Quality and Performance Guidance on Selection of Pregnancy Tests for Procurement
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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 CFR 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).


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.

\(^1\) 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

### Regulatory Landscape

- **Manufacturer's conformity with quality management system standards**
  - cGMP / QSR
  - ISO 13485

#### Classification of pregnancy tests
- Class II (Australia, Canada, Japan and USA) / Class I, self-test medical device (EU) / Class B medical device (IMDRF)

#### Regulatory requirements for marketing clearance
- **US FDA 510(k)** Determination of substantial equivalence
- **EU requirements:** Assessment of conformance to EU directives by a notified body
- **IMDRF members:** Briefly addressed in this document; relevant references have been provided for IMDRF member states in Annex 3 for further review
- **Rest of the World Regulatory Authorities**

- **510(k) clearance**
- **CE mark**
- **Various product clearance approaches**

- Market approval and registration; additional country level registration requirements

### Selection of Pregnancy Tests for Procurement:

Evaluators are recommended to request following documentations from manufacturers for each product being evaluated:

- **Quality and Regulatory Documentations**
- **IFU, QC Lot Release Certificate or Technical Files**
- **Shelf Life Reports**
- **Conformance with labeling requirements**

- **Proof of 510(k) clearance**
- **Copy of ISO 13485 certification**
- **CE declaration of conformity**

Links have been provided for verification of regulatory approval from IMDRF members, Australia, Canada and Japan.

#### Performance Specifications
- Analytical sensitivity
- Analytical specificity
- Accuracy
- Other criteria (interferents and clinical sensitivity and clinical specificity)

**Accelerated Stability Evaluation Report** for initial claim to be followed up with Real Time Stability Evaluation Report

- **IFU**
- **Primary packaging**
- **Secondary packaging**

*Dependent on regulator requirements*

*If the IFU or QC Lot Release Certification does not carry relevant information, it is recommended that the evaluator requests the manufacturer to glean missing information from the Technical File.*
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 < 25 mIU/mL) detect pregnancy as early as the first day of missed menses. Lower sensitivity tests (analytical sensitivity ≥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.

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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).

![Figure 3. Comparison of CE marking of conformity and nonconformity (32)](image)

<table>
<thead>
<tr>
<th>CE marking of conformity</th>
<th>CE marking of conformity with identification number of the Notified Body</th>
<th>CE marking of nonconformity: spacing between letters is incorrect</th>
<th>CE marking of nonconformity: CE marking is not to be in a frame</th>
</tr>
</thead>
</table>

- 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/](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:


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.
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

<table>
<thead>
<tr>
<th>Regulatory Authority</th>
<th>Classification</th>
<th>Documentary Evidence</th>
</tr>
</thead>
</table>
| Health Canada                |                | - Medical device license: [https://health-products.canada.ca/mdall-limh/index-eng.jsp](https://health-products.canada.ca/mdall-limh/index-eng.jsp)  
- ISO 13485 certificate issued by the Canadian Medical Device Conformity Assessment System |
- TGA issued ISO 13485 Certificate |
| PMDA and MHLW, Japan         |                | - Certification by registered certification body                                      
- PMDA General information: [https://www.pmda.go.jp/english/](https://www.pmda.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 Other 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). 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

\[ p \]

7 If using highly sensitive pregnancy tests (analytical sensitivity ≤ 25 mIU/mL), pregnancy can be detected as early as the first day of missed menses. If using tests with lower sensitivity (analytical sensitivity >_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

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).

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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

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. Absence of the control line indicates a problem with the test, and renders the test invalid.

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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).
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

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<thead>
<tr>
<th>QUALITY STANDARDS AND REGULATORY SPECIFICATIONS</th>
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<td><strong>CURRENT GENERAL STATUS</strong></td>
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<td>- ISO 13485 and/or CE marking or US FDA clearance</td>
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<th>LABELING SPECIFICATIONS</th>
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<td><strong>Analytical Sensitivity</strong></td>
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<th>INSTRUCTIONS FOR USE (IFU): TEST PROCEDURE AND RESULT INTERPRETATION</th>
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<td>- Summary of test</td>
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<td>- Reference intervals</td>
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<td>- Limitations of procedure: describe opportunities for false positives and false negatives</td>
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<tr>
<td>- Circumstances needing consultation with healthcare provider</td>
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<td>- Procedural control in the test</td>
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<thead>
<tr>
<th>INCREASING QUALITY STANDARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on an exploratory evaluation of 16 pregnancy tests; results are summarized in Annex 2</td>
</tr>
<tr>
<td>Enhanced Quality Practices are inclusive of Recommended Quality Standards &amp; Performance Specifications</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

Desiccants with air-permeable packaging with printed warnings

2–30 ºC

Transport validation documentation for heat stability during transport

Humidity indicator desiccants with air-permeable packaging with printed warnings

2–40 ºC
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

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


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


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


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.

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

Client with amenorrhea
- Implants, pills, ring, injectables, or patch
- IUDs
- Copper or LNG

Take history using pregnancy checklist. If pregnancy is ruled out, provide method.

If pregnancy is not ruled out, use a pregnancy test.

If pregnancy test is negative (or test is not immediately available), provide the method now.

Schedule a follow-up pregnancy test in 3-4 weeks.

Client between two regular menses
- Implants, pills, ring, injectables, or patch
- IUDs
- Copper or LNG

Do not use a pregnancy test (in most cases, it is too early for it to be effective).

Take history using pregnancy checklist. If pregnancy is ruled out, provide method.

If pregnancy is not ruled out, provide the method now.

Counsel the woman to get a pregnancy test if her next menses are delayed.

Client with late/missed period
- Implants, pills, ring, injectables, or patch
- IUDs
- Copper or LNG

Pregnancy checklist is not useful after a period is missed; use a pregnancy test.

If using a highly sensitive pregnancy test (e.g., 25 mIU/ml) and it is negative, provide desired method.

If using a test with lower sensitivity (e.g., 50 mIU/ml) and it is negative during the time of her missed period, wait until at least 10 days after expected date of menses and repeat the test. Advise woman to use condoms or abstain in the interim. If the test is still negative, provide desired method.

If test sensitivity is not specified, assume lower sensitivity.

Counsel all women to come back any time they have a reason to suspect pregnancy (e.g., miss a period).

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.

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

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Institution</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>National Health Surveillance Agency</td>
<td><a href="http://portal.anvisa.gov.br/wps/portal/anvisa-ingles">http://portal.anvisa.gov.br/wps/portal/anvisa-ingles</a></td>
</tr>
<tr>
<td>Canada</td>
<td>Health Canada</td>
<td><a href="http://www">http://www</a> hc-sc gc.ca/index-eng.php</td>
</tr>
<tr>
<td>China</td>
<td>China Food and Drug Administration</td>
<td><a href="http://eng.sfda.gov.cn/WS03/CL0755/">http://eng.sfda.gov.cn/WS03/CL0755/</a></td>
</tr>
<tr>
<td>Japan</td>
<td>Pharmaceutical and Medical Device Agency &amp; Ministry of Health, Labor and Welfare</td>
<td><a href="https://www.pmda.go.jp/english/">https://www.pmda.go.jp/english/</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="http://www.mhlw.go.jp/english/">http://www.mhlw.go.jp/english/</a></td>
</tr>
<tr>
<td>Russia</td>
<td>Russian Ministry of Health</td>
<td><a href="https://www.rosminzdrav.ru/">https://www.rosminzdrav.ru/</a></td>
</tr>
<tr>
<td>Singapore</td>
<td>Health Science Authority</td>
<td><a href="http://www.hsa.gov.sg/content/hsa/en.html">http://www.hsa.gov.sg/content/hsa/en.html</a></td>
</tr>
<tr>
<td>United States of America</td>
<td>Food and Drug Administration</td>
<td><a href="http://www.fda.gov/">http://www.fda.gov/</a></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Checklist for Evaluation of Pregnancy Tests for Procurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of assessor</td>
</tr>
<tr>
<td>Date of assessment</td>
</tr>
<tr>
<td>Name of pregnancy test (brand name)</td>
</tr>
<tr>
<td>Test format</td>
</tr>
<tr>
<td>Manufacturer and address</td>
</tr>
<tr>
<td>Lot number</td>
</tr>
<tr>
<td>Catalog number</td>
</tr>
<tr>
<td>Has a ISO 13485 certification been provided?</td>
</tr>
<tr>
<td>Sources of documentation provided as proof of regulatory clearance</td>
</tr>
<tr>
<td>Has a QC Lot Release Certificate been provided from a recent Lot/batch for evaluation?</td>
</tr>
<tr>
<td>Has an Accelerated Stability Evaluation Report been provided?</td>
</tr>
</tbody>
</table>

**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 |
<table>
<thead>
<tr>
<th>For assessment of CE declaration of conformity only:</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Manufacturer’s name is correctly indicated</td>
</tr>
<tr>
<td>7. Manufacturer’s address is correctly indicated</td>
</tr>
<tr>
<td>8. Name of pregnancy test is correctly indicated</td>
</tr>
<tr>
<td>9. Essential characteristics of pregnancy test are provided</td>
</tr>
<tr>
<td>10. Name of regulatory authority/notified body</td>
</tr>
<tr>
<td>11. License number</td>
</tr>
<tr>
<td>12. A legally binding signature on behalf of the organization is present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For assessment of U.S. FDA 510(k) clearance only:</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. A 510(k) clearance letter for the pregnancy test has been provided</td>
</tr>
<tr>
<td>14. U.S. FDA 510(k) clearance website confirms clearance of pregnancy test</td>
</tr>
<tr>
<td>15. Product being evaluated has been manufactured with same quality standard applicable to a U.S. FDA cleared product</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For assessment of other regulatory authorities only:</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Name of regulatory authority</td>
</tr>
<tr>
<td>17. License number</td>
</tr>
<tr>
<td>18. Other information</td>
</tr>
<tr>
<td>19. Have you confirmed clearance/approval in country of manufacture?</td>
</tr>
<tr>
<td>20. Product being evaluated has been manufactured with same quality standard applicable to a country of origin cleared product</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IFU/QC Lot release certificate (If listed information is not available, request from the manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. Indicates analytical sensitivity of test</td>
</tr>
<tr>
<td>22. Indicates analytical specificity of test</td>
</tr>
<tr>
<td>23. Indicates accuracy of test</td>
</tr>
<tr>
<td>24. Indicates any clinical sensitivity and clinical specificity metrics, if available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Labeling/Marking on Secondary Packaging (Carton and Boxes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Name or trade name of test included</td>
</tr>
<tr>
<td>26. Batch/Lot number included</td>
</tr>
<tr>
<td>27. Expiry date/shelf life included</td>
</tr>
<tr>
<td>28. Name of manufacturer included</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>29.</strong> Address of manufacturer included</td>
</tr>
<tr>
<td><strong>30.</strong> If CE-marked, CE marking is accompanied by identification number of notified body</td>
</tr>
<tr>
<td><strong>31.</strong> CE-marking is conformant</td>
</tr>
<tr>
<td><strong>32.</strong> Catalog number included</td>
</tr>
<tr>
<td><strong>33.</strong> Storage/handling conditions included</td>
</tr>
<tr>
<td><strong>34.</strong> Intended purpose of test indicated</td>
</tr>
<tr>
<td><strong>35.</strong> Listing of materials provided and items required but not provided</td>
</tr>
<tr>
<td><strong>36.</strong> Indication that the test is for IVD use</td>
</tr>
<tr>
<td><strong>37.</strong> Number of tests included in the box</td>
</tr>
</tbody>
</table>

### Packaging and Kit Content

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>38.</strong> Secondary packaging/box containing the tests is in good condition and not torn, wet or with illegible writing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>39.</strong> Pregnancy tests are in individually sealed, intact pouches</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>40.</strong> Desiccant is present in each individually sealed pouch</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>41.</strong> Desiccant is packaged in material permeable to air</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>42.</strong> Desiccant packaging has adequate labeling</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>43.</strong> Desiccant is of humidity-indicator type</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Labeling/Marking on Primary Packaging/IFU/Product Insert (individual pouches containing pregnancy tests)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>44.</strong> Name or trade name of pregnancy test is printed.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>45.</strong> Catalog number/product code</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>46.</strong> Name of manufacturer included</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>47.</strong> Address of manufacturer included</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>48.</strong> If test is imported, name of authorized representative within the importing country (if required).</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>49.</strong> Batch/Lot number</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>50.</strong> Expiration date/shelf life YYYY-MM-DD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>51.</strong> Tests are stable up to 30°C</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>52.</strong> If product is CE marked, CE marking includes identification number of notified body</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>53.</strong> CE-marking is conformant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>Yes</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>54.</td>
<td>Where not obvious, intended use of test is indicated</td>
<td>Yes</td>
</tr>
<tr>
<td>55.</td>
<td>An indication that test is for IVD use</td>
<td>Yes</td>
</tr>
<tr>
<td>56.</td>
<td>Net quantity of pregnancy tests included in the primary package is indicated</td>
<td>Yes</td>
</tr>
<tr>
<td>57.</td>
<td>Test is intended for single use as indicated</td>
<td>Yes</td>
</tr>
<tr>
<td>58.</td>
<td>Materials provided and those required but not provided are listed</td>
<td>Yes</td>
</tr>
<tr>
<td>59.</td>
<td>Analytical sensitivity included (25 mIU/mL\textsuperscript{11} is recommended)</td>
<td>Yes</td>
</tr>
<tr>
<td>60.</td>
<td>Analytical specificity included</td>
<td>Yes</td>
</tr>
<tr>
<td>61.</td>
<td>Accuracy included</td>
<td>Yes</td>
</tr>
<tr>
<td>62.</td>
<td>Step-by-step test procedure is provided with illustrations</td>
<td>Yes</td>
</tr>
<tr>
<td>63.</td>
<td>Timing: minimum to maximum time for reading results provided</td>
<td>Yes</td>
</tr>
<tr>
<td>64.</td>
<td>Interpretation of results is explained using illustrations that display four possible outcomes</td>
<td>Yes</td>
</tr>
<tr>
<td>65.</td>
<td>Warnings or precautions included</td>
<td>Yes</td>
</tr>
<tr>
<td>66.</td>
<td>Contents of packaging (including desiccant) listed</td>
<td>Yes</td>
</tr>
<tr>
<td>67.</td>
<td>Recommended storage conditions on label</td>
<td>Yes</td>
</tr>
<tr>
<td>68.</td>
<td>Interference substances indicated</td>
<td>Yes</td>
</tr>
<tr>
<td>69.</td>
<td>Summary of test included</td>
<td>Yes</td>
</tr>
<tr>
<td>70.</td>
<td>Principle of the procedure included</td>
<td>Yes</td>
</tr>
<tr>
<td>71.</td>
<td>Description of procedural/reagent/sample quality control measures included</td>
<td>Yes</td>
</tr>
<tr>
<td>72.</td>
<td>Limitations of the procedure included</td>
<td>Yes</td>
</tr>
<tr>
<td>73.</td>
<td>Transport Validation Document: Tests are stable up to 40 °C (if required by country setting)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\textsuperscript{11} If using highly sensitive pregnancy tests (analytical sensitivity \( \leq 25 \text{ mIU/mL} \)), pregnancy can be detected as early as first day of missed menses. If using tests with lower sensitivity (analytical sensitivity \( \geq 50 \text{ mIU/mL} \)), 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*

<table>
<thead>
<tr>
<th>Step 1. DEFINE setting of use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHAT?</strong> Self-test pregnancy tests using urine as a sample</td>
</tr>
<tr>
<td><strong>WHERE?</strong> Tropical environments with exposure to high temperature or temperature controlled environment, including during transport and storage</td>
</tr>
<tr>
<td><strong>WHO?</strong> For use by care providers in family planning or healthcare setting and/or by community health care workers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2. REVIEW pregnancy test quality and performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>» Indication of compliance with an established quality standard system</td>
</tr>
<tr>
<td>» Endorsement by an established regulatory authority for market clearance</td>
</tr>
<tr>
<td>» <strong>Availability and provision of documents by manufacturer for assessment:</strong> Quality system certification, proof of 510(k) clearance or CE declaration of conformity, COA with performance characteristics and stability study report</td>
</tr>
<tr>
<td>» Availability and alignment of Sensitivity, Specificity and Accuracy characteristics with programmatic needs</td>
</tr>
<tr>
<td>» Integrity of primary and secondary packaging and compliance with established labeling criteria</td>
</tr>
<tr>
<td>The checklist provided in Annex 4 should aid in summarizing applicable criteria for this section. Procurers are advised to proceed with caution if the manufacturer is unable to provide supporting documentation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3. APPLY national guidelines and experience in use of pregnancy tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines applicable to procurement of in vitro medical devices and registration requirements</td>
</tr>
<tr>
<td>Guidelines applicable to diagnosis of pregnancy and use in family planning</td>
</tr>
<tr>
<td>Any in-country experience with various self-test pregnancy test brands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4. Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product lot testing results (in development by FHI 360)</td>
</tr>
<tr>
<td>Other procurement criteria such as budget and price</td>
</tr>
</tbody>
</table>
Annex 5: Recommended Guidance Documents on Procurement Process and Supply Chain Management

   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


5. Manual for Procurement of Diagnostics and Related Laboratory Items and Equipment. WHO  

6. Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies. PATH  

   https://www.k4health.org/sites/default/files/LogiHand_0.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\(^\text{12}\) 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.

\(^\text{12}\) 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.

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
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).


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**

<table>
<thead>
<tr>
<th>Item</th>
<th>Purpose of use/criteria to meet</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **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:** | • Enables appropriate decision making for accurate and safe outcomes | Enhanced quality and performance practices |  
- interpretation of color changes  
- Steps to follow if test is exposed to humidity  
- Safe disposal of desiccants
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

<table>
<thead>
<tr>
<th>Symbols and Their Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="IVD" /></td>
</tr>
<tr>
<td>In vitro diagnostic medical device</td>
</tr>
<tr>
<td><img src="image" alt="Sigma" /></td>
</tr>
<tr>
<td>Contents sufficient for &lt;n&gt; tests</td>
</tr>
<tr>
<td><img src="image" alt="LOT" /></td>
</tr>
<tr>
<td>Lot number</td>
</tr>
<tr>
<td><img src="image" alt="Calendar" /></td>
</tr>
<tr>
<td>Date of manufacture YYYY-MM-(DD)</td>
</tr>
<tr>
<td><img src="image" alt="No Reuse" /></td>
</tr>
<tr>
<td>Do not reuse</td>
</tr>
<tr>
<td><img src="image" alt="Temperature" /></td>
</tr>
<tr>
<td>Temperature limitation</td>
</tr>
</tbody>
</table>