 (Group M/N/O) and 2/hepatitis C/hepatitis B/malaria/Human papillomavirus/Vibrio cholerae/ add]</i>.</p>
Function of the IVD	<p>The function of the assay is for the <i>[screening/diagnosis or aid for diagnosis/monitoring/staging or aid for staging/determining genetic predisposition/prognosis]</i>.</p> <p><i>[Reactive results should be confirmed by a supplemental assay/additional testing/add details of confirmatory step]</i>.</p>
Clinical indication	The assay is used to <i>[detect a specific disorder/detect, define or differentiate a condition or risk factor of interest/add how and why the user will use the results of the test]</i> .
Qualitative/quantitative	The assay is <i>[qualitative, semiquantitative or quantitative]</i> .
Automation	The assay is <i>[automated/semi-automated/manual]</i> .
Specimen type	Human <i>[capillary whole blood/venous whole blood/plasma processed with EDTA, heparin, citrate/serum/plasma preparation tubes/serum/separator tubes/oral mucosal transudate/cervical fluid/ add]</i> are validated for use.
Intended testing population	<p>The intended testing population is <i>[symptomatic/ asymptomatic general population through provider-initiated or client-initiated testing/key populations or populations at risk/diagnosed/recipients of blood or tissue products/ add]</i>.</p> <p>This assay is not intended for use in <i>[neonates below 6 months of age/people on antiretroviral therapy/screening blood, organ, tissue donations/add uses that are not validated relating to population, user, clinical indication, function]</i>.</p>

Intended user	The assay is for [use by <i>a trained testing provider/trained lay provider</i>]/ <i>health-care professional/laboratory professional</i>]/ <i>self-testing/use with self-collected specimens</i>].
Operational setting	The assay is to be used in a [<i>clinical setting/health-care setting/laboratory setting/point-of-care (POC)/near-POC</i>]/ <i>home-setting or similar environment/ add</i>].

Annex 2: Example tabulated performance characteristics for IFU

The tables below are examples only, they are not an exhaustive list.

A2 – 1 Example table: analytical performance study – precision (repeatability and reproducibility)

Table 4. Summary of assay precision (repeatability)

Quality control panel member	Number of replicate tests	Standard to cut-off (S/Co)		Within-condition % coefficient of variation (CV)
		Mean	Standard deviation (SD)	
Negative control	(Value)	(Value)	(Value)	(Value)
QC-1 (low titre positive)	The table is for illustrative purposes. WHO expects manufacturers to provide all results for the studies in an easy to read format.			(Value)
QC-2 (mid-range positive)				(Value)
QC-3 (high-titre positive)	(Value)	(Value)	(Value)	(Value)

CV coefficient of variation, QC quality control, S/Co standard to cut-off, SD standard deviation.

Table 5. Summary of assay precision (reproducibility) for quality control panel member QC-1 (low titre positive)

Results for quality control panel member QC-1 (low titre positive)	Number of replicate tests	S/Co		Between-condition % CV
		Mean	SD	
Between-day	The table is for illustrative purposes. WHO expects manufacturers to provide all results for the studies in an easy to read format.			(Value)
Between-user				(Value)
Between-lot				(Value)
Between-instrument				(Value)

CV coefficient of variation, QC quality control, S/Co standard to cut-off, SD standard deviation.

A2 – 2 Example table: analytical performance study – interfering (endogenous) substances)

Table 6. Summary of test results for determination of analytical specificity: potentially interfering endogenous substances

Interfering substance	Specimen identification (ID)	Test results		
		Unspiked specimen	Specimen spiked with substance-1	Specimen spiked with substance-2
Substance-1 (xx g/mL)	ID-1	(Value)	(Value)	(Value)
	ID-2	The table is for illustrative purposes. WHO expects manufacturers to provide all results for the studies in an easy to read format.		
	ID-3			
	ID-4			
Substance-2 (x/ millimolar)	ID-1, etc.	(Value)	(Value)	(Value)

A2 – 3 Example table: analytical performance study – cross-reacting infections, diseases and medical conditions

Table 7. Summary of test results for determination of analytical specificity: potentially cross-reacting unrelated infections, diseases and medical conditions

Infection/disease/medical condition	Number of specimens tested	Test results	
		IVD being evaluated	Reference test
Organism 1	(Value)	(Value)	(Value)
Medical condition 1	(Value)	The table is for illustrative purposes. WHO expects manufacturers to provide all results for the studies in an easy to read format.	
Etc....	(Value)		

A2 – 4 Example table: clinical performance study – diagnostic sensitivity

Table 8. Summary of results of a clinical study to determine diagnostic sensitivity – finger-prick whole blood

Study site	Number of specimens tested	Number of specimens reactive by reference method	Number of valid tests	Number of specimens reactive in the IVD	Number of specimens falsely-nonreactive	% sensitivity	95% CI
1	(Value)	(Value)	(Value)	(Value)	(Value)	(Value)	(Value)

CI confidence interval

A2 – 5 Example table: clinical performance study – diagnostic specificity

Table 9. Summary of results of a clinical study to determine diagnostic specificity – serum

Study site	Number of specimens tested	Number of specimens reactive by reference method	Number of valid tests	Number of specimens non-reactive in the IVD	Number of specimens falsely-reactive	% Specificity	95% CI
1	(Value)	(Value)	(Value)	(Value)	(Value)	(Value)	(Value)

CI confidence interval

Annex 3: Preferred terms and harmonization of labelling for malaria IVDs

The WHO Global Malaria Programme (GMP) – in collaboration with the Roll Back Malaria Secretariat, the Roll Back Malaria Procurement and Supply Management and Case Management working groups and partners, and the Institute of Tropical Medicine, Antwerp – developed a harmonization task force recommending harmonization of the labelling of IVD, boxes and accessories, language and format of the IFU. The task force has published its recommendations, which can be accessed in the WHO/GMP publications (5, 10). The recommendations include a generic IFU template and a checklist for completeness of malaria RDT labelling. WHO encourages manufacturers where possible to adopt these recommendations for IVD applications for WHO Prequalification.

WHO/EMP/RHT/PQT/TGS5/2017.05

The Technical Guidance Series for submission to WHO Prequalification – Diagnostic Assessment is developed to assist manufacturers in meeting prequalification requirements for their IVD. Further information on this guidance and other Technical Guidance series documents email

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