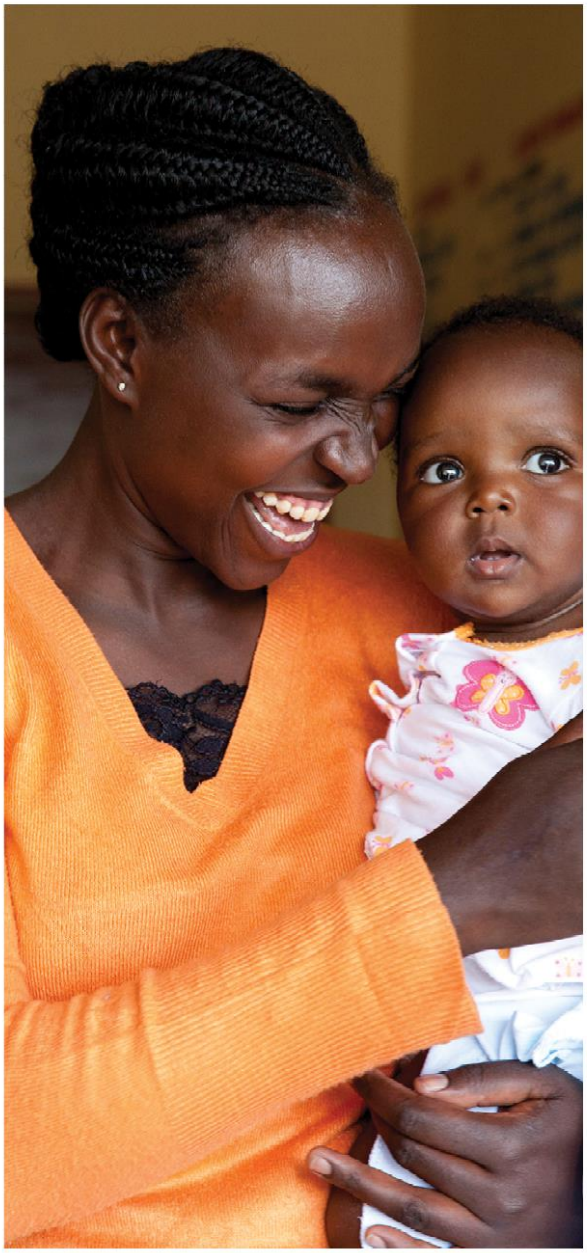

Quality and Performance Guidance on Selection of Pregnancy Tests for Procurement

USAID FROM THE AMERICAN PEOPLE

fhi360 THE SCIENCE OF IMPROVING LIVES

Envision FP

Reproductive Health SUPPLIES COALITION

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3 Abbreviations

21 CFR	Title 21 of the U.S. Code of Federal Regulations
CE	European Conformity
cGMP	Current Good Manufacturing Practice
COA	Certificate of Analysis
DOC	Declaration of Conformity
EC	European Commission
EU	European Union
FIND	Foundation for Innovative New Diagnostics
FDA	Food and Drug Administration (United States)
GHTF	Global Harmonization Task Force
hFSH	Human Follicle Stimulating Hormone
hCG	Human Chorionic Gonadotrophin
hLH	Human Luteinizing Hormone
IFU	Instructions for Use
IMDRF	International Medical Device Regulatory Forum
IVD	In Vitro Diagnostic
ISO	International Organization for Standardization
MHLW	Ministry of Health, Labor and Welfare (Japan)
MRDTs	Malaria Rapid Diagnostic Tests
NGO	Nongovernmental Organizations
NRA	National Regulatory Authority
PMDA	Pharmaceutical and Medical Device Agency
POC	Point of Care
RDT	Rapid Diagnostic Tests
SRA	Stringent Regulatory Authority
hTSH	Human Thyroid Stimulating Hormone
TGA	Therapeutic Goods Administration (Australia)
USAID	United States Agency for International Development
WHO	World Health Organization

4 Glossary

Provided below is a compilation of common definitions copied and referenced from normative documents or peer-reviewed journals. Some definitions have been adapted to apply to pregnancy tests, as indicated.

21 CFR 820: Also known as Quality System Regulation (QSR), 21 CRF 820 outlines current good manufacturing practice (cGMP) regulations that govern the methods used in, and the facilities and controls used for the design, manufacture, packaging, labeling, storage, installation and servicing of all finished medical devices intended for human use. These requirements are intended to ensure safety and effectiveness of medical devices for the end user. All medical device manufacturers supplying medical devices to the U.S. are required by the U.S. FDA to maintain a quality management system in compliance with that described in 21 CFR 820 (1).

510(k) clearance: A premarket submission made to U.S. FDA to demonstrate that the device to be marketed is at least as safe and effective (i.e., substantially equivalent) to a legally marketed device that is not subject to 'premarket approval.' Submitters must compare their device to one or more similar, legally-marketed devices and make and support their substantial equivalency claims (2). While human data are not required for this assessment, laboratory testing data are almost always required.

Accelerated stability evaluation: Study designed to increase the rate of chemical and/or physical degradation or change of an in vitro diagnostic (IVD) reagent by using stress environmental conditions to predict shelf life (3).

Note: The design of an accelerated stability evaluation can include extreme conditions of temperature, humidity, light or vibration.

Accuracy: Amount of agreement between results from the test under evaluation compared with results obtained with the reference standard on the same subjects. Accuracy can be expressed in a number of ways, including sensitivity-specificity pairs, likelihood ratios, diagnostic odds ratios and area under the curves (adapted from (4)).

Analytical sensitivity: Represents the smallest amount of substance in a sample that can accurately be measured by an assay (5).

Analytical specificity: Refers to the ability of an assay to measure a particular organism or substance, rather than others, in a sample (5).

Ancillary items: Items required to perform the pregnancy test at point-of-use, such as the urine collection cup and dropper (adapted from (6)).

Antibody: Immunoglobulin with a particular amino acid sequence and tertiary structure that binds to a complementary structure on the antigen, called the epitope. The combining sites on the antibody and the antigen fit tightly together with a strong attractive force because the matching areas on the surface of each molecule are relatively large (6).

Antigen: A substance that can elicit a specific immune response due to specific configurations (epitopes) on the surface of the high molecular mass molecules (e.g. proteins, polysaccharides and nucleic acids) (6). The predominantly used target antigen in pregnancy tests is human chorionic gonadotropin (hCG).

Assay principle: Fundamental concepts on the composition and operation of pregnancy tests.

Analytical performance: The ability of an IVD medical device to detect or measure a particular analyte (7).

Authorized Representative: Any natural or legal person established within a country or jurisdiction who has received a mandate from the manufacturer to act on its behalf for specified tasks with regard to the latter's obligation under that country or jurisdiction's legislation (7).

Batch: A defined quantity of product manufactured in a single process or series of processes and therefore expected to be homogeneous (6) (sometimes used interchangeably with 'Lot.')

Expiry date: Date on a container (usually on the label) of a product up to and including which the product is expected to meet specifications, if stored correctly. The shelf life, as established by adequate stability studies, is defined for each batch at the date of manufacture (6).

CE mark: On pregnancy test packaging, a mark certifying that the product conforms to the essential requirements of European Medical Device Directive 98/79/EEC (adapted from (8)).

current Good Manufacturing Practices (cGMP): That part of quality assurance which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorization (9).

Clinical sensitivity: Also known as diagnostic sensitivity, it is the test's ability to detect persons with the condition of interest in a population or group and is expressed as a proportion or percentage: the number of persons who have both the condition and a positive test result divided by the number of persons who have the condition (adapted from (5)).

Clinical specificity: Also known as diagnostic specificity, it is the ability of an assay to correctly identify a person who does not have the condition in question and is expressed as a proportion or a percentage: the number of persons who do not have the condition and produce negative results divided by the number of persons who do not have the condition (adapted from (5)).

Compliance/conformity: Fulfillment of regulatory requirements (7).

Directive 98/79/EC: Specific to safety, quality and performance of in vitro diagnostic (IVD) medical devices; manufacturers must meet criteria specified in the directive to qualify for CE marking and legal placement of an IVD on the European Market.

Effectiveness: Degree to which activities produce the effects planned (9).

Efficiency: Relationship between the results of activities and the corresponding effort expended in terms of money, resources and time (9).

EU Declaration of Conformity: The document in which the manufacturer states that the product satisfies the essential requirements of the applicable legislation. By drawing up and signing the European Union (EU) Declaration of Conformity, the manufacturer assumes responsibility for the compliance of the product (10).

Human chorionic gonadotropin (hCG): A hormone produced by trophoblastic tissue when fertilization has occurred. In a 28-day cycle with ovulation occurring at Day 14, upon fertilization, hCG can be detected in urine or serum in minute quantities around Day 23, or five days before expected menstruation. Its function includes facilitation of implantation as well as maintenance and development of corpus luteum. In normal subjects, hCG in urine provides an early indication of pregnancy (adapted from (11)).

Instructions for use (IFU): Information provided by the manufacturer to inform device user of the medical device's intended purpose and proper use and of any precautions to be taken (7).

Intended use/purpose: 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 (7).

In vitro diagnostic (IVD) medical device: A 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 (7).

Note: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments/apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status. In some jurisdictions, certain IVD medical devices may be covered by other regulations.

Invalid test: Test wherein the control line does not appear (6).

IVD medical device for self-testing: Any in vitro diagnostic medical device intended by the manufacturer for use by lay persons (7).

International Medical Device Regulatory Forum (IMDRF): A voluntary group of international medical device regulators whose aim is to accelerate international medical device harmonization and convergence, and builds on foundational work done by the Global Harmonization Task Force on Medical Devices.

ISO 15223: Standard that identifies the requirements for symbols used in medical device labeling to convey information on the safe and effective use of devices (12).

ISO 13485: A quality management system created by the ISO for medical device manufacturing. The standard prescribes the documentation, procedures and structures that must be followed in all types of organizations to facilitate the production of medical devices of consistent standard (adapted from (13).

Labeling: The label, instructions for use, and any other information related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documentation (7).

Lay person: Individual who does not have formal training in a specific field or discipline (7).

Lot: A homogeneous collection of tests made under essentially identical manufacturing conditions using the same lots of raw materials. Manufacturer's lot identification and recording are required to permit effective product recall in the event of a problem with device quality (adapted from (8)).

Lot number or code: A unique identifying alphanumeric code assigned to a Lot (8).

Manufacturer: The natural or legal person with responsibility for the design, manufacture, packaging and labeling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party (14).

Notified body: A certification organization that the national (competent) authority of a EU Member State designates to carry out one or more conformity assessment procedures described in the annexes of the European Union Directives. The Medicines and Healthcare Products Regulatory Agency is the competent authority in the United Kingdom under the three medical device directives. A notified body must be qualified to perform all the functions set out in any annex for which it is designated. The designation may be restricted to specified types of devices or annexes (6).

Packaging: Any material, including printed material, used in the packaging of a medical device but excluding any outer packaging used for transport or shipment. Packaging materials are referred to as 'primary' or 'secondary' according to whether they are intended to be in direct contact with the product (6). Primary packaging is intended to be in direct contact with the product while secondary packaging is intended to enclose primary packaging.

Performance evaluation: The assessment and analysis of data to establish or verify the ability of an in vitro diagnostic medical device to achieve its intended use (13).

Point-of-care: A diagnostic test that is performed near the patient or treatment facility, has a fast turnaround time, and may lead to a change in patient management (15) .

Procurement process: The process of acquiring supplies from private or public suppliers or through direct purchases from manufacturers, distributors or agencies (6).

Quality: The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs (16).

Quality management system: The organizational structure, responsibilities, procedures, processes and resources for implementing quality management. For the purpose of these guidelines, 'implementing quality management' includes both the establishment and maintenance of the system (7).

Quality assurance: A wide-ranging concept covering all matters that individually or collectively influence product quality. The totality of arrangements made with the objective of ensuring that products are of the quality required for their intended use (9).

Real time stability evaluation: A study designed to establish or verify the shelf life of the IVD reagent when exposed to the storage conditions specified by the manufacturer (3).

Note: Conditions that can affect stability of an IVD reagent include temperature, transport conditions, vibration, light, and humidity.

Regulatory approval: The process by which a party submits information to the regulatory authority in a jurisdiction, regarding the identification and establishment of location(s) of the manufacturer and other parties, responsible for supplying a medical device to the market in that jurisdiction (7).

Regulatory authority: A government body or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and that may take enforcement action to ensure medical products marketed within its jurisdiction comply with legal requirements (7).

Regulatory requirements: Any part of a law, ordinance, decree, or other regulation which applies to medical device manufacturers (7).

Note: Guidelines, draft documents or the like should not be used as regulatory documents and should not be considered as such, unless formally widely known. For purposes of this guidance, regulatory requirements are restricted to those pertaining to the quality management system.

Specimen: Material collected directly from a patient; the term '**sample**' is reserved for aliquots (portion of a larger whole) of the patient specimen and for processed material (17).

Self-testing: Testing performed by lay persons (7). Device is intended by the manufacturer to be able to be used in a clinical setting or home environment.

Shelf life: Period of time until the expiry date during which an IVD device/reagent in its original packaging maintains its stability under storage conditions specified by the manufacturer (18).

Stability: Ability of an IVD to maintain its performance characteristics within limits specified by the manufacturer (18).

Stability testing: Long-term accelerated (and intermediate) studies undertaken on batches according to a prescribed protocol to establish or confirm the re-test period (or shelf life) of a product (6).

Specification: A detailed statement of a product's requirements, as established by the buyer. Usually, a specification is based on an established standard (8).

Standard: A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory body (8).

Technical documentation/file: The documented evidence, normally an output of the quality management system that demonstrates conformity of a device to the *Essential Principles of Safety and Performance of Medical Devices (7)*.

5 Background

Ensuring access to low-cost, high quality, pregnancy tests[1] has been shown to increase same-day provision of family planning, and aid in the timely provision of antenatal care (19-22). However, in many settings, pregnancy tests are not routinely available for clients, are marked up to unaffordable prices, are of questionable quality and/or of variable performance. In 2015, FHI 360 partnered with Marie Stopes International to conduct an assessment in Kenya, Malawi and Mali to document the availability, affordability and quality of pregnancy tests. This project was completed with support from the Reproductive Health Supplies Coalition through an Innovation Fund grant. The assessment noted:

- Concerns about falsified products or falsely CE-marked pregnancy tests entering markets;
- A lack of knowledge among consumers, providers, importers, distributors, pharmacists and regulatory personnel on internationally recognized quality standards for pregnancy tests, including what existing standards mean and how they can be used to ensure that only pregnancy tests meeting quality and performance standards enter national markets;
- No publicly available protocol for product qualification or pre-and post-shipment lot verification testing customized for pregnancy tests;
- Limited visibility for procurers on the supply side (e.g., limited information about suppliers' prior performance); and
- A lack of focus and harmonization around quality and performance specifications to be used when selecting pregnancy tests for procurement.

Ruling out Pregnancy when Providing Family Planning Services

In many countries, non-menstruating women are routinely denied same-day family planning services because of a concern among healthcare providers that these women may be pregnant. Several tools can be used by healthcare providers to rule out pregnancy.

One is the "Pregnancy Checklist" - a job aid with simple questions that a provider can ask a client to rule out pregnancy. Endorsed by the World Health Organization (WHO) and USAID, the Checklist has been adopted by more than a dozen countries. A simple, low-cost, high quality pregnancy test is another tool. Neither the checklist nor a pregnancy test is clinically effective in all situations. The two tools complement each other.

See **Annex 1** for more information on when a healthcare provider should use the checklist versus a pregnancy test.

[1] Throughout this document, "pregnancy tests" refer to rapid in vitro diagnostic (IVD) pregnancy test used in a point-of-care setting.

Concurrently, FHI 360 carried out an exploratory evaluation of a small number of pregnancy tests, collected from low-resource settings over a two-year period, to develop an understanding of prevailing quality status based on labeling criteria. Preliminary results from this analysis, as summarized in **Annex 2**, illustrate significant quality, performance and operational gaps in labeling, such as inadequate instructions for use, absence of performance characteristics and standard quality assessment by recognized regulatory authorities.

In most developing countries, regulations for IVDs can be inadequate and/or poorly enforced. Global efforts towards harmonization of regulatory approaches have led to internationally accepted standards for a risk-based approach for pre-market assessment of safety, quality and performance of diagnostics. These include a number of regulatory authorities that are founding members of the Global Harmonization Task Force (GHTF): European Union (EU), U.S. Food and Drug Administration (U.S. FDA), Health Canada, Therapeutic Goods Administration (TGA), Australia, and Pharmaceutical and Medical Device Agency (PMDA) and Ministry of Health, Labor and Welfare (MHLW), Japan. The GHTF was later disbanded and its mission was taken over by the International Medical Device Regulatory Forum (IMDRF), which allows for wider participation of some additional regulators – the National Health Surveillance Agency of Brazil; China Food and Drug Administration, Russian Ministry of Health and Singapore's Health Science Authority (links to main websites provided in **Annex 3**).

In 2016, this guidance document was developed to address some of these gaps in knowledge and practice by outlining requirements for quality standards and performance specifications, derived mainly from the ISO standards, EU and U.S. FDA requirements for marketing clearance, and IMDRF/GHTF and WHO normative documents.

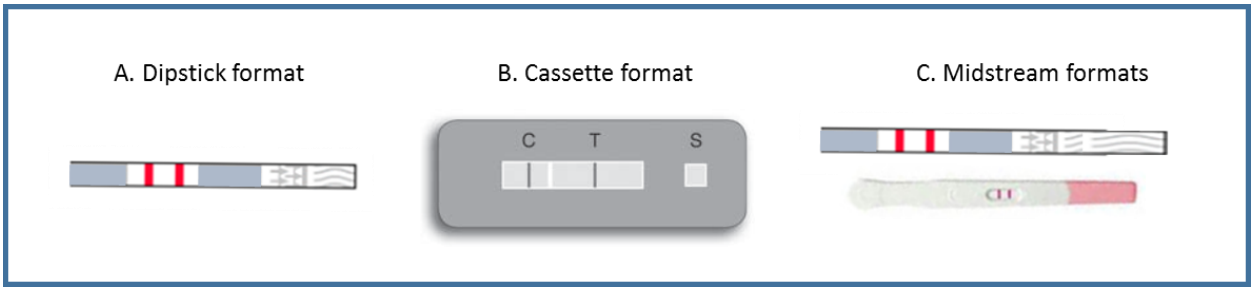
This work effect was completed with support from USAID, through its *Envision FP* award, led by FHI 360 and in consultation with key stakeholder groups.

6 Scope

Guidance provided herein is specific to pregnancy tests used in point-of-care (POC)[2] settings. It is applicable to the three most common immunochromatographic formats (**Figure 1**), which are designed to use urine as a specimen, and can be read visually without the aid of an additional device. However, this guidance does not apply to pregnancy tests that use venous or capillary whole blood or serum as a specimen**.**

Specifications cover quality, performance (sensitivity, specificity and accuracy), operational aspects (instructions for use, claimed shelf life, packaging and labeling) and safety criteria, as applicable to pregnancy tests (23).

Figure 1: Three formats of pregnancy tests covered in this document



[2] POC tests may be performed by non-laboratory personnel, such as physicians, nurses, community healthcare workers, pharmacists and the patient herself (self-test).

7 Intended Audience

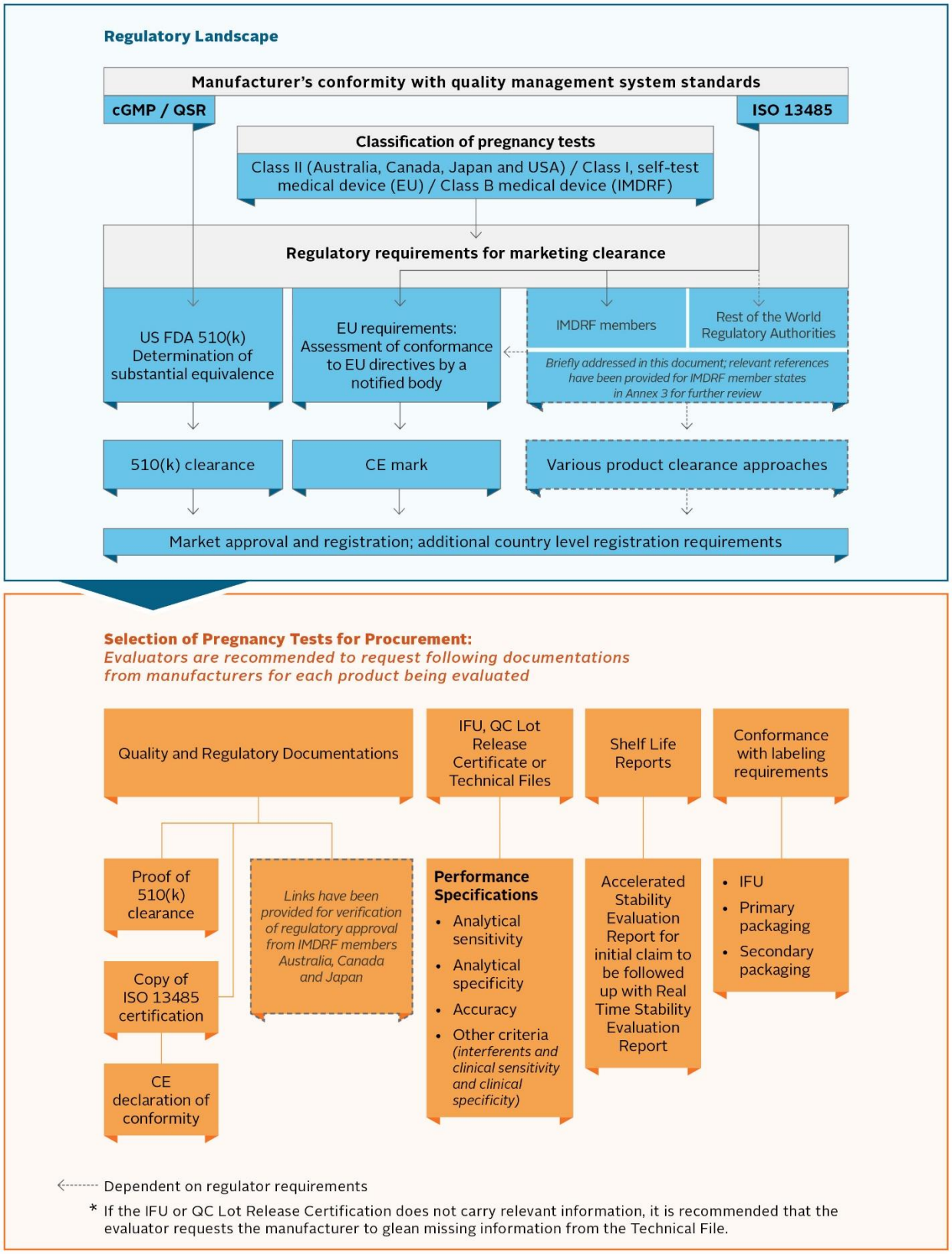
This document has been designed to provide guidance to personnel involved in *product selection* in the procurement process. While those who carry out product selection vary depending on country and program context, this group generally includes procurement officers, health officers, quality assurance specialists and/or pharmacists. This group will be collectively referred to as *evaluators* in this document.

This guidance is also relevant to those manufacturers who wish to supply pregnancy tests to global, national and/or local public health programs as well as to policy makers and social marketing and service delivery groups.

8 How to Use this Document

Broadly, this document provides recommendations on quality standards (Section 10.1), regulatory requirements (Section 10.2), performance (Section 11) and operational specifications (Section 12) for selection of pregnancy tests. As outlined in **Figure 2**, areas covered are derived from ISO standards, U.S. FDA and EU regulatory requirements, and GHTF/IMDRF and WHO guidance for IVDs. References for further evaluation by other IMDRF members are provided in **Annex 3**, while Rest of the World (ROW) regulations are briefly discussed in Section 10.2.4.

Figure 2: Areas of guidance covered in this document



When using this document, please note the following:

- In developing this document, careful consideration was given to the unique challenges in low-resource settings. Recommendations discussed herein were, through a consensus-driven process, considered as adoptable by most countries, regardless of maturity level of regulatory infrastructure.
- 'Enhanced quality and performance practices' have been included in green boxes for consideration by countries with more mature regulatory infrastructure.

- Recommended documentation for evaluators to request from manufacturers is summarized in orange boxes. For a listing of all documentation that evaluators should request from manufacturers, see checklist in **Annex 4**.

- Blue call-out boxes with a magnifying glass highlight further clarifications.

- This document is not intended to replace existing guidance on product selection processes, but rather to provide additional guidance *tailored specifically to selecting pregnancy tests* that meet high quality and performance standards.
    - For guidance on procurement processes and supply chain management, see **Annex 5** for a recommended reading list.
    - For information on the logistics cycle and on continuous quality monitoring and evaluation, see **Annex 6**.
- Involvement of technical and quality assurance experts with specific insight into product selection and procurement of health commodities—in particular, IVDs and rapid diagnostic tests (RDTs)—is recommended.
- Detailed annexes on other pertinent areas also have been provided for those wanting more information.

9 Overview of Pregnancy Tests

Pregnancy tests are also known as 'urine pregnancy tests,' 'home pregnancy tests,' 'hCG/HCG tests,' and 'over-the-counter pregnancy tests.' In addition, the term 'point-of-care pregnancy test' is often used when the test is administered by a provider. Typical pregnancy tests are designed to provide only a positive or a negative (yes/no) result. The principle behind this type of pregnancy diagnosis is shown schematically in **Annex 7**. Briefly, a dipstick is assembled by layering a sample pad, a conjugate pad with detection antibodies, a nitrocellulose membrane with test and control lines and an absorbent pad, on to a plastic backing. Test and control lines carry antibodies against human chorionic gonadotrophin (hCG) and mouse immunoglobulin, respectively. For cassette and some midstream pregnancy tests, the dipstick is encased in plastic housing. Adding urine specimen to the dipstick triggers detection antibodies to mobilize through capillary action. Presence of hCG leads to localization of the detection antibody to the *test line* yielding a positive signal. Localization of the detection antibody to the *control line* is independent of hCG, and by yielding a signal, it validates that the assay and the reagents are operating as expected. If the test is positive for hCG (and therefore pregnancy), both the test and control lines should develop; if the test is negative, only the control line should develop.

A woman begins to produce hCG hormone six to 12 days after egg fertilization. As the pregnancy progresses, hCG levels continue to rise, and plateau around 45 days post-conception (11). Ninety-eight percent of pregnant women have urine concentrations of hCG > 25 mIU/mL by the day of their next expected period (11, 24-26). Due to natural fluctuations in menstrual cycles and variable analytical sensitivity of pregnancy tests, pregnancy diagnosis prior to one or two weeks after the missed period remains challenging (27).[3]

Other service delivery tools also can be used to rule out pregnancy; this is particularly important when non-menstruating clients present for family planning services. In these cases, providers can often exclude pregnancy with a simple client history, sometimes taken with the help of the "**Pregnancy Checklist**" job aid (21, 28). The Pregnancy Checklist has been endorsed by the World Health Organization and adopted by many countries. If client history remains inconclusive when using the Pregnancy Checklist, a pregnancy test can help the provider be reasonably certain that the client is not pregnant (and thus eligible for a hormonal contraceptive or an intrauterine device). See **Annex 1** for more information about using the Checklist in tandem with pregnancy tests.

[3] Highly sensitive tests (analytical sensitivity $\leq$ 25 mIU/mL) detect pregnancy as early as the first day of missed menses. Lower sensitivity tests (analytical sensitivity $\geq$50 mIU/mL) detect about 10 days after missed menses (27).

10 Quality Standards and Regulatory Requirements

This document briefly discusses quality standards applicable to IVDs, as detailed in ISO 13485 and market clearance regulatory requirements of U.S. FDA and EU directives. A brief description of regulatory information pertaining to Health Canada, TGA, PMDA, MHLW and ROW is also included. Demonstration of compliance to quality standards and regulatory requirements involves a choice of testing pathways that depends on medical device classification**.** Such classification is based on perceived risk to the user associated with the device. The U.S. FDA, Health Canada, PMDA, MHLW and TGA have classified the pregnancy test as a *Class II device* (medium risk), while the EU has classified it as a *self-test* under *Class I device* (low risk).[4]

10.1 Quality Standards

Quality standards are documented agreements containing technical specifications or other precise criteria used as rules, guidelines or definitions of characteristics, to ensure that materials, products and process fit their purpose (29). A well-established quality management system ensures quality consistency and provides the basis for greater reliability in device safety and performance (29). It is critical for manufacturers to conform with quality standards, and for this conformity to be periodically audited by governmental or third party agencies (29).

It is recommended that pregnancy test manufacturing sites comply with quality management system standard **ISO 13485**,[5] a globally recognized system for the design, development and manufacture of medical devices. The U.S. FDA equivalent is 21 CFR part 820 **cGMP/QSR**. Since pregnancy tests are classified in the low to medium risk category, their compliance with quality-related regulations often depends on the declarations of manufacturers. Manufacturers are expected to prepare technical documentation illustrating how each pregnancy test product has been designed, developed and manufactured. This documentation is typically controlled by quality management systems.

[4] Several different international classification systems for IVDs are in use in the world today. Generally, the classification is assigned by the intended use and the risk the device presents to the patient. As the classification level increases from Class I to Class IV, the risk to the patient and regulatory control increases.

[5] ISO 13485:2016 was released in 2016 and will coexist with ISO 13485:2003 through March, 2019, after which point only ISO 13485:2016 will be accredited.

Documentation for Evaluators on Quality Standards: It is recommended that evaluators request a copy of the manufacturer's ISO 13485 certification at the time of evaluation. The certificate of conformity should include:

- Manufacturer's certified quality management system standard
- Name and country of assessment body
- Date of last audit
- Date of expiration.

In addition, the certification should have the same manufacturing site address as that on product labeling, and explicitly include the manufacture of IVDs in its statement of scope.

It is recommended that ISO certification be checked and verified on the website of the certification body or by directly contacting the certification body. Verification will have value if the certification body is accredited by the competent body for the country in question.

The industry standard for quality management, ISO 9001, should not be confused with quality system standard ISO 13485. Proof of compliance with ISO 9001 alone, as commonly seen with pregnancy tests, is not adequate for compliance with ISO 13485.

ISO 9001: This standard sets the requirements for an organization-wide quality management system with continual improvement. It helps businesses and organizations be more efficient and improve customer satisfaction (30).

ISO 13485: This quality management system standard sets requirements for an organization to demonstrate its ability to provide *medical devices* and *related services* that consistently meet customer and regulatory requirements. All ISO 13485 requirements are specific to organizations providing medical devices, regardless of the type or size of the organization (13). This standard is required in many countries as the basis for quality assurance management of IVDs for their registration and regulatory control.

10.2 Regulatory Requirements for Marketing Clearance

IVDs must satisfy safety, performance, quality system and labeling requirements to meet the varying regulatory requirements of different regulatory bodies (29). The degree of regulatory scrutiny is based on the potential risks of IVDs, and pregnancy tests are classified as low to medium risk. Regulatory authorities acknowledge product clearance for market in various ways. Key mechanisms are summarized below in Section 10.2.1 for the EU and Section 10.2.2 for the

U.S. FDA. Approval by other regulatory authorities who were founding members of GHTF also can be considered, subject to evaluators' understanding and knowledge of these groups (Section 10.2.3). **Annex 3** provides a list of regulatory authorities with links to their websites.

10.2.1 CE Marking

In the European system, IVD directive 98/79/EC addresses safety, quality and performance of IVDs. It aims to ensure that IVDs do not compromise the health and safety of users and third parties, and that performance levels specified by the manufacturer are attained (14). It also provides regulatory requirements for obtaining the CE marking.

- Since pregnancy tests belong to the "self-test" classification, the conformance process requires involvement of a notified body within the EU. Upon receipt of the EC certificate from a notified body, the manufacturer places the CE mark on or with the device (29).
- The CE marking should comply with the schematics indicated in **Figure 3** and elaborated in **Annex 8.** It must be accompanied by the identification number of the notified body (usually a 4-digit number). The CE marking and notified body identification number must appear on the device (if practicable), on primary and secondary packaging, and in the product insert.
- **Avoid selecting products that carry nonconforming CE markings,** as noted in **Figure 3** (31).[6]

Figure 3. Comparison of CE marking of conformity and nonconformity (32)

CE	CE marking of conformity
CE xxxx	CE marking of conformity with identification number of the Notified Body
CE	CE marking of nonconformity; spacing between letters is incorrect
CE CE CE	CE marking of nonconformity; CE marking is not to be in a frame

- It is recommended that the manufacturer draw up a Declaration of Conformity (DoC) to declare sole responsibility for conformity to the relevant directive. The DoC should detail

[6] Please refer to the WHO fact sheet to find out more about prevalence of substandard, spurious, falsely labeled, falsified and counterfeit medical products: http://www.who.int/mediacentre/factsheets/fs275/en/

the information highlighted in the orange box below. The DoC should be made available to evaluators at the time of tender submission or supplier selection.

Documentations for Evaluators on CE Marking: It is recommended that evaluators request a copy of *EU/EC Declaration of Conformity* from the manufacturer at the time of assessment. The Declaration of Conformity should indicate:

- Manufacturer's name and address
- Name of device
- Essential characteristics of device
- Information of regulatory authority/notified body
- Marketing clearance with indication of license number
- Legally binding signature of corporate officer signing on behalf of the organization.

10.2.2 U.S. FDA 510(k) Clearance

A manufacturer who intends to market a pregnancy test in the U.S. is required to submit a 510(k) application, also known as a Premarket Notification. For this process, the manufacturer must provide evidence demonstrating that the device to be marketed is at least as safe and effective as a legally marketed/predicate device. This is also known as demonstration of 'substantial equivalence'(2). Once the manufacturer receives written notification of FDA clearance that confirms 'substantial equivalence' to a legally marketed product, the test can be marketed in the U.S. Note that FDA clearance is not indicated on the package labeling.

510(k) clearance is required only for pregnancy tests intended for sale in the U.S. market. For international procurers considering pregnancy test products that claim to be U.S. FDA-cleared, it is highly recommended to confirm that the manufacturer holds 510(k) clearance by visiting the 510(k) pre-market notification website: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

Pregnancy test 'product code': LCX
Refer to **Annex 9** for a screenshot of the FDA website.

It is likely that a different quality 'export only' version of the FDA-approved product is manufactured for use outside of the U.S. It is important for evaluators to check and verify these quality discrepancies for alignment with programmatic needs.

Documentation for Evaluators on U.S. FDA Clearance: It is recommended that the evaluator request a 510(k) device clearance letter. In addition, the evaluator should check for 510(k) clearance on the U.S. FDA website (**Annex 9**)

10.2.3 Stringent regulatory assessment by Health Canada, TAG, PMDA and MHLW

Authorities acknowledge product clearance for market in various ways. Helpful information to verify pregnancy tests manufactured/approved in Canada, Australia, and Japan is provided below (**Table 1**).

Table 1: Tools to verify pregnancy test regulatory clearance in Canada, Australia, and Japan

Regulatory Authority	Classification	Documentary Evidence
Health Canada	Class II	- Medical device license: https://health-products.canada.ca/mdall-limh/index-eng.jsp - ISO 13485 certificate issued by the Canadian Medical Device Conformity Assessment System
TGA, Australia		- TGA conformity assessment certificate: https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg - TGA issued ISO 13485 Certificate
PMDA and MHLW, Japan		- Certification by registered certification body - PMDA General information: https://www.pmda.go.jp/english/ - MHLW General Information: http://www.mhlw.go.jp/english/ Contact PMDA directly for product-specific information

10.2.4 National Registrations and ROW Approvals

For some markets, ISO 13485 is not sufficient for the regulatory approval of medical devices, and an appropriate regulatory certification issued by the National Regulatory Authority (NRA) also may be required. However, in a number of countries, regulations applicable to diagnostics range from generally weak to non-existent. Given this lack of regulatory oversight, an assessment by another regulatory authority is often used as an alternative or complementary

strategy to gain national approval. It is recommended that the device go through stringent regulatory approval in addition to meeting ISO 13485.

While a number of regulatory agencies in developing countries have not yet established regulatory requirements for medical devices (including IVDs such as pregnancy tests), many are in the process of developing such guidelines. The landscape is changing rapidly and different NRAs will have different requirements. Prior to purchasing pregnancy tests for specific markets, evaluators are advised to check the national regulatory requirements of the country in question. The Contraceptive Technology Innovation Exchange provides links to several regulatory agencies and resources.

Pregnancy tests may be approved in the country of origin/manufacture either '*for sale and use in the country of origin*' or '*for export only'*(33). Given differences in regulatory requirements, manufacturers often supply different regulatory versions of the '*same diagnostic'* for markets with stringent regulatory controls versus those with little or no regulatory control (the latter group is often referred to as 'Rest of the World' regulatory versions). While a manufacturer may produce a stringent, regulated version of the product, it may also supply a less regulated or unregulated version of the same product without any assurance that the same quality control components and procedures were used to manufacture it. Regulatory requirements for 'export only' products are usually less stringent than those 'for sale and use.' Approval for 'export only' generally does not provide sufficient evidence of regulatory review of safety, quality and performance (33). It is therefore crucial that evaluators request supportive documentation to verify the exact regulatory status of the product to be procured.

Documentation for Evaluators on <u>Other</u> Regulatory Approvals:

It is recommended that evaluators:

- Check the regulatory requirements of the country in question prior to purchasing pregnancy tests
- Verify regulatory approvals applicable to the pregnancy tests that have been approved by other stringent regulators.

11 Performance Specifications

Performance specifications include sensitivity, specificity and accuracy parameters, and are instrumental in identifying performance requirements of pregnancy tests to meet programmatic needs. By knowing the analytical sensitivity of a pregnancy test, service providers can more fully understand how accurately a particular test can diagnose early pregnancy (27).[7] This information may be included in the Quality Control (QC) Lot Release Certification, Instructions for Use (IFU) and/or the Technical File.

11.1 Analytical Performance Characteristics of Pregnancy Tests

The specifications and test panels recommended below have been derived from scientific literature and best practices, as outlined in documentation in GHTF, WHO, U.S. FDA and EC directives. Manufacturers' inclusion of these performance metrics in the IFU and/or QC lot release certification aids the procurement decision-making process.

11.1.1 Target Antigen/Analyte

As described in Section 9, pregnancy tests are designed to identify hCG protein in urine. In this context, hCG protein is typically considered as the antigen or analyte, which is detected and qualitatively measured by the test.

11.1.2 Analytical Sensitivity (also known as Detection Limit)

It is recommended that the pregnancy test detect 25 mIU/mL as the criterion for analytical sensitivity; 98% of women who conceive have been shown to have 25 mIU/mL of hCG in urine on the first day after the missed period (24, 26, 34). If clinical evidence exists, the manufacturer may state the number of days after the missed period/menses to yield a positive test result (11). It is further recommended that the manufacturer state the analytical sensitivity in the IFU and have supporting evidence on file that can be made available for review, upon request.

11.1.3 Analytical Specificity

It is strongly recommended that the manufacturer state the outcomes of any specificity/cross-reactivity testing done with human form of luteinizing hormone (hLH), follicle stimulating hormone (hFSH) and thyroid-stimulating hormone (hTSH). Recommended concentrations for

[7] If using highly sensitive pregnancy tests (analytical sensitivity $\leq$ 25 mIU/mL), pregnancy can be detected as early as the first day of missed menses. If using tests with lower sensitivity (analytical sensitivity $\geq$ 50 mIU/mL), it is recommended to wait up to 10 days after expected date of menses before testing.

testing are: 300 mIU/mL for hLH, 1000 mIU/mL for hFSH, and 1000 µIU/mL for hTSH. It is recommended that the manufacturer state the analytical specificity in the IFU and have supporting evidence on file that can be made available for review, upon request.

11.2 Clinical Performance Characteristics of Pregnancy Tests

Clinical performance characteristics demonstrate that the IVD achieves its intended performance during normal conditions of use in the intended environment (e.g., laboratory, physician's office, healthcare center, home environment) and in the intended population (35). Clinical performance metrics confirm aspects that cannot be determined by analytical performance metrics.

11.2.1 Clinical Sensitivity and Clinical Specificity

Regulatory authorities, such as the U.S. FDA, do not require clinical evidence for approval/ clearance of the pregnancy test formats discussed in this document. While manufacturers are encouraged to provide clinical performance metrics, such as clinical/diagnostic sensitivity or clinical/diagnostic specificity, it is not mandatory.

11.2.2 Accuracy

Diagnostic accuracy can be expressed in a number of ways, leading to exaggerated results that may result from poorly designed studies (4). The U.S. FDA recommends that accuracy claims not exceed 99% (11). Statements such as '100% accurate, virtually 100% accurate, nearly 100% accurate' must always be proven by detailed clinical evidence (performance evaluation).

11.2.3 Interfering Agents

Interfering agents can be a significant source of error in diagnostic measurements, also leading to falsely increased or decreased results. Potentially interfering agents may originate either endogenously (e.g., hemoglobin, albumin, bilirubin) or exogenously (e.g., a drug or its metabolites, a specimen preservative) (17). Pregnancy test interference screening should take into consideration substances that are likely to be present in urine, the chemistry of the testing procedure and its intended use. Since pregnancy tests are based on immunochemical principles, special attention must be given to cross-reactivity of hCG antibodies and endogenous human antibodies that can yield false positives, as observed with malaria rapid diagnostic tests (MRDTs) (36).

Details of any substance that has been tested and shown to cause interference with test performance should be stated. Commonly used medications, such as pain relievers, antibiotics and oral contraceptives, should not interfere with test performance; evidence should be

provided to support claims of noninterference (11). Comprehensive guidelines for interference testing can be found in the CLSI EP7-A2 manual (17).

Documentations for Evaluators on Performance Specifications: It is recommended that evaluators ask that manufacturers to provide IFU or a QC Lot Release Certification containing performance specifications that reflect:

- Analytical sensitivity
- Analytical specificity
- Clinical sensitivity and clinical specificity (if available)
- Accuracy

If the IFU or other QC certification does not contain this information, it is recommended that the evaluator ask the manufacturer to provide this information from Technical Files.

Enhanced Quality and Performance Practices on Performance Specifications:

Include a list of interfering agents

12 Operational Specifications

Operational specifications are equally as important as performance specifications; both must be used in product selection (37). The following sections cover areas of operational specifications, including test formats, ancillary items, test procedure, result interpretation, claimed shelf life, packaging and labeling. Many of the recommended criteria in this section are based on WHO and FIND efforts to standardize and harmonize malaria rapid diagnostic tests (MRDTs), which follow the same assay principle as pregnancy tests (6, 36).

12.1 Test Format and Ancillary Items

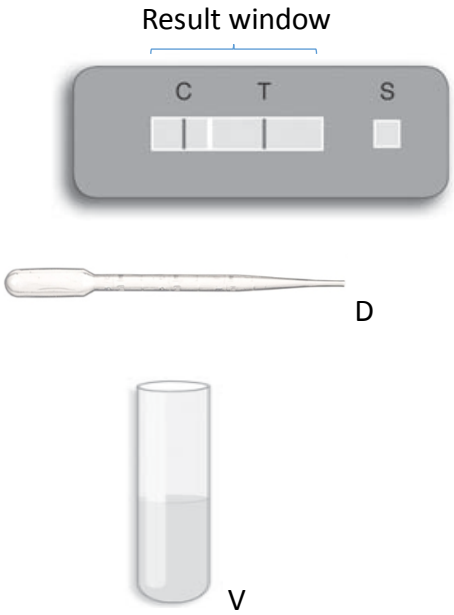
Because the three pregnancy test formats operate slightly differently in terms of specimen application, additional components are required to carry out the testing. The sections below discuss these requirements and testing methods, as applicable to each format.

12.1.1 Components of a Pregnancy Test

Pregnancy tests usually come in three formats: cassette, dipsticks and midstream test strips. Note that certain ancillary items, e.g., sample transfer device/droppers or the urine collection cup as shown in **Figure 4**, are required but not provided. It is recommended that evaluators determine the need for these items and include them in tender requirements, as appropriate.

Figure 4. Examples of the three pregnancy test formats, ancillary items and their usage[8]

A. Cassette with a well for urine specimen



Cassette

The test strip is encased in a plastic cassette. Key features are: control line (C), test line (T) and a sample-well indicating where urine specimen is to be added (S).

Ancillary item

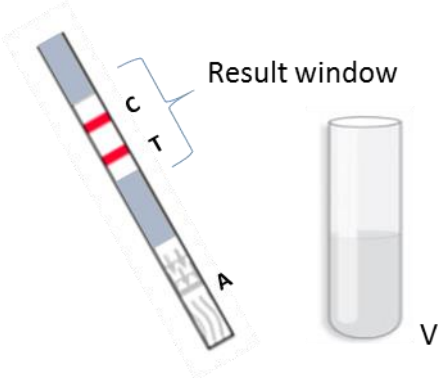
Sample transfer device/dropper (D), clean cup/tube for urine collection (V)

How test is to be used:

Collect urine in a clean cup/tube → Using the sample transfer device/dropper, transfer a specified volume of urine into the sample-well, placed on a flat surface with result window facing up → Read results after the specified period of time (and before the maximum reading time).

➢ Based on programmatic point-of-care needs, a space on the cassette to write patient identification information, date and test number is recommended.

B. Dipstick



Dipstick

The test strip is mounted on a laminated strip. Key features are: control line (C), test line (T), and absorbent pad to wick the urine (A).

Ancillary item

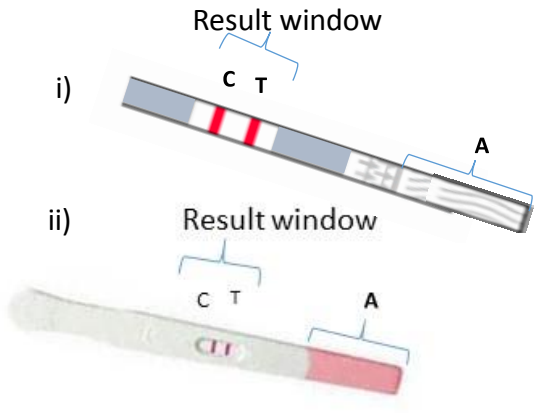
A clean cup/tube for urine collection (V)

How test is to be used:

Collect urine in a clean cup/tube → Dip the dipstick in urine up to the line indicated by arrows (A) for the specified period of time → Place the dipstick flat on a surface, with the result window facing up, for the specified period for results to develop. → Read results after the specified period (and before the maximum reading time).

[8] Diagrams have been adapted from Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of MRDTs; Round 5 (2013).

C. Midstream test strip



Midstream test strip

This format is essentially identical to the dipstick format, but has a longer absorbent pad to enable positioning of it directly in the urine stream. Key features are: control line (C), test line (T), and longer absorbent pad to directly hold in the urine stream (A).

In an alternate format of midstream test, the dipstick is encased in plastic. Encasing prevents urine from wetting areas other than where intended to capture and absorb it.

How test is to be used:

Hold the absorbent tip (A) in urine stream for the specified period of time → Place the dipstick flat on a surface, with the result window facing up, for a specified period for results to develop. → Read results after the specified period (and before the maximum reading time).

12.1.2 The Test Line and Control Line

Pregnancy tests usually have two lines: one control line and one test line (**Figure 4 A, B & C,** marked with 'C' and 'T'). It is recommended that IFU include information on exact labeling of these lines per their orientation (i.e., which line is where on the strip). Although not common in low-resource settings, some pregnancy tests may show a 'plus' sign (+) or the word 'positive,' if positive for pregnancy.

12.2 Test Procedure and Result Interpretation

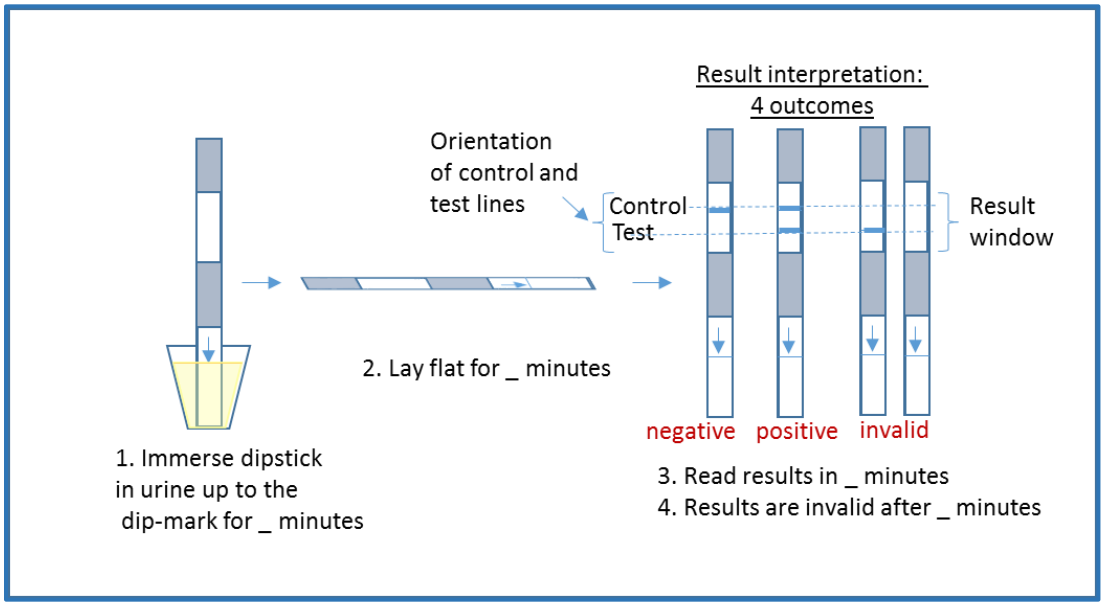
The test procedure should be documented in sufficient detail to enable an operator to perform a measurement (38). Although RDTs are seemingly robust and simple, they pose significant operational problems due to variations in test procedures and differences in reading and interpreting results (39). Included in the IFU, the test procedure documentation should include step-by-step instructions from collection of urine specimen to reading of results. It should be easy to read and accompanied by illustrations, as highlighted in **Figure 5** (39).

Timing: When using a pregnancy test, the test and control lines develop, fade and change in intensity over time (6). Because the rate at which this fading takes place depends on the

product, 'stability of results' must be established by the manufacturer. The time period between when the urine specimen is applied and the results are read is defined as the 'declared reading time' (6). As it may not be possible to read a result at an exact moment, especially in point-of-care settings, manufacturers may provide this information as a time range, as in 'minimum time to results' and 'maximum reading time' or as a 'recommended reading time'. It is important that the manufacturer display this 'reading range.' As outlined in **Figure 5**, four time points need to be specified by the manufacturer:

1. Time to keep the dipstick immersed in urine or, if using a midstream test strip, time to hold the dipstick in urine stream
2. Time to place the test flat on a surface for the results to develop
3. Time to read the results
4. Time beyond which test results should not be read.

Figure 5: Example of test procedure and result interpretation



Result interpretation: Figure 5 illustrates four possible result outcomes; all four outcomes should be illustrated in the instructions for use.[9] Absence of the control line indicates a problem with the test, and renders the test invalid.

[9] The exploratory evaluation of pregnancy tests (Annex 2) illustrates that 66% of pregnancy tests only provide one 'invalid result' outcome (the development of test line alone). However, it is important also to include the outcome of a blank result window, which indicates failure in the performance and/or of the procedure of the test.

12.3 Claimed Shelf Life

Claimed shelf life is the period of time during which the test, in its original packaging, maintains its performance characteristics under storage conditions specified by the manufacturer (6, 37). It is the responsibility of the manufacturer to ensure that all claims made regarding shelf life are supported by evidence. It is recommended that manufacturers follow ISO 23640[10] when designing shelf life studies.

- Recommended storage conditions and shelf life should be clearly indicated on the product labeling for all components.
- It is recommended that pregnancy tests be stable for storage up to 30°C, with stability claims supported by evidence. To assess heat compatibility based on climate conditions of the country/province of supply, an 'Accelerated Stability Evaluation Report' with extrapolated data is acceptable for initial shelf life claims, but a 'Real Time Stability Evaluation Report' should be provided when it becomes available (3, 37).

Documentations for Evaluators on Shelf Life: It is recommended that evaluators request an Accelerated Stability Evaluation Report for initial shelf life claims, but follow up with a Real-time Stability Evaluation Report, when it becomes available.

12.3.1 Transportation Stability

The basic stability claim for an IVD is claimed shelf life. Two other types of stability claims are 'in-use claim' (duration that a product may be used after first opening the primary packaging) and 'transport stability' (appropriate shipping and handling conditions for the IVD). Testing for transport stability involves reproducing extreme environmental conditions potentially occurring during transport, such as high and low temperatures, high humidity and light exposure (40).

The World Health Organization recommends heat stability testing at 35°C and 40°C for MRDTs as these tests may be subject to extreme temperatures during transport (36). Compromised performance of some MRDT products exposed to high temperatures has been documented (41, 42). Given that the assay principle for MRDTs and pregnancy tests is the same, albeit with different antibodies, it is recommended that evaluators ask manufacturers to provide Transport

[10] Current version is ISO 23640:2013

Validation documentation to demonstrate a heat stability profile within this recommended range, where appropriate.

Enhanced Quality and Performance Practices for Confirming Transportation Stability:

To evaluate the tolerance of IVDs to the anticipated transportation conditions, a Transport Validation Document stating minimum and maximum transport temperatures and durations should be made available.

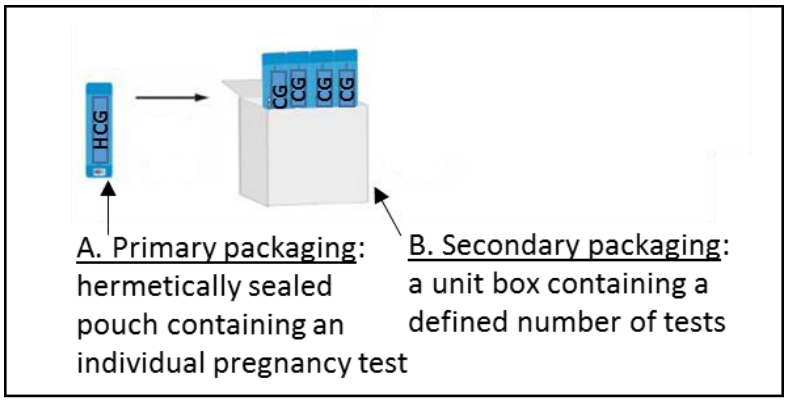
For countries that experience high temperatures and high humidity, evaluators are advised to request supporting data demonstrating IVD stability up to 35-40°C.

12.4 Packaging and Kit Content

While packaging covers a range of containers, levels of packaging are usually described as:

- **Primary packaging:** individually-sealed pouches containing pregnancy tests (**Figure 6A**)
- **Secondary packaging:** a unit box containing a defined number of pregnancy tests (**Figure 6B**) (6).

Figure 6: Examples of primary and secondary packaging



- Since pregnancy tests can be sensitive to temperature and humidity, primary and secondary packaging should ensure their protection from high temperatures and humidity throughout the supply chain path (i.e., from manufacturing site, through transport and storage, to point-of-use).

- Based on WHO recommendations for MRDTs for packaging, the addition of desiccants inside primary packaging of pregnancy tests is strongly recommended to preserve the performance of the test (40, 43). Refer to **Annex 10** for additional details on desiccants.
- Packaging specifications should provide sufficient detail on measures taken to ensure integrity of sealing, with no weakness in the sealed areas which could adversely affect performance of the IVD (6).

Enhanced Quality and Performance Practices for Packaging and Kit Content:

Include humidity-/self-indicator (desiccant that changes color upon exposure to humidity) desiccant in primary packaging, correctly packaged with adequate labeling.

12.5 Labeling Requirements

Labeling intends to identify the device and its manufacturer, and communicate information on quality, performance, operation and safety to the intended professional or lay user as well as to regulatory authorities (44). In general, labeling should be concise and easy to understand and contain clear illustrations, as applicable. It should cater to the technical knowledge and education of the intended user (44). In regulatory terms, 'labeling' includes labels on IVD packaging as well as instructions for use (39).

12.5.1 Instructions for Use (IFU)

IFU should contain information supplied by the manufacturer to enable safe and proper use of the IVD. Within the context of pregnancy tests, this information should include test procedure and result interpretation, troubleshooting, IVD disposal, warnings, precautions and limitations (38). In low-resource settings, IFUs are typically printed on the primary packaging, which limits the level of detail that can be included. In the developed world, detailed IFU are printed on paper and included as a product insert. Per GHTF (44) and MRDT labeling harmonization recommendations (39), IFU content, tailored to pregnancy tests, should include:

a. Name or trade name of pregnancy test
b. If not obvious, the device's intended use/purpose: what is detected (hCG/pregnancy); type of specimen required (urine)
c. Intended user: Professional use (may include lay person)
d. Indication that test is for IVD use

e. List of provided materials, along with a list of materials required but not provided (such as urine collection cups and sample transfer devices/droppers, described in **Figure 4**).

f. Performance characteristics (analytical sensitivity, analytical specificity, accuracy, and clinical sensitivity and clinical specificity, if available)

g. Indication of special storage and/or handling conditions that apply (e.g., temperature, light, humidity, etc.)

h. Warnings, precautions and measures to be taken:

- For IVD use only
- Read instructions carefully before performing the test
- Apply standard biosafety precautions for handling and disposal of potentially infective material and wear gloves while handling specimen and performing test
- Do not use IVDs beyond the expiration date
- Do not use if packaging is damaged
- Do not use if the product has been exposed to excessive heat or humidity
- Perform the test immediately after opening of primary packaging
- Do not reuse

i. Name and address of the manufacturer in a format that is recognizable and allows the location of the manufacturer to be established, together with a telephone number and/or fax number and/or website address to obtain technical assistance

j. Date of issue or latest revision of the instructions for use

k. Test procedure including interpretation of results with illustrations: see Section 12.2 and **Figure 5**.

Enhanced quality and performance practices for IFU labeling:

- Description/summary of the test
- Principle of the assay procedure
- Description of the procedural/reagent/specimen volume control in the test
- Reference intervals
- Limitations of the procedure: health conditions that can cause a false or irregular result; opportunities for false negative results
- Circumstances where the user should consult a healthcare professional
- Instructions for use in national language (e.g., could be glued to the primary packaging as long as labeling is not covered over)

12.5.2 Labeling on Primary Packaging

In low-resource settings, labeling on primary packaging also includes IFUs. Use of internationally recognized symbols conveying information on safe and effective use of tests is highly recommended. **Annex 11** provides an illustration of recommended labeling for primary and secondary packaging using established symbols per ISO 15223-1 (12). As per GHTF recommendation and MRDT labeling harmonization recommendations, the following information should be included on primary packaging labeling (39, 44):

a. Name or trade name of pregnancy test
b. If not obvious, the device's intended use/purpose: diagnosis of pregnancy/POC
c. Catalog number/product code
d. Name and address of the manufacturer in a format that is recognizable and allows the location of the manufacturer to be established, together with a telephone number and/or fax number and/or website address to obtain technical assistance
e. Indication that it is for IVD use
f. Batch/lot number
g. Expiration date (YYYY-MM-(DD))
h. Indication of quantity of tests per packaging
i. Storage conditions (symbols)
j. Warnings or precautions in symbols (e.g., do not use if package is damaged, read instructions before use, only for single use)
k. For CE-marked IVDs, a conformant CE mark with authorized representative's identification number
l. Contents of packaging (including desiccant)

12.5.3 Labeling on Secondary Packaging (Cartons and Boxes)

The large carton of smaller boxes, as well as the smaller boxes containing pregnancy tests in primary packaging, should include the label information listed below (39):

a. Name or trade name of the test
b. Catalog number/product code
c. If not obvious, intended use: diagnosis of pregnancy
d. Number of tests provided in the box
e. Indication that test is for IVD use
f. Name and address of the manufacturer in a format that is recognizable and allows the location of the manufacturer to be established, together with a telephone number

and/or fax number and/or website address to obtain technical assistance (or name and address of authorized representative, if applicable)

g. Batch/Lot number

h. Expiration date (YYYY-MM-(DD))

i. For CE-marked IVDs, a conformant CE mark with authorized representative's identification number

j. Storage conditions (symbol)

k. Materials (a list of materials provided and a list of items required but not provided)

Important Note to Evaluators

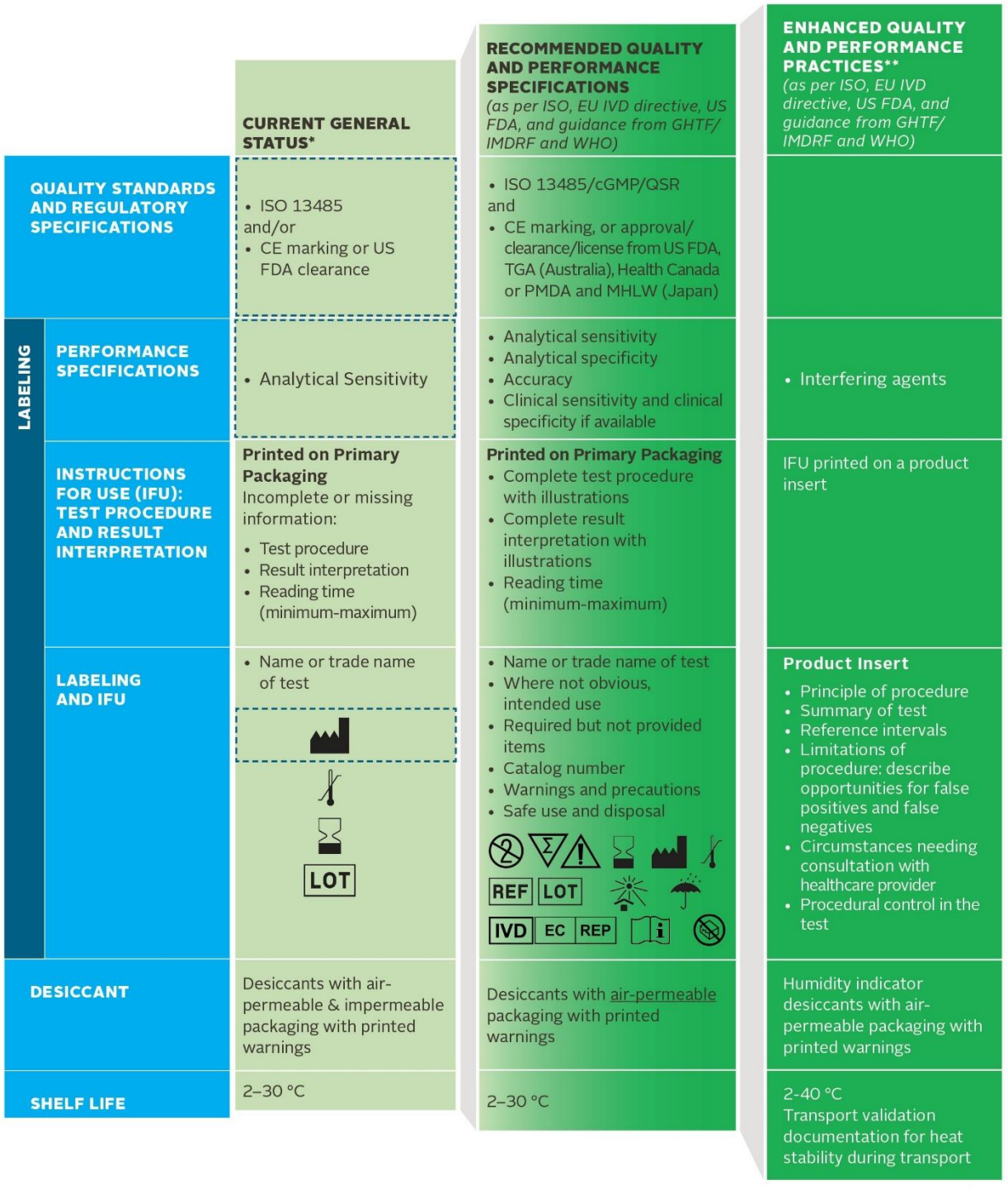
Evaluation of manufacture's documentations and visual assessment of product labeling, in conformance with guidance provided, is a vital *first step* to selection of pregnancy tests meeting high quality standards. However, document review alone does not guarantee selection of high quality products. The *next step* should be to ensure that the tests perform to the required performance and operational specifications through Lot testing/laboratory evaluation. This type of testing should be carried out and confirmed by an independent 3rd party ISO 17025 certified testing laboratory or WHO prequalified laboratory. FHI 360 has prepared work instructions for laboratory level evaluation of performance and operational characteristics of pregnancy tests (Section 14).

13 Summary of Current, Recommended and Enhanced Quality and Performance Practices

This guidance document has been prepared taking into consideration potential cost constraints and other challenges commonly present in resource-poor settings. As national-level regulatory mechanisms and overall healthcare landscapes continue to improve, countries may apply increasingly stringent quality review standards for pregnancy tests.

Figure 7 illustrates currently prevalent, recommended, and enhanced quality practices. Distinctions between recommendations and enhanced quality practices were determined through stakeholder consensus.

Figure 7: Summary of current, recommended and enhanced quality and performance guidance for pregnancy test selection



* Based on an exploratory evaluation of 16 pregnancy tests; results are summarized in Annex 2
** Enhanced Quality Practices are inclusive of Recommended Quality Standards & Performance Specifications
⬚ Indicates minimal practice , as observed with the exploratory pregnancy test evaluation described in Annex 2
Please refer to Annex 11 for definitions of the symbols used under labeling

14 Work instructions for quality evaluation of pregnancy tests

FHI 360's Product Quality and Compliance group has developed detailed work instructions (method manual) that could be used by international or in-country laboratories to evaluate the quality and performance of pregnancy tests. Sampling plans and criteria are provided for three different scenarios (**Table 2**), based on ISO 2859 standards: 1) product qualification (for potential inclusion within a procurement program) 2) pre-shipment and pre- and post-distribution testing, and 3) temperature stability assessment. The purpose of this document is to provide detailed procedures, in the form of Standard Operating Procedures (SOP), to evaluate performance (inclusive of analytical sensitivity and analytical specificity) under recommended storage and/or heat stressed conditions, and package seal integrity. The SOPs will be designed to suit the requirements of the laboratories in low-resource settings. Additional validation of the procedures may be necessary (i.e., regarding the exact type of standard to use, standard stability and conditions used for package seal integrity).

Implementation of the respective procedures for product qualification, pre-shipment, pre- and post-distribution, and/or stability study evaluations should be done while balancing the product source risk and resources, as appropriate, for specific program needs.

Table 2: Overall sampling plan and specifications for different testing scenarios

Assumed Lot size (35,000-150,000)	Product Qualification (total units)	Acceptance/ Rejection Criteria	Pre-shipment or pre- and post-distribution (total units)	Acceptance/ Rejection Criteria	Temperature Stability Assessment	Acceptance/ Rejection Criteria
	Large Scale Evaluation		Medium Scale Evaluation		Small Scale Evaluation	
Category 1 - Performance						
Test for claimed analytical sensitivity	102	Verify claimed analytical sensitivity – positive control testing provides ≥ 95% positive results at claimed sensitivity Accept if number of failing results are ≤ 3	30	Accept if lot provides ≥ 95% of tests results as positive at label claim sensitivity	14 total units/condition	Report % compliance at label claim sensitivity
Test for analytical specificity	98		50	Accept if number of failing results are ≤ 2	6 total units/condition	Accept if number of failing results are ≤ 1
Category 2 - Package Integrity Testing						
Package Integrity	32	Acceptance/Rejection of 2/3	20	Acceptance/Rejection of 1/2	5	Acceptance/Rejection of 0/1

15 References

1. United States Food and Drug Administration. Quality System (QS) Regulation/Medical Device Good Manufacturing Practices. [http://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/qualitysystemsregulations/.

2. United States Food and Drug Administration. Premarket notification 510(k). [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm2005718.htm.

3. International Organization for Standardization. ISO 23640:2011 In vitro diagnostic medical devices - Evaluation of stability of in vitro diagnostic reagents. Geneva; 2011. http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=54868

4. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Clin Chem. 2003;49(1):7-18.

5. Saah AJ, Hoover DR. "Sensitivity" and "specificity" reconsidered: the meaning of these terms in analytical and diagnostic settings. Ann Intern Med. 1997;126(1):91-4.

6. World Health Organization. Good practices for selecting and procuring rapid diagnostic tests for malaria. Geneva; 2011. http://apps.who.int/iris/bitstream/10665/44530/1/9789241501125_eng.pdf

7. Global Harmonization Task Force. Glossary and definitions of terms used in GHTF documents (Document No. GHTF/SC/N4:2012 (Edition 2)). 2012. http://www.imdrf.org/docs/ghtf/final/steering-committee/procedural-docs/ghtf-sc-n4-2012-definitions-of-terms-121109.pdf#search="glossary"

8. World Health Organization, United Nations Population Fund. TCu380A intrauterine contraceptive device 2016. https://www.unfpa.org/sites/default/files/resource-pdf/TCu380A_IUD_WHO-UNFPA_Tech._Spec_and_PQ_guidance_2016_final.pdf

9. World Health Organization. A model quality assurance system for procurement agencies. Geneva; 2007. http://www.who.int/medicines/publications/ModelQualityAssurance.pdf

10. CEMARKING.NET. Declaration of conformity. [https://cemarking.net/declaration-conformity/.

11. United States Food and Drug Administration. Guidance for over-the-counter (OTC) human chorionic gonadotrophin (hCG) 510(k)s. [http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm092792.pdf.

12. International Organization for Standardization. ISO 15223-1:2012 Medical devices - symbols to be used with medical device labels, labelling and information to be supplied. Geneva; 2012. http://www.iso.org/iso/catalogue_detail.htm?csnumber=50335

13. International Organization for Standardization. ISO 13485:2003 Medical devices. Geneva. http://www.iso.org/iso/home/standards/management-standards/iso13485.htm

14. European Commission. Directive 98/79/EC of the European parliment and of the council. Official Journal of the European Communities; 1998. http://www.gmp-compliance.org/guidemgr/files/IVD_DIRECTIVE.PDF

15. Schito M, Peter TF, Cavanaugh S, Piatek AS, Young GJ, Alexander H, et al. Opportunities and challenges for cost-efficient implementation of new point-of-care diagnostics for HIV and tuberculosis. J Infect Dis. 2012;205 Suppl 2:S169-80.

16. International Organization for Standardization. ISO 8402:1986 Quality Vocabulary. Geneva; 1986. http://www.iso.org/iso/catalogue_detail.htm?csnumber=15570

17. Clinical and Laboratory Standards Institute. Interference tesing in clinical chemistry; approved guidelines - second edition (EP7-A2). USA; 2005.

18. International Organization fo Standardization. ISO/IEC Guide: Standardization and general activities-general vocabulary. Geneva; 2004. http://www.iso.org/iso/catalogue_detail?csnumber=39976

19. Comfort A, Chankova S, Juras R, His N, Peterson L, Hathi P. Proviing free pregnancy test kits to community health workers increases distribution of contraceptives: results from an impact evaulation in Madagascar http://www.contraceptionjournal.org/article/S0010-7824%2815%2900586-7/abstract

20. Morroni C, Moodley J. The role of urine pregnancy testing in facilitating access to antenatal care and abortion services in South Africa: a cross-sectional study. BMC Pregnancy Childbirth. 2006;6:26.

21. Stanback J, Vance G, Asare G, Kasonde P, Kafulubiti B, Chen B, et al. Does free pregnancy testing reduce service denial in family planning clinics? A cluster-randomized experiment in Zambia and Ghana. Global Health Science Practice. 2013;3.

22. Family Health International 360. How to be reasonably sure a client is not pregnant. 2008. https://www.fhi360.org/sites/default/files/media/documents/checklist-pregnancy-english.pdf

23. World Health Organization. Guidance for procurement of in vitro diagnostics and related laboratory items and equipment. Geneva; 2016. http://www.who.int/diagnostics_laboratory/procurement/170131_guidance_for_procurement_of_ivds_draft.pdf?ua=1

24. Gnoth C, Johnson S. Strips of hope: accuracy of home pregnancy tests and new developments. Geburtshilfe Frauenheilkd. 2014;74(7):661-9.

25. Johnson SR, Miro F, Barrett S, Ellis JE. Levels of urinary human chorionic gonadotrophin (hCG) following conception and variability of menstrual cycle length in a cohort of women attempting to conceive. Curr Med Res Opin. 2009;25(3):741-8.

26. Larsen J, Buchanan P, Johnson S, Godbert S, Zinaman M. Human chorionic gonadotropin as a measure of pregnancy duration. Int J Gynaecol Obstet. 2013;123(3):189-95.

27. Reproductive Health Supplies Coalition. Pregnancy tests for family planning. 2013. http://www.rhsupplies.org/fileadmin/uploads/rhsc/Working_Groups/New_Underused_RH_Technologies_Caucus/Documents/Technical_Briefs/rhsc-brief-pregnancy_A4.pdf

28. Stanback J, Diabate F, Dieng T, de Morales TD, Cummings S, Traore M. Ruling out pregnancy among family planning clients: the impact of a checklist in three countries. Stud Fam Plann. 2005;36(4):311-5.

29. World Health Organization. Medical device regulations: global overview and guiding principles. Geneva; 2003. http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf

30. International Organization for Standardization. ISO 9000: 2015 Quality management. Geneva. http://www.iso.org/iso/home/standards/management-standards/iso_9000.htm

31. World Health Organization. Substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products. 2016. http://www.who.int/mediacentre/factsheets/fs275/en/

32. What is CE marking? [http://www.ce-marking.org/what-is-ce-marking.html.

33. World Health Organization. Manual for procurement of diagnostics and related laboratory items and equipment. Geneva; 2013. http://www.who.int/diagnostics_laboratory/publications/130627_manual_for_procurement_of_diagnostics-001-june2013.pdf

34. Johnson S, Cushion M, Bond S, Godbert S, Pike J. Comparison of analytical sensitivity and women's interpretation of home pregnancy tests. Clin Chem Lab Med. 2015;53(3):391-402.

35. Global Harmonization Task Force. Clinical evidence for IVD medical devices - key definitions and concepts (Document No. GHTF/SG5/N6:2012). 2012. http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n6-2012-clinical-evidence-ivd-medical-devices-121102.pdf

36. World Health Organization, Foundation for Innovative New Diagnostics, Center for Disease Control and Prevention. Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTs, Round 5 2014. http://apps.who.int/iris/bitstream/10665/128678/1/9789241507554_eng.pdf

37. World Health Organization. Instructions for compilation of a product dossier: Prequalification of in vitro diagnostic program. Geneva; 2014. http://www.who.int/diagnostics_laboratory/evaluations/141015_pqdx_018_dossier_instructions_v4.pdf?ua=1

38. International Organization fo Standardization. ISO 18113-2009: In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 1-5. 2011. https://www.iso.org/obp/ui/#iso:std:iso:18113:-1:ed-1:v1:en

39. Jacobs J, Barbe B, Gillet P, Aidoo M, Serra-Casas E, Van Erps J, et al. Harmonization of malaria rapid diagnostic tests: best practices in labelling including instructions for use. Malar J. 2014;13:505.

40. World Health Organization. Establishing stability of an in vitro diagnostic for WHO prequalification. Geneva; 2015. http://www.who.int/diagnostics_laboratory/guidance/160613_tgs2_stability.pdf

41. Albertini A, Lee E, Coulibaly SO, Sleshi M, Faye B, Mationg ML, et al. Malaria rapid diagnostic test transport and storage conditions in Burkina Faso, Senegal, Ethiopia and the Philippines. Malar J. 2012;11:406.

42. Jorgensen P, Chanthap L, Rebueno A, Tsuyuoka R, Bell D. Malaria rapid diagnostic tests in tropical climates: the need for a cool chain. Am J Trop Med Hyg. 2006;74(5):750-4.

43. Barbe B, Gillet P, Beelaert G, Fransen K, Jacobs J. Assessment of desiccants and their instructions for use in rapid diagnostic tests. Malar J. 2012;11:326.

44. Global Harmonization Task Force. Label and instructions for use for medical devices (Document No. GHTF/SG1/N70:2011). 2011. Report No.: GHTF/SG1/N70:2011. http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n70-2011-label-instruction-use-medical-devices-110916.pdf

45. Johns Hopkins Bloomberg School of Public Health, World Health Organization. Family planning: a global handbook for providers. 2011. http://apps.who.int/iris/bitstream/10665/44028/1/9780978856373_eng.pdf

46. Center for Disease Control and Prevention. Selected practice recommendations for contraceptive use. USA; 2013. https://www.cdc.gov/mmwr/volumes/65/rr/rr6504a1.htm?s_cid=rr6504a1_w

47. World Health Organization. Selected practice recommendations for contraceptive use. Geneva; 2004. http://apps.who.int/iris/bitstream/10665/252267/1/9789241565400-eng.pdf?ua=1

48. Stanback J, Yacobson I, Harber L. Proposed clinical guidance for excluding pregnancy prior to contraceptive initiation. Contraception. 2016.

49. United States Agency for International Development. The logistics handbook: A practical guide for the supply chain management of health commodities. USA; 2011. https://www.k4health.org/sites/default/files/LogiHand_0.pdf

50. The Partnership for Maternal, Newborn and Child Health. PMNCH knowledge Summary 20, Access to FP 2012. http://www.who.int/pmnch/knowledge/publications/summaries/ks20.pdf?ua=1

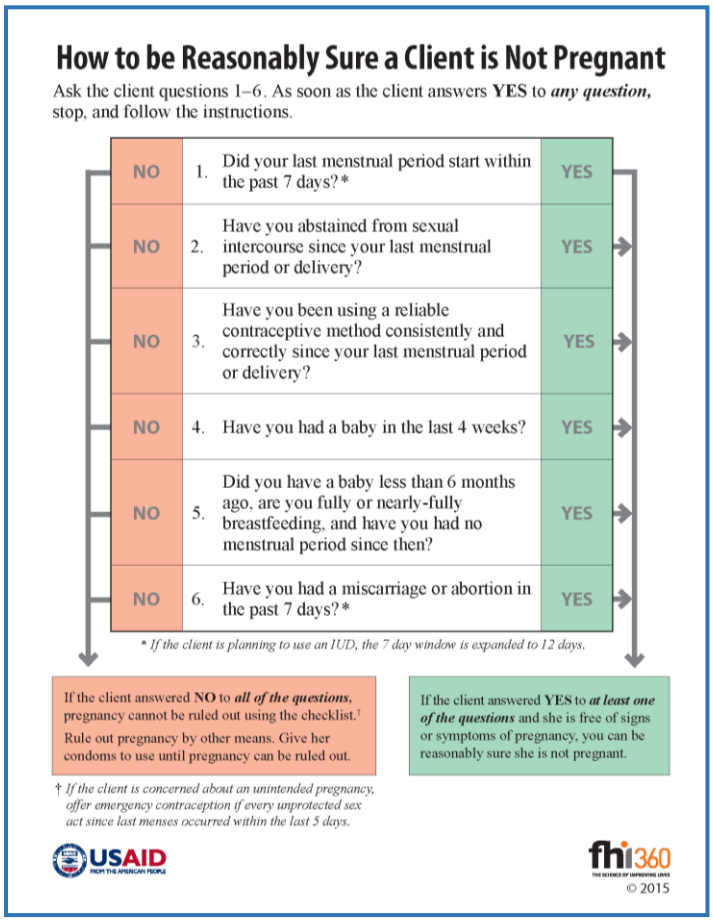
51. Gillet P, Maltha J, Hermans V, Ravinetto R, Bruggeman C, Jacobs J. Malaria rapid diagnostic kits: quality of packaging, design and labelling of boxes and components and readability and accuracy of information inserts. Malar J. 2011;10:39.

16 Annexes

Annex 1: Use of Pregnancy Tests and Pregnancy Checklist in Family Planning Programs

Current clinical guidance indicates that pregnancy should be ruled out prior to initiation of hormonal contraception and intrauterine devices (IUDs) (45-47). The rationale for excluding pregnancy is simple: to avoid providing unnecessary contraception and, in the case of the IUD (including hormonal IUDs), to avoid possible harm to the pregnant woman or her fetus.

Figure 8: Pregnancy Checklist



Because exposure of ongoing pregnancies to contraceptive hormones carries no known risk, it is now widely accepted that hormonal methods can be provided—along with follow-up pregnancy testing—to women for whom pregnancy has not been ruled out conclusively. Pregnancy screening is nonetheless recommended for all family planning clients, and typically constitutes a substantial part of the workload of family planning providers.

Family planning providers have three tools at their disposal to help exclude pregnancy in women requesting contraception: medical history (often obtained by using the WHO-endorsed "Pregnancy Checklist"), pregnancy tests, and delay of contraceptive method initiation until the next menses.

While each approach has its advantages and limitations, providers sometimes use a combination of these tools. Careful judgment is required because the consequences of denying immediate initiation may be more serious than the risks inherent in contraceptive use while pregnant. The Pregnancy Checklist is shown here in **Figure 8** while proposed new guidance for when and how providers should use client history, pregnancy tests, and delayed services in varying circumstances is shown in **Figure 9** (48).

Figure 9: Job aid for ruling out pregnancy prior to contraceptive initiation

1 Women choosing to initiate implant use when pregnancy cannot be ruled out should be counseled about the need to remove the implant if pregnancy is confirmed and she wishes to continue it.

2 The pregnancy checklist is included on the reverse side of this job aid.

3 Offer emergency contraceptive pills if unprotected sex occurred within the last 5 days; provide injection or implant the same day or instruct the woman to start pills, patch or ring the next day.

4 Women should be advised to come back for a pregnancy test if their next menses are delayed/ missed or if the onset of their next menses is masked by menstrual irregularities associated with DMPA.

Annex 2: Prevailing Quality and Performance Characteristics of Pregnancy Tests in Low Resource Settings

To gain a preliminary understanding of quality and performance status of pregnancy tests in low-resource settings, an in-house assessment of 16 individually packed pregnancy tests collected over a 2-year period from pharmacies and clinics in Africa was carried out. These tests were benchmarked against 26 relevant labeling criteria as detailed in this document (**Table 3**).

Table 3: Prevailing quality and performance status of 16 pregnancy tests collected in low-resource settings

Indicators used for benchmarking	Number of conformant tests (n = 16)	Percent of conformant tests
International quality standards and regulatory criteria		
An accepted quality mark (ISO 13485, CE mark or U.S. FDA clearance)	7	44%
Of those carrying CE mark, tests that indicate a conformant CE mark	3	43%
Of those carrying CE mark, tests that indicate a notified body number	5	71%
Packaging/labeling/product insert information		
Lot number	15	94%
Manufacturer	14	88%
Contact information of manufacturer	7	44%
Date of manufacture	7	44%
Date of expiry	15	94%
Temperature limitations	15	94%
Number of units per package	8	50%
Intended use	13	81%
Indication that test is for IVD use	12	75%
Indication of 'do not reuse'	5	31%
Inclusion of any form of desiccant	Not assessed	Not assessed
Safety warnings	1	6%
Disposal instructions	0	0%
Description of test procedure	15	94%
Illustrations for test procedure	14	88%
'Declared reading time'	12	75%
Stability of test results	6	38%
Instructions for result interpretation	15	94%
Complete instructions for result interpretation	9	56%
Test performance characteristics		
Analytical sensitivity	2	13%
Analytical specificity	0	0%
Accuracy	1	6%
Test limitations	0	0%

Annex 3: IMDRF Management Committee

The International Medical Device Regulatory Forum (IMDF) is a voluntary group of medical device regulators from around the world, who have come together to build on the foundational work of the former Global Harmonization Task Force (GHTF). Their aim is to accelerate international medical device regulatory harmonization and convergence. Current IMDRF member countries include Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore and the United States of America (**Table 4**). The World Health Organization is an official observer.

Table 4: IMDRF Management Committee

Country	Institution	Website
Australia	Therapeutic Goods Administration	https://www.tga.gov.au/
Brazil	National Health Surveillance Agency	http://portal.anvisa.gov.br/wps/portal/anvisa-ingles
Canada	Health Canada	http://www.hc-sc.gc.ca/index-eng.php
China	China Food and Drug Administration	http://eng.sfda.gov.cn/WS03/CL0755/
Europe	European Commission Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs	http://ec.europa.eu/growth/sectors/medical-devices/
Japan	Pharmaceutical and Medical Device Agency & Ministry of Health, Labor and Welfare	https://www.pmda.go.jp/english/ http://www.mhlw.go.jp/english/
Russia	Russian Ministry of Health	https://www.rosminzdrav.ru/
Singapore	Health Science Authority	http://www.hsa.gov.sg/content/hsa/en.html
United States of America	Food and Drug Administration	http://www.fda.gov/

Annex 4: Checklist for Evaluation of Pregnancy Tests

It is recommended that evaluators use this checklist (**Table 5**) to verify a manufacturer's compliance with recommended quality, regulatory, performance and operational specifications as part of the product selection process. Line items shaded in *green* are 'enhanced quality and performance practices,' and are recommended for adoption as the country regulatory infrastructure improves or at the evaluators' discretion, based on organizational risk analysis.

Table 5: Checklist for evaluation of pregnancy tests

Checklist for Evaluation of Pregnancy Tests for Procurement			
Name of assessor			
Date of assessment			
Name of pregnancy test (brand name)			
Test format	**Dipstick**	**Cassette**	**Midstream**
Manufacturer and address			
Lot number			
Catalog number			
Has a ISO 13485 certification been provided?	**Yes**		**No**
Sources of documentation provided as proof of regulatory clearance	**CE marking**	**U.S. FDA**	**Other RA (specify)** _____
Has a QC Lot Release Certificate been provided from a recent Lot/batch for evaluation?	**Yes**		**No**
Has an Accelerated Stability Evaluation Report been provided?	**Yes**		**No**
Check for consistency of details across labeling, quality and regulatory documentations.			
For assessment of ISO 13485 certification only:			
1. Manufacturer's certified quality management system standard is specified as ISO 13485	Yes		No
2. Name and country of assessment body	Name:		Country:
3. Last audit date:	4. Expiration date:		
5. Has certification been verified by checking the website of the certification body or by directly contacting the certification body?	Verified using website		Verified by calling

For assessment of CE declaration of conformity only:			
6.	Manufacturer's name is correctly indicated	Yes	No
7.	Manufacturer's address is correctly indicated	Yes	No
8.	Name of pregnancy test is correctly indicated	Yes	No
9.	Essential characteristics of pregnancy test are provided	Yes	No
10.	Name of regulatory authority/notified body		
11.	License number		
12.	A legally binding signature on behalf of the organization is present	Yes	No
For assessment of U.S. FDA 510(k) clearance only:			
13.	A 510(k) clearance letter for the pregnancy test has been provided	Yes	No
14.	U.S. FDA 510(k) clearance website confirms clearance of pregnancy test	Yes	No
15.	Product being evaluated has been manufactured with same quality standard applicable to a U.S. FDA cleared product	Yes	No
For assessment of other regulatory authorities only:			
16.	Name of regulatory authority		
17.	License number		
18.	Other information		
19.	Have you confirmed clearance/approval in country of manufacture?	Yes	No
20.	Product being evaluated has been manufactured with same quality standard applicable to a country of origin cleared product	Yes	No
IFU/QC Lot release certificate (If listed information is not available, request from the manufacturer)			
21.	Indicates analytical sensitivity of test	Yes	No
22.	Indicates analytical specificity of test	Yes	No
23.	Indicates accuracy of test	Yes	No
24.	Indicates any clinical sensitivity and clinical specificity metrics, if available	Yes	No
Labeling/Marking on Secondary Packaging (Carton and Boxes)			
25.	Name or trade name of test included	Yes	No
26.	Batch/Lot number included	Yes	No
27.	Expiry date/shelf life included	Yes	No
28.	Name of manufacturer included	Yes	No

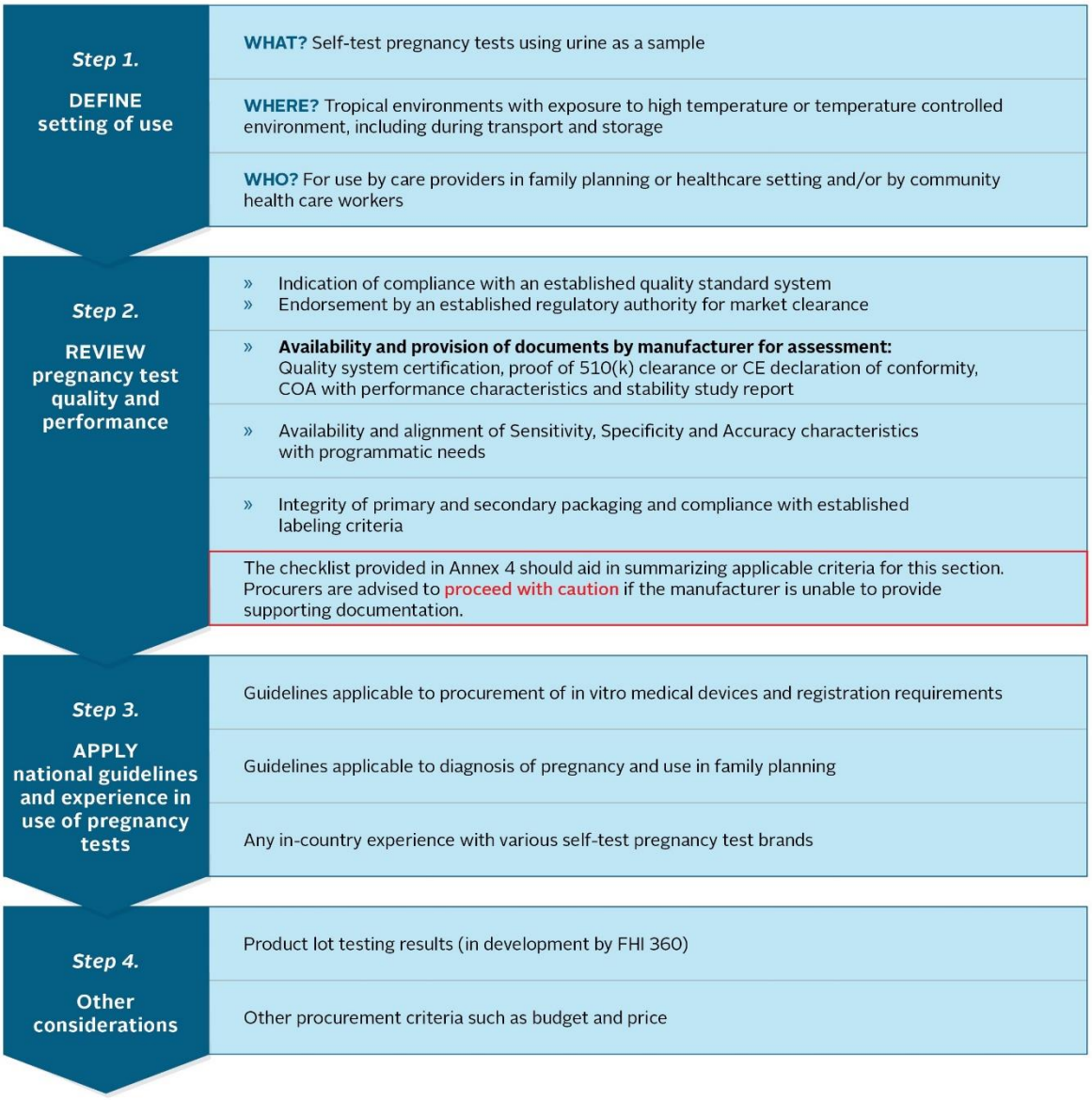
29.	Address of manufacturer included	Yes	No
30.	If CE-marked, CE marking is accompanied by identification number of notified body	Yes	No
31.	CE-marking is conformant	Yes	No
32.	Catalog number included	Yes	No
33.	Storage/handling conditions included	Yes	No
34.	Intended purpose of test indicated	Yes	No
35.	Listing of materials provided and items required but not provided	Yes	No
36.	Indication that the test is for IVD use	Yes	No
37.	Number of tests included in the box	Yes	No
Packaging and Kit Content			
38.	Secondary packaging/box containing the tests is in good condition and not torn, wet or with illegible writing 	Yes	No
39.	Pregnancy tests are in individually sealed, intact pouches	Yes	No
40.	Desiccant is present in each individually sealed pouch	Yes	No
41.	Desiccant is packaged in material permeable to air	Yes	No
42.	Desiccant packaging has adequate labeling	Yes	No
43.	Desiccant is of humidity-indicator type	Yes	No
Labeling/Marking on Primary Packaging/IFU/Product Insert (individual pouches containing pregnancy tests)			
44.	Name or trade name of pregnancy test is printed.	Yes	No
45.	Catalog number/product code	Yes	No
46.	Name of manufacturer included 	Yes	No
47.	Address of manufacturer included	Yes	No
48.	If test is imported, name of authorized representative within the importing country (if required).	Yes	No
49.	Batch/Lot number 	Yes	No
50.	Expiration date/shelf life YYYY-MM-(DD) 	Yes	No
51.	Tests are stable up to 30 °C 	Yes	No
52.	If product is CE marked, CE marking includes identification number of notified body 	Yes	No
53.	CE-marking is conformant 	Yes	No

54.	Where not obvious, intended use of test is indicated	Yes	No
55.	An indication that test is for IVD use IVD	Yes	No
56.	Net quantity of pregnancy tests included in the primary package is indicated Σ	Yes	No
57.	Test is intended for single use as indicated 2	Yes	No
58.	Materials provided and those required but not provided are listed	Yes	No
59.	Analytical sensitivity included (25 mIU/mL[11] is recommended)	Yes	No
60.	Analytical specificity included	Yes	No
61.	Accuracy included	Yes	No
62.	Step-by-step test procedure is provided with illustrations	Yes	No
63.	Timing: minimum to maximum time for reading results provided	Yes	No
64.	Interpretation of results is explained using illustrations that display four possible outcomes	Yes	No
65.	Warnings or precautions included	Yes	No
66.	Contents of packaging (including desiccant) listed	Yes	No
67.	Recommended storage conditions on label.	Yes	No
68.	Interference substances indicated	Yes	No
69.	Summary of test included	Yes	No
70.	Principle of the procedure included	Yes	No
71.	Description of procedural/reagent/sample quality control measures included	Yes	No
72.	Limitations of the procedure included	Yes	No
73.	Transport Validation Document: Tests are stable up to 40 °C (if required by country setting)	Yes	No

[11] If using highly sensitive pregnancy tests (analytical sensitivity ≤ 25 mIU/mL), pregnancy can be detected as early as first day of missed menses. If using tests with lower sensitivity (analytical sensitivity≥50 mIU/mL), it is recommended to wait about 10 days after expected date of menses.

The flowchart below illustrates how and where the above checklist can be incorporated into the pregnancy test selection process, and takes into consideration relevant customization at the country and programmatic level to support the procurement process (36).

Figure 10: A step-by-step guide to selecting pregnancy tests meeting high quality and performance standards



Annex 5: Recommended Guidance Documents on Procurement Process and Supply Chain Management

1. A Model Quality Assurance System for Procurement Agencies. WHO, UNICEF, UNDP, UNFPA & World Bank
   http://www.who.int/medicines/publications/ModelQualityAssurance.pdf

2. Guidelines for the Storage of Essential Medicines and Health Commodities. WHO
   http://apps.who.int/medicinedocs/pdf/s4885e/s4885e.pdf

3. Guidelines for Warehousing Health Commodities. USAID
   http://apps.who.int/medicinedocs/documents/s16875e/s16875e.pdf

4. Managing Access to Medicines and Health Technologies (MDS-3). WHO
   http://www.msh.org/sites/msh.org/files/mds3-fm-revised-nov2012.pdf

5. Manual for Procurement of Diagnostics and Related Laboratory Items and Equipment. WHO
   http://www.who.int/diagnostics_laboratory/procurement/130627_manual_for_procurement_of_diagnostics-001-june2013.pdf

6. Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies. PATH
   http://www.path.org/publications/detail.php?i=1652

7. The Logistics Handbook: A Practical Guide for the Supply Chain Management of Health Commodities. USAID
   https://www.k4health.org/sites/default/files/LogiHand_0.pdf

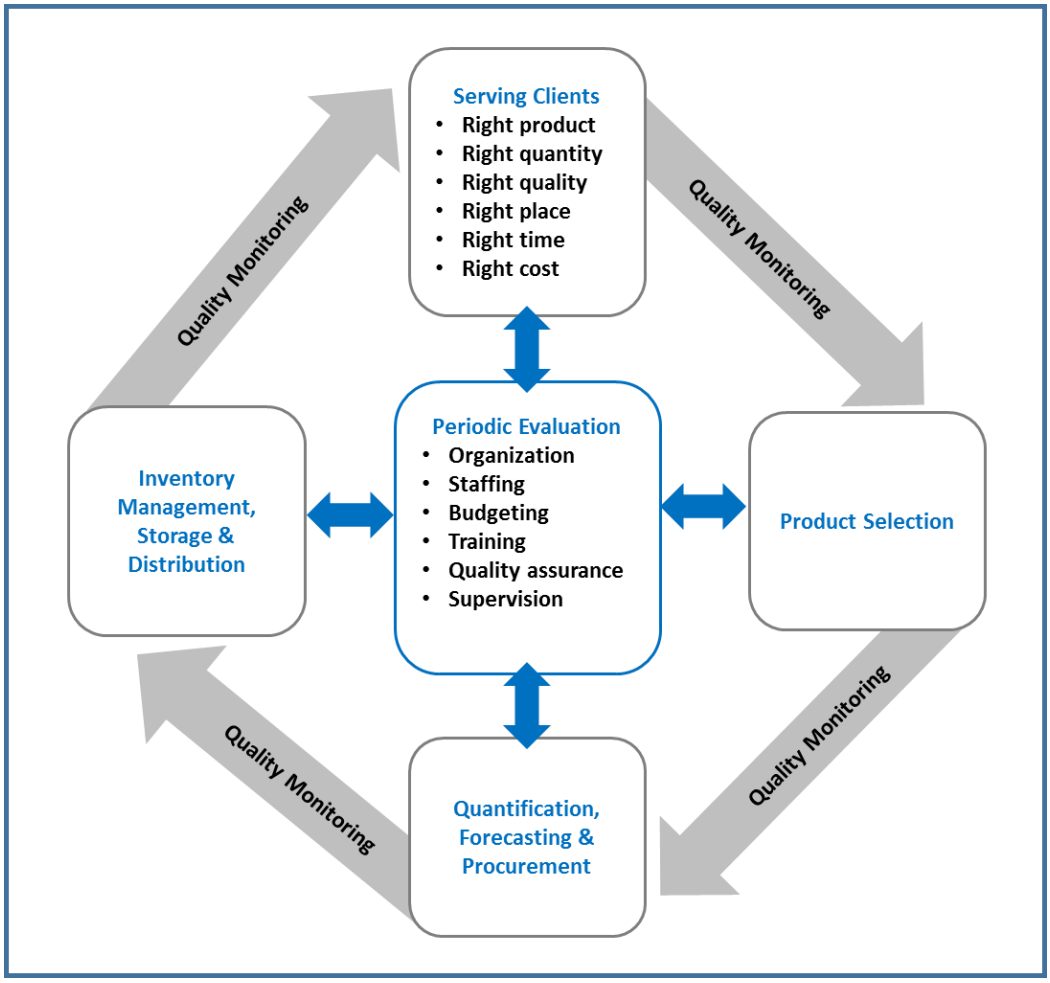
8. General Technical Provisions for in vitro Diagnostic (IVD) Medical Devices. UNICEF
   https://www.unicef.org/supply/files/140330_BAZ_Tech_Prov_IVD_Medical_Devices_March_2014.pdf

9. The Supply Chain Manager's Handbook, A Practical Guide to the Management of Health Commodities. John Snow, Inc.
   http://supplychainhandbook.jsi.com/wp-content/uploads/2017/02/JSI_LogisticHandbook_Final-1.pdf

Annex 6: The Logistics Cycle

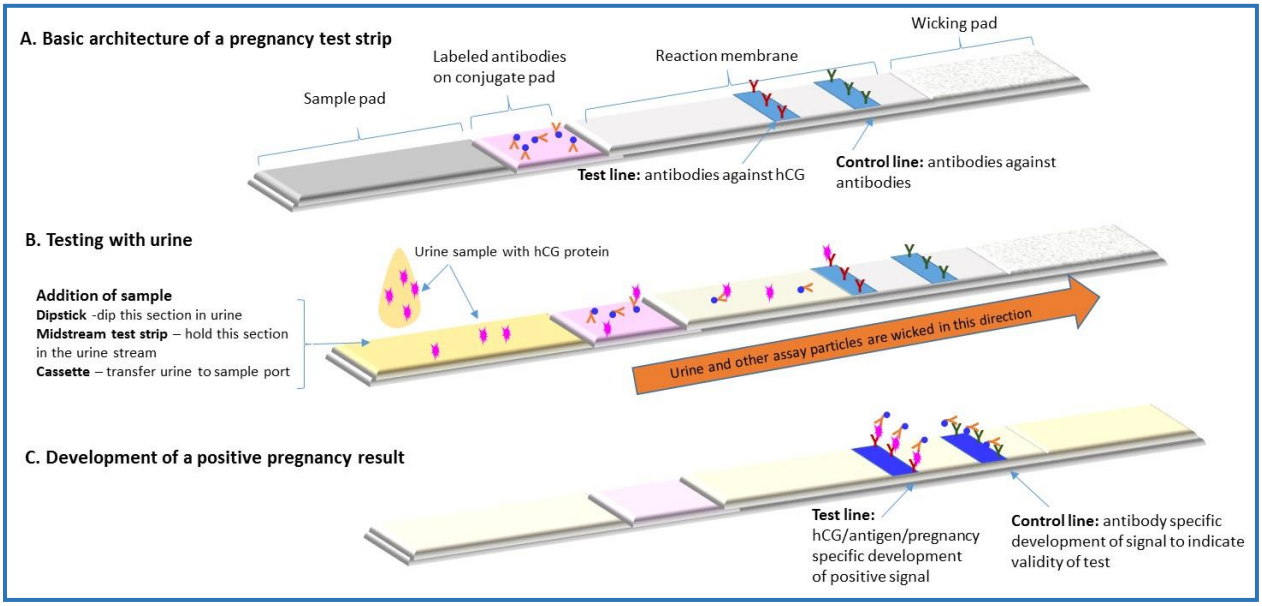
The goal of every public health logistics system is to ensure that every person is able to obtain and use essential health supplies when needed (49). The logistics cycle determines the success or failure of public health programs. The schematic of the logistic cycle presented in **Figure 11** was adapted by those created by the Partnership for Maternal, Newborn and Child Health and USAID (49, 50). As shown in rectangles below, the cycle consists of four elements whose functions depend on each other: 1) serving clients 2) product selection 3) quantification, forecasting and procurement and 4) inventory management. Activities in the center box represent management support functions that inform and impact the other four elements. Quality monitoring, as depicted in the gray arrows, contributes to efficiency and effectiveness of this cycle. Serving clients, the key focus of a logistic cycle, can be fulfilled by 'six rights': 1) right product 2) right quantity 3) right quality 4) right place 5) right time and 6) right cost.

Figure 11: Logistics cycle



Annex 7: Assay Principle of Pregnancy Test

Figure 12: Basic components of the pregnancy test and how it works



A. **Basic architecture of a pregnancy test strip** (**Figure 12A**)**:** A typical rapid test consists of several components adhered to an inert backing: 1) sample pad designed for specimen application and to enable liquid flow, 2) conjugate pad where dried labeled antibodies are deposited, 3) reaction membrane with a test line carrying pregnancy-specific antibodies[12] and a control line carrying antibodies that recognize other antibodies, and 4) wicking pad designed to draw the specimen across the reaction membrane.

B. **Testing with urine** (**Figure 12B**)**:** Upon application of urine, the liquid moves via capillary action, hydrating labeled antibodies and enabling their migration across the membrane towards the test and control lines. During this process, hCG proteins bind the labeled antibodies as well as those on the test line.

C. **Development of a positive result** (**Figure 12C**): Recruitment of labeled antibodies to the test line occurs dependent of hCG; accumulation of these labeled antibodies results in the development of a positive test line. Recruitment of labeled antibodies to the control line is independent of hCG, and results in development of a control line indicating that the reagents and the assay have operated as expected.

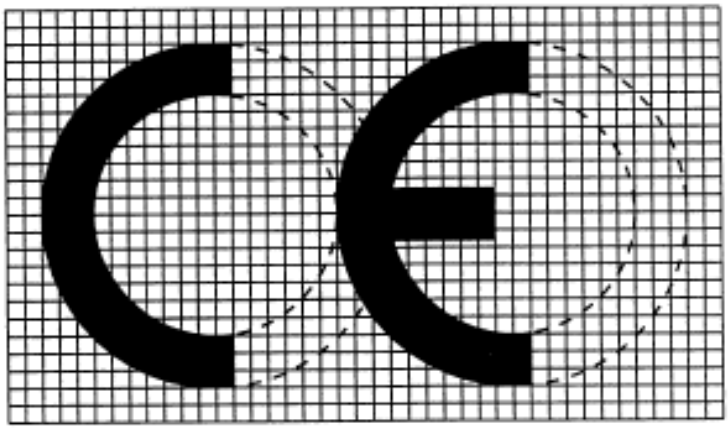
[12] Pregnancy tests typically carry two forms of hCG antibodies: those raised against the alpha subunit of hCG for capture, and those raised against the beta subunit of hCG for detection.

Annex 8: CE Marking Conformity as specified in Directive 98/79/EC of the European Parliament and of the Council

The illustration in **Figure 13** is an excerpt from EU directive 98/79/EC (14). Please refer to the **WHO fact sheet** to find out more about prevalence of substandard, spurious, falsely labeled, falsified and counterfeit medical products (31).

Figure 13: CE marking of conformity

The CE conformity marking shall consist of the initials 'CE' taking the following form:



— If the marking is reduced or enlarged the proportions given in the above graduated drawing must be respected,

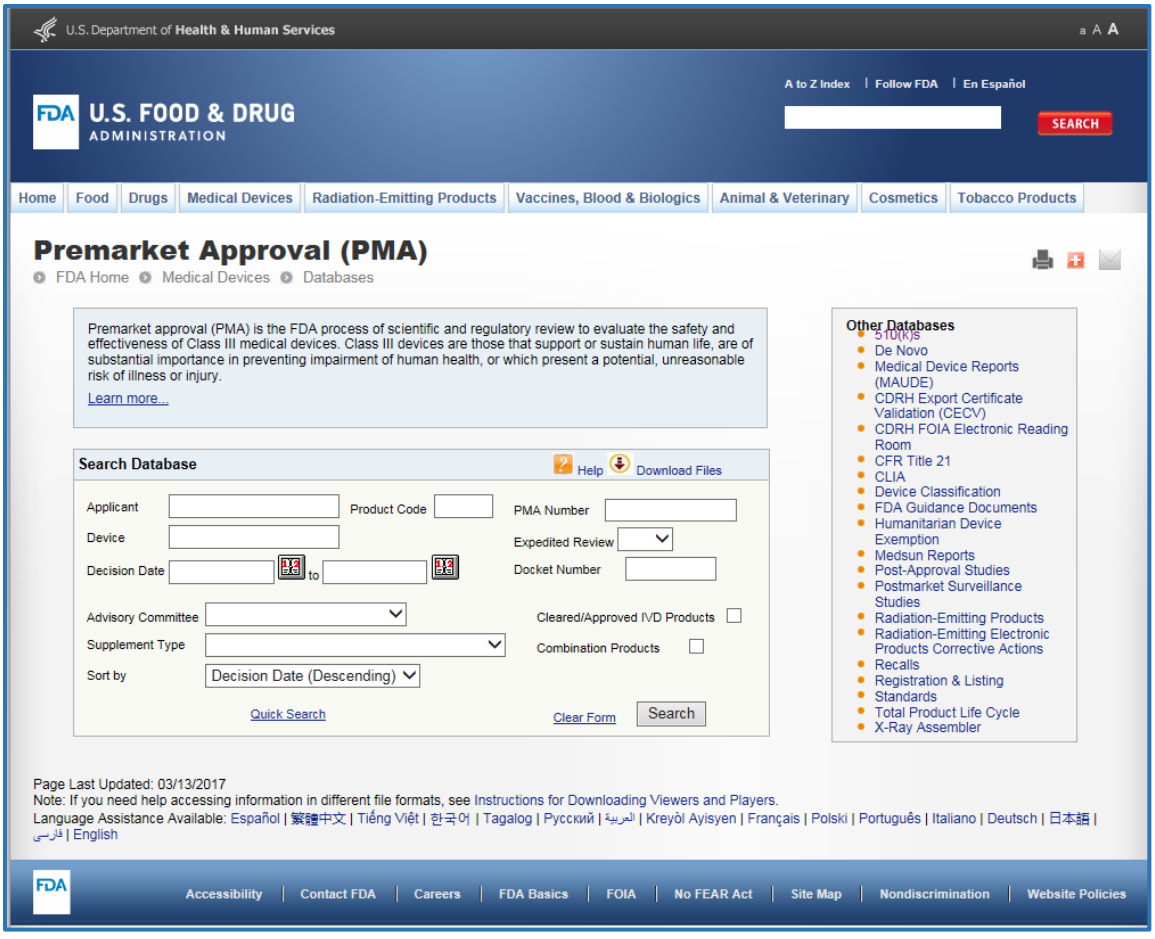
— the various components of the CE marking must have substantially the same vertical dimension, which may not be less than 5 mm. This minimum dimension may be waived for small-scale devices.

Annex 9: Screenshot of FDA Premarket Notifications 510(k) Clearance Webpage for Verification Purposes

Confirm that the manufacturer holds 510(k) clearance by visiting the 510(k) premarket notification site:

(U.S. FDA home page → Medical Devices Tab → Medical Device Database (under Tools & Resources) → select the 'Premarket Notifications (510(k)' database →type 'LCX' under 'product code' (**Figure 14**)→ Search for the product of interest).
Current website URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Figure 14: A screenshot of FDA 510(k) clearance webpage for regulatory status verification of pregnancy tests under evaluation



Annex 10: Desiccants and Their Usage

Information below has been summarized in consultation with MRDT guidelines (6, 36, 43).

Table 6: Desiccants and their usage

Item	Purpose of use/criteria to meet	Recommendation
Desiccant	• Protects test from exposure to humidity • Humidity has been shown to decrease analytical performance of RDTs	Recommended
Desiccant with humidity indicator	• Indicates if desiccant, and therefore the test, was exposed to humidity • Color indicator desiccant is preferred over non-indicating desiccants • Partial indicators are difficult to view for presence of humidity • Avoid use of cobalt dichloride as an indicator as it is a carcinogen	Enhanced quality and performance practices
Material of desiccant package should be permeable to air	• Enables uptake of humidity by desiccant • Avoid use of sachets with plastic packaging as they are impenetrable to air • Paper-based sachets are penetrable to air	Recommended
Sachet with desiccant should be transparent or have a window that allows easy visualization of color change	• Aids safe and easy visualization of color change in desiccant	Enhanced quality and performance practices
Warning message indicating not to eat desiccant	• Desiccant could be harmful if swallowed and should be kept away from children	Recommended
Sachet with desiccant should carry instructions for: - interpretation of color changes - Steps to follow if test is exposed to humidity - Safe disposal of desiccants	• Enables appropriate decision making for accurate and safe outcomes	Enhanced quality and performance practices

Annex 11: Definitions of Symbols Recommended for Labeling

For the safe and effective use of medical devices, ISO 15223-1:2012 has identified the symbols in **Figure 15** for use in labeling standards (12). This information is provided as a source of information for interpreting the meaning of symbols as they appear on various packaging, and to ensure that accurate labeling is used when procuring pregnancy tests. Other normative documents were also referenced in summarizing this information (39, 44, 51).

Figure 15: Definitions of symbols recommended for labeling

Symbols and Their Definitions		
 In vitro diagnostic medical device	 Keep away from sunlight/heat	 Keep dry
 Contents sufficient for <n> tests	 Consult instructions for use	 Do not use if packaging is damaged
 Lot number	 Product code/catalog number	 Conformant CE mark and identification number of notified body
 Date of manufacture YYYY-MM-(DD)	 Manufacturer	 Authorized representative in the European Community
 Do not reuse	 Use by YYYY-MM-(DD)	 Caution, consult accompanying document
 Temperature limitation	 Upper limit of temperature	 Lower limit of temperature

For more information about FHI 360's work in Quality and Performance Guidance on Selection of Pregnancy Tests for Procurement, email us at envisionfp@fhi360.org

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