

A Guidance Document to Assess Quality of Self-Test Pregnancy Tests: A Guide for Procurers

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Abstract

This paper describes the development of a guidance document for the procurement of high quality self-test pregnancy tests, intended for use in low resource settings. Pregnancy tests play a key role in sexual and reproductive health by facilitating rapid diagnosis of pregnancy status, and thereby enabling appropriate follow up care inclusive of family planning, antenatal or abortion services. Access to pregnancy tests, in terms of cost/affordability, availability, and quality, is a key factor required to streamline the provision of reproductive health related services. Although availability of pregnancy tests has increased and the cost has decreased over time, there remains a significant gap in regulatory control of the quality of these tests, which may lead to prevalence of spurious and counterfeit pregnancy tests in the low-income markets. This paper focuses on the role of pregnancy tests in family planning programs, provides preliminary evidence for current pregnancy test quality gaps, and introduces the content area covered by the new guidance document that was drafted in 2016. The draft guidance document covers applicable international quality standards and performance specifications, which would enable procurers to make informed decisions on selecting and maintaining high quality self-test pregnancy tests for improving family planning services and beyond.

Keywords: self-test pregnancy tests, quality, procurement, standards, regulatory, specifications

Introduction

One of the key criteria for family planning provision is to rule out pregnancy. The combination of the 'pregnancy checklist' with a self-test pregnancy test can rule out pregnancy in most cases, and is advocated for use in low resource setting. The pregnancy checklist is a job aid designed to rule out pregnancy with six simple criteria presented in a question format. However, some studies have demonstrated a provider and client preference for use of pregnancy tests over a checklist, and the adoption of the checklist remains low (Comfort, Chankova, Juras, Hsi, Peterson, & Hathi, 2016; Crossing the thin blue line, 2016). Additionally, the checklist does not work in ruling out pregnancy in certain cases where a pregnancy test does, particularly among women who are on long acting reversible contraceptives (LARCs) and those who have missed their period.¹ Moreover, recent evidence demonstrates that lack of access to pregnancy tests leads to denial of contraception services (Stanback, Vance, Asare, Kasonde, Kafulubiti, Chen & Janowitz, 2013; Crossing the thin blue line, 2016). Taking into consideration the key role of pregnancy tests in family planning, it makes public health sense to make these tests available for family planning either free of charge or at a minimal cost.

Although evidence regarding the availability and cost of pregnancy tests is emerging, the quality of these tests remains largely unknown. A preliminary internal analysis carried out at Family Health International 360 (FHI 360), an international NGO, to evaluate quality of pregnancy tests in low resource setting, illustrates quality gaps suggestive of potentially spurious and counterfeit products in the market (personal communication). Some of the key

¹ If using highly sensitive pregnancy tests (limit of detection 25 mIU/ml), pregnancy can be detected as early as first day of missed menses. If using tests with lower sensitivity (\geq limit of detection 50 mIU/ml), it is recommended to wait till about 10 days after expected date of menses (Pregnancy tests for family planning, 2013).

concerns observed were a lack of conformance with international quality standards, inadequate instructions to carry out and interpret the results, and scarce to non-existent information on analytical sensitivity of the test. Based on this analysis, FHI 360 is developing a document to provide guidance on selecting high quality pregnancy tests to procurers. This paper provides an overview of family planning, barriers for uptake of contraception and role of pregnancy tests in family planning, and informs the reader on prevalent quality gaps and introduces areas covered by the guidance document, followed by a description of the harmonization process and dissemination plans of the document.

Significance of Family Planning for Global Health Outcomes

Contraception enables couples and individuals to have control over their sexuality and reproduction, and affects many other key areas relating to health, education, women's status in society, economy and the environment. Ensuring healthy timing and spacing of pregnancies has been shown to reduce maternal and infant morbidity and mortality rates (WHO, 2016). Reducing rates of unintended pregnancies also reduces the need for unsafe abortion and its associated sequelae (WHO, 2016). In addition, access to family planning can reduce rates of adolescent pregnancies and use of barrier methods can reduce transmission of sexually transmitted diseases such as HIV/AIDS (WHO, 2016).

Most authorities categorize withdrawal and periodic abstinence as 'traditional contraceptive' methods', and "products and medical procedures that interfere with reproduction from sexual intercourse" as 'modern contraceptive methods' (Hubacher and Trussell, 2015; Westoff & Westoff, 2012). Recent estimates demonstrate that if all women who

wanted to avoid pregnancy used a modern contraceptive method, unintended pregnancies would drop by 70%, and 26 million abortions could be averted (Singh, Darroch & Ashford, 2014). Family planning programs play a dual role in accomplishing this goal by reducing unmet need² through increased access to contraceptive methods and services, and by creating a rise in demand² for contraception through education and communication (Bongaarts, 2014).

Barriers to Use of Contraceptives for Women with Unmet Need

Although universal access to family planning has been included in both the Millennium Development Goals (MDGs) and in the Sustainable Development Goals (SDGs), per estimates made in 2014, a staggering 225 million women in developing countries who wanted to avoid pregnancy were not using an effective contraceptive method; this gap has been demonstrated to have remained stagnant since (Singh et al., 2014). According to the United Nations Population Fund (UNFPA), the majority of the women with an unmet need for family planning live in the 69 of the poorest countries in the world (Family planning, 2014). At the same time, trends in contraceptive needs in developing countries indicate that the number of women wanting to avoid pregnancy with the use of modern methods of contraception was 57% in 2012 (Darroch & Singh, 2013). This report also illustrates that the number of women wanting to avoid pregnancies in the 69 poorest countries increased by 36% from 2003 to 2012, when compared to a 10% increase for higher-income countries.

² Married women who are fertile and do not wish to become pregnant in the near future are assumed to have a demand for contraception. While some of these women practice contraception, some do not. The former are considered as 'current users' whose contraception needs have been met, and the latter are considered as those with an 'unmet need' for contraception. These definitions are expressed in the formula: demand=current use + unmet need (Bongaarts, 2004)

Research into non-use of contraception among women with unmet need in low and middle income countries has demonstrated that access as a barrier is becoming less frequent indicating that contraceptive supplies are becoming increasingly available (Sedgh and Hussain, 2014; Westoff & Westoff, 2012). Trends in contraception use also demonstrates a shift from the most effective method of contraception, sterilization, towards modern injectable drugs and barrier methods (Cottingham, Germain & Hunt, 2012). Overall, these observations support increased access to modern contraception globally. More often, non-use of contraceptives is attributed to infrequent sexual activity and concerns over side effects (Sedgh & Hussain, 2014; Westoff & Westoff, 2012). Based on these findings, the major future interventions to increase use seem to be through educating these populations on the contraceptive options available to them, developing better mechanisms through which women can switch methods based on reproductive life-cycle needs, and expanding access to a wider selection of options inclusive of more recent methods such as intra-uterine devices, patch, implantables and injectable forms of contraceptives. These require improved family planning services and supplies. Barriers to providing these are described below.

Barriers to Quality Family Planning Services and Role of Pregnancy Tests in Service Provision

Although the coverage of family planning services has increased in many countries, women are commonly denied services based on six types of medical barriers: 1) contraindications (e.g., headache as a exclusionary symptom (not supported by evidence) in a community based distribution worker's oral contraceptive checklist) 2) eligibility (e.g., age limits on types of contraceptives) 3) process hurdles (e.g. some programs may require a women to undergo a physical examination prior to receiving contraceptives), 4) service provider's

qualifications (e.g., requirements for specialists to prescribe injectable contraceptives when a trained personnel can carry out the procedure) 5) provider bias, and 6) country level regulations (e.g., restrictions on advertising contraception) (Shelton, Jacobstein & Angle, 1992). One of the main barriers for the uptake of modern contraceptive methods is the need for a woman to present herself to family planning services while menstruating, to prove non-pregnancy (Stanback et. al, 2013). Although the presence of menses can help rule out pregnancy, this requirement often results in denial of contraception to non-menstruating women until they can return to the clinic when they are menstruating (Stanback et. al, 2013). Without adequate family planning, these women remain at risk of unintended pregnancy in the interim. This barrier stems from the entrenched belief that contraception can harm an undiagnosed pregnancy, even though a plethora of evidence supports the claim that neither oral, hormonal or spermicidal contraceptives increase congenital abnormalities (Bracken, Holford, White & Kelsey, 1978; Simpson, 1985; Simpson & Phillips, 1990).

Given these constraints, there are significant challenges to implementing the interventions described above to increase use, since women who are denied service may be unlikely to return or seek counseling for advanced services. Finding solutions to reduce service denial is useful and providing access to pregnancy tests appears to have promise. A study carried out in Zambia to evaluate if access to free pregnancy testing reduces service denial in family planning clinics demonstrated that while the baseline denial rate for intervention and control were at 15% and 17%, follow up denial rate for intervention and control were 4% and 17% respectively (Stanback et al., 2013). Another study carried out in Nepal, where trained community health volunteers provided a low-cost pregnancy test to their communities,

demonstrated empowerment of women to make timely reproductive health choices (Andersen, Singh, Shreshta, Shah, Pearson & Hessini, 2013). Similarly, the provision of free pregnancy tests to community health workers in Madagascar has been demonstrated to increase sales of contraception to their clients (Comfort, Chankovas, Juras, Hsl, Peterson & Hathi, 2016). Additionally, a cross-sectional study carried out in South Africa has illustrated that having access to self-test pregnancy tests decreases the gestational age at the time of presentation to both antenatal care and abortion clinics (Morrone & Moodley, 2006). Given the proven benefits of pregnancy status testing and its public health impact, priority should be given to making pregnancy tests either free or at a low cost to family planning services.

Advantages of Self-Test Pregnancy Tests over Checklists

Although the reference standard for ruling out pregnancy is a urine pregnancy test, due to availability and affordability issues, in 2004 the World Health Organization (WHO) endorsed a simple 'pregnancy checklist' to rule out pregnancy with a reasonable amount of certainty (WHO, 2015). The pregnancy checklist includes six criteria to rule out pregnancy, and if a woman meets any of the criteria, a provider can be reasonably certain that the woman is not pregnant. However, the checklist cannot always rule out pregnancy: 1) in a woman who is amenorrheic (not menstruating), either because she has recently given birth and is not protected by lactational amenorrhea method (LAM) or because she has been using LARC contraception method such as injectable progestin, and is returning late for reinjection and 2) in a woman has missed her menses. Additionally, the performance of the checklist has been shown to vary depending on the study, with sensitivity ranging from 55-100% and specificity ranging from 39-89% (Tepper, Marchbanks & Curtis, 2013). There is also evidence for provider

and client preference for a pregnancy test over the checklist (Comfort et al., 2016). Based on these additional benefits pregnancy tests offer, it makes public health sense to provide access to free or low-cost pregnancy tests as a complement to the checklist (Stanback et al., 2013).

Quality Challenges Associated with Self-Test Pregnancy Tests

Clearly, if the use of self-test pregnancy tests is to be promoted in low- and middle-income settings, there has to be an assurance of their quality. In the USA, the Food and Drug Administration (FDA) requires a 510(k)³ clearance of any self-test pregnancy test prior to introduction to the market. Similarly, for the countries within the European Union (EU), a notified body⁴ carries out a conformity testing of pregnancy tests for CE marking⁵. However, even in wealthy countries, these quality assurance processes do not have common definitions or performance specifications (Gnoth & Johnson, 2014) contributing to marketing messages about their sensitivity that are often not accurate (Cole, Khanllan, Sutton, Davies & Rayburn, 2003; Davlaud, Ballongue, Guillem, Leblanc, Casellas, & Pau, 1993; Gnoth & Johnson, 2014; Wilcox, 2001). Conditions are even worse in resource poor settings where regulatory standards are often lacking for diagnostics, and quality assessment of pregnancy tests remains sparse to non-existent. Within this weak regulatory framework, prevalence of spurious and counterfeit pregnancy tests is highly likely, similar to pharmaceuticals. According to the WHO, 25% of the pharmaceuticals in the developing world are estimated to be counterfeit (WHO, 2006).

Counterfeit and fake pharmaceuticals are suggested to be a significant incentive in the

³ 510(k) is a USFDA requirement for certain classes of medical devices to make a premarket submission to demonstrate that the device is as safe and effective (substantial equivalence) as a predicate device.

⁴ Notified body is an entity that has been assigned by a member state of the EU to determine if a product to be placed on the EU market meets relevant European Directives.

⁵ CE is the abbreviation for European Conformity, and the CE marking on a product is the manufacturer's claim that the product conforms with EU's health, safety and environment legislations/product directives.

developing world due to “poverty, high cost of medicines, lack of an official supply chain, legislative lacunae, easy accessibility to computerized technology, ineffective law enforcement machinery and light penalties” (Gautam, Utreja & Singal, 2009); it is likely that these same factors hold true for the diagnostic sector as well. To this end, a study carried out by FHI 360 in Mali, Malawi and Kenya to assess access to pregnancy tests, demonstrated that only 68 out of 103 tests had a CE mark indicating conformance with an established quality assessment pathway (Crossing the thin blue line, 2016).

Exploratory Analysis of Prevalent Status of Pregnancy Tests in the Developing World

To gain a preliminary understanding of quality status of pregnancy tests in the developing world, an assessment of 16 pregnancy tests collected over a 2-year period from a mix of low- and middle-income countries in the African region was carried out. These were purchased from pharmacies as individually packaged items. Three normative regulatory documents representing US, European and global standards: 1. The US FDA 510(k) for pregnancy tests 2. ISO 13485 and 3. in vitro Diagnostic Directive 98/79/EC, were used to compile approximately 30 criteria for assessment. Based on this assessment, some of the key strengths and weakness of the pregnancy tests are summarized in Table 1. This analysis demonstrated that over 50% of the pregnancy tests were not manufactured conformant to an internationally recognized quality standard. Even those that claimed to conform to the widely recognized CE marking did not demonstrate a conformant quality seal, which suggests that they are a spurious or a counterfeit product (Table 1, section 1.1). Moreover, while a majority of the tests contained ‘instructions for use’, many still did not have have adequate information for a client or provider to carry out the testing correctly (Table 1, section 1.3). Similar observations

were made for the interpretation of results (Table 1, section 1.3) and information on analytical performance of the tests (Table 1, section 1.4). These deficiencies bring into question the quality of these tests for testing pregnancy, be it in the context of self-testing or point of care, to improve the quality of life of people who could benefit from it the most. The outcome from this analysis confirmed some of the speculations of fake and counterfeit pregnancy tests entering the market in low and middle -income countries.

Table 1: Current quality status of 16 pregnancy tests purchased from several developing countries

Quality Criteria Being Evaluated	% Conformance Rate Among Self-Test Pregnancy Tests (N=16)
1.1 Quality standards	
Presence of an internationally recognized quality endorsement	44%
From those indicating CE marking, those that have a conformant CE mark	71%
1.2 Labeling	
Indication of a manufacturer and contact information	44%
Indication of a lot number	94%
Indication of date of expiry	94%
Indication of number of units/pkg	50%
Indication of 'do not reuse'	31%
1.3 Instructions for use and result interpretation	
Indication of intended use	81%
Indication of instructions for use	94%
Indication of instructions for use with schematics	88%
Indication of when to read results (declared reading time)	75%
Indication of a time period beyond which results are not valid	38%
Indication of result interpretation with schematics	94%
Indication interpretation with all four possible outcomes	44%
1.4 Analytical performance information	
Indication of analytical sensitivity	13%
Indication of analytical specificity	0%
Indication of limitations of tests	0%

Development of Guidance on Quality Assurance for Self-Test Pregnancy Tests in the Developing World

There is clearly a need for improved guidance on assuring the quality of pregnancy tests. FHI 360, with funding from United States Agency for International Development (USAID) and in consultation with members of the Reproductive Health Supplies Coalition (RHSC), has prepared a guidance document for procurers on selection of self-test pregnancy tests that meet established international quality standards. The complete draft version of this document is in Annex 1. We present a summary here.

Target audience and focus area

This document has been designed specifically for procurers of pregnancy tests at both national and international level in the public and private sectors. Two of the main procurers of pregnancy tests are USAID and Marie Stopes International (MSI). The procurement process is generally complex and involves multiple steps, agencies, ministries and manufacturers (Woldeyesus, Fresle, Grayston & Hogerzell, 1999). The WHO has proposed four strategic objectives for pharmaceutical procurement: “1) Procure the most cost-effective drugs in the right quantities 2. Select reliable suppliers of high-quality products 3. Ensure timely delivery 4. Achieve the lowest possible total cost” (Woldeyesus et al., 1999). The focus of the guidance document is to address the second objective: ‘selection of high-quality products.’ In many low- and middle-income countries, procurement officials have limited experience in the product selection process, as well as limited or no access to unbiased market information on product quality and manufacturers’ performance (WHO Manual for procurement of diagnostics

and related laboratory equipment, 2013). Even if/when product quality information is available, screening products and identifying and applying acceptable standards requires time and skill. These challenges in procurement, combined with weak systems and inadequate regulatory infrastructure, can lead to wasting of scarce funding on procuring inferior products that may not meet the public health objectives. This guidance document aims to provide procures the necessary knowledge in a form that can be easily integrated into a procurement logistic cycle, which are the processes for selecting, procuring, managing and using a product.

Overview of guidance document

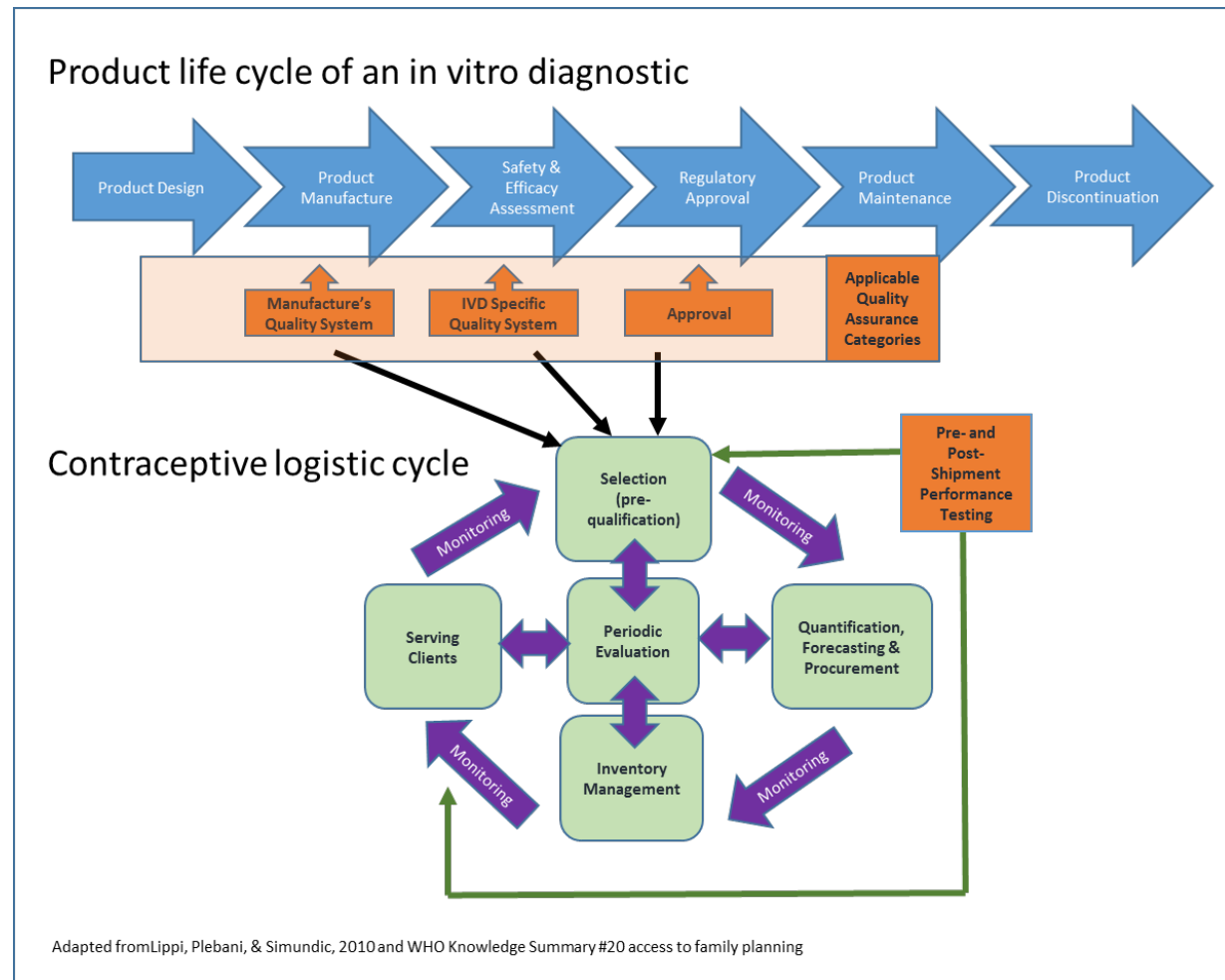
Quality considerations must be addressed during all stages of a product design and manufacture process. To this end, a pregnancy test has a 'product life cycle' constituting of several stages that has been put in place by the manufacturer to ensure the product meets these quality standards and customer expectations as shown in Figure 1, along with the procurement logistic cycle described above. Documents for assessing the quality of a product are generated directly from the design and manufacturing steps of the product life cycle process, as illustrated by the orange arrows in Figure 1.

The guidance document provides details on what a procurer can request from a manufacturer/supplier to make an informed decision about selecting high quality pregnancy tests (figure 1, black arrows). To provide procurers with information on how to interpret this documentation, a series of normative documents and primary literature were used to compile quality standards and specifications relevant to pregnancy tests/in vitro diagnostics that are applicable in the US and in the EU. As there are many pregnancy tests in the international

market that do not meet the US and EU quality standards, additional references to assess compliance with other Stringent Regulatory Authorities (SRAs) have also been provided. Since there are differences in the regulatory landscape across countries, the standards are categorized under Recommended Practices and Enhanced Quality Practices; while 'recommended practices' are strongly recommended to be incorporated immediately, 'enhanced quality practices' are recommended to make procurers aware of higher standards being applicable in the developed world, which could be incorporated with improvements to regulatory infrastructure over time. Every effort has been made to make the document practical and actionable to procurers; the recommendations have been summarized in a checklist format for ease of integration into the contraceptive logistic cycle.

In addition, FHI 360, with funding from USAID, is also in the process of preparing simple work instructions for carrying out performance testing of pregnancy tests, referred to in the diagram as 'pre- and post-shipment performance testing' (Fig. 1, thin green arrows), which would allow countries to test mainly the analytical sensitivity of the test against the manufacturer's specification. Based on the experience with malaria rapid diagnostics, it is likely that most countries do not have this capacity for independent testing, and this is an area that governments should give priority to when strengthening regulatory mechanisms.

Fig. 1: Guidance on streamlining quality of manufacturing with the contraceptive logistic cycle:



Quality criteria for assessment

Criteria on which procurement decisions are made largely depend on various factors including funders, funding, transparency, country level needs and infrastructure. The recommended criteria, as outlined below, are broadly applicable in multiple procurement settings.

- 1) *Quality systems requirements for manufacturers:* Manufacturers must establish organizational structure, responsibilities, resources, procedures and processes to ensure that their products consistently meet applicable quality standards and specification.

The document recommends adoption of quality systems ISO13485 (international) or 21 CFR part 820 (US).

- 2) *Product specific directives*: Product- or class-specific quality standards that are required to be incorporated into pregnancy tests based on country level classification. The guidance is derived from the US FDA over-the-counter human chorionic gonadotrophin (hCG) 510(k) directive and EU in vitro Diagnostic Directive 98/79/EC.
- 3) *Technical specifications*: These specifications are instrumental in assuring that the pregnancy test performs effectively as intended, and reduces the wastage across the supply chain. Within this category, the document discusses test format and ancillary items, analytical performance (sensitivity, specificity, accuracy and limitations), shelf-life, packaging, kit content and labeling requirements.

Stakeholder feedback

Stakeholders involved with review and development of the draft procurement guidelines include members of RHSC, who are involved in reproductive health procurement programs, or are advising on quality and procurement standards. A subcommittee was developed to review the draft and advise on additions or revisions that were required. The subcommittee involves representatives from Abt Associates, Management Sciences for Health, MSI, RHSC, UNICEF, UNFPA, USAID and WHO.

Two stakeholder meetings have been carried out to date to discuss and gain input on the content of the guidance document. During the first round of reviews, feedback was garnered through an open-ended discussion. During the second round of discussions, points needing specific feedback were entered into a structured questionnaire to solicit feedback and

drive consensus. Follow-up discussions were carried out with individual groups to gain clarity on individual feedback when needed. Although two manufacturers of pregnancy tests were invited to the second meeting, they preferred to provide feedback on the document via email.

Dissemination platform for guidance document

Dissemination efforts will be planned and intended, and adoption by procurers will be assessed (Kerner, Rimer & Emmons, 2005). To this end, FHI 360 is partnering with RHSC, a group that brings together manufacturers/suppliers, donors, service delivery groups, policymakers and buyers for procurement of reproductive health needs. Their strategy includes increasing access to reproductive health supplies through increasing availability and access, improving quality and overcoming inequity. RHSC already serves as a platform for awareness building around the need for free or low-cost pregnancy tests and improving their quality. RHSC website will house this guidance document. Inclusion of translations, support, FAQs and other supplementary information is likely to increase adoption and integration.

It is likely that some country level procurers will have challenges with adopting the guidelines due to lack of technical knowledge, and other program based needs. To address some of these implementation challenges, a website with information on manufacturer's that carry compliant pregnancy tests is likely to be very helpful.

Conclusions

As a variety of modern contraceptive choices become available to women globally, the success of uptake and sustainment depends on the improvement of family planning services, supplies and empowerment of women to make informed choices regarding their reproductive

health. To this end, increased availability of accurate and affordable self-test pregnancy tests can help accomplish these goals. In order for a pregnancy self-test to work effectively, it should meet certain performance criteria, which is built into its design and manufacture. In the absence of specifications for these criteria for the developing world, there may be spurious and counterfeit pregnancy tests in the market. To fill this gap, a new guidance document to assist in the procurement of quality pregnancy tests has been developed with input and agreement from major stakeholders involved in procurement and family planning. The guidance is harmonized with standards established by normative international authorities. The document provides tools for procurers to easily and practically incorporate quality product selection into their workflow. Dissemination followed by adoption of the documents by procurers is the next key step in this process. In our march towards achieving universal access to reproductive health and rights, strengthening the quality component of supply chain management is one of many steps required for the successful achievement of the ambitious reproductive health targets set forth by the SDGs.

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Annex 1

Draft-Not for Circulation

Not for Circulation

DRAFT RECOMMENDED GUIDANCE FOR PROCUREMENT OF SELF-TEST PREGNANCY TESTS: FOCUS ON QUALITY



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Committee members include:

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3 Abbreviations

21 CFR	Title 21 of the US Code of Federal Regulation
CE	European Conformity
cGMP	Current Good Manufacturing Practice
EC	European Commission
EU	European Union
US FDA	US Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
FSH	Follicle Stimulating Hormone
hCG	Human Chorionic Gonadotrophin
IVD	In Vitro Diagnostic
ISO	International Organization for Standardization
LH	Luteinizing Hormone
MRDTs	Malaria Rapid Diagnostics
NGO	Nongovernmental Organizations
POC	Point of Care
RDT	Rapid Diagnostic Tests
SRA	Stringent Regulatory Authority
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization

4 Glossary (WORK IN PROGRESS)

The following definitions were taken or adapted from the following documents: X, Y and Z.”

21 CFR 820: All medical device manufacturers supplying medical devices to the U.S. are required by the USFDA to maintain a quality management system in compliance with that described in 21 CFR 820.

510(k): A premarket submission made to US FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device. Submitters must compare their device to one or more similarly legally marketed devices and make and support their substantial equivalence.

Accuracy: Based on test efficiency and defined as ‘True positive plus true negative results divided by the total number of samples tested’ (9).

Antigen: A substance that causes the immune system to produce antibodies against it. In pregnancy tests, hCG is used as the antigen for producing antibodies that are used in tests to diagnose pregnancy.

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

Analytical performance: Refers to the reliability and validity of the hCG measurement results produced by a self-test pregnancy test. Typical properties assessed are interferents and accuracy, as relevant to this document (27).

Authorized Representative: A legal entity who has been appointed by the manufacturer to represent its interest in a country

Batch: Defined quantity of product manufactured in a single process or series of processes and therefore expected to be homogeneous (49) (sometimes used interchangeably with ‘Lot’).

Expiry Date: The date at which the product is no longer considered acceptable for use.

CE marking: On pregnancy test packaging, manufacturer’s declaration that the product meets the essential criteria of the European Medical Device Directive 98/79/EC.

cGMP (current Good Manufacturing Practices): The component of the quality assurance system for US FDA, which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

Certificate of Analysis (COA): (to be defined)

Declaration of Conformity:

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

Diagnostic performance: Refers to the capability of the test to differentiate between pregnancy and non-pregnancy. Typical properties assessed are sensitivity and specificity, as relevant to this document (27).

False-positive rate: Percentage of all tests of a particular product that returned a positive result when it should not have, when obtained within the manufacturer's recommended reading time (1).

Human chorionic gonadotropin (hCG): A hormone made by the cells in the placenta during pregnancy that is used to monitor pregnancy status.

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 they provide.

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 (2).

Invalid test: A pregnancy test in which the control line does not appear during the result reading period. (3)

IVD medical device for self-testing: Any device intended by the manufacturer for use by lay persons.

ISO 15523: Identifies the requirements for symbols used in medical device labeling that convey information on the safe and effective use of devices. ISO 15523 applies to symbols used in a broad spectrum of globally marketed medical devices and therefore needs to meet different regulatory requirements.

ISO 13485: [year]: A quality management scheme created by the ISO for medical device manufacturing. The standards prescribe the documentation, procedures and structures that must be followed in all types of organizations to facilitate the production of medical devices of consistent standard.

Manufacturer: Any natural or legal person with responsibility for the design, manufacture, fabrication, assembly, packaging or labeling of a medical device, for assembling a system, or adapting a medical device before it is placed on the market and/or put into service, regardless of whether these operations are carried out by that person or on their behalf by a third party (4).

Notified body: An independent body involved in the compliance assessment process, as detailed in the European Union directives.

Point-of-care: Testing that is performed near or at the site of a patient which may result in a possible change in care of the patient (4)

Procurement: The process of acquiring supplies from private or public suppliers or through purchases from manufacturers, distributors or agencies (3).

Quality assurance: Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that products are of the quality required for their intended use]

Registration: Any statutory system of approval required at national level as a precondition for introducing a product in the market (3)

Self-testing: Testing [examination to align with labelling standard] performed by lay persons.

Shelf-life: Period of time until the expiry date during which an IVD device/reagent in its original packaging maintains its stability under the storage conditions specified by the manufacturer (4).

Stability: Ability of an IVD to maintain its performance characteristics within the limits specified by the manufacturer (4).

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

Specification: ALT DEF: a statement of the procurer's requirements and covers all product attributes necessary for acceptance. For procurement, the purchaser must provide a specification that details the characteristics and quality of the product to be manufactured. These include essential general and performance requirements as well as discretionary design requirements.

Stringent Regulatory Authority (SRA): The national drug regulatory authorities who are members, observers or associates of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Standards: Standards are published by national, regional and international standard bodies to establish the minimum performance, quality and safety requirements for products that are made, imported and sold within a particular country or region. They are usually generic in nature and not design restrictive. Standards also specify standardized test methods to be used when testing products for quality assurance and conformance purposes

5 Background

Ensuring access to low-cost, high quality, self-test pregnancy tests has been shown to increase same-day provision of family planning, and aid in the timely provision of antenatal care (5-8). However, in many settings, pregnancy tests are not routinely available for clients, are marked up to unaffordable prices and/or are of questionable quality. In 2015, FHI 360 partnered with Marie Stopes International to conduct an assessment in three countries (Kenya, Malawi and Mali) to document availability, affordability and quality of pregnancy tests. This project was completed with support from the Reproductive Health Supplies Coalition through an Innovation Fund grant.

Key findings from the assessment included that there were:

- Concerns about fake and counterfeit products or suspect 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 quality pregnancy tests enter national markets;
- No publicly available protocol for pre-and post-shipment testing of pregnancy tests;
- Limited visibility for procurers on the supply side (e.g., limited information about suppliers' prior performance);
- A lack of coordination, focus and harmonization around pregnancy test procurement guidelines.

In addition, FHI 360 carried out an exploratory evaluation of a small number of pregnancy tests, collected from developing countries over a two-year period, to develop an understanding of prevailing quality status. The preliminary results from this analysis, as summarized in [Annex S1](#), illustrates significant quality gaps in terms of conformance with international quality standards and technical performance criteria.

Given the lack of regulatory oversight for diagnostics in many countries, assessment by a more stringent regulatory authority (SRA) is often used as an alternative or complementary strategy for national approval or for ensuring international quality standards. Global efforts towards harmonization of regulatory approaches have led to internationally accepted standards for a risk-based approach for the pre-market assessment of safety, quality and performance of diagnostics – these include a number of SRAs that are founding members of the Global

Harmonization Task Force -i.e., European Union (EU), US Food and Drug Administration (US FDA) and other SRAs ([Annex S2](#)).

In 2016, with support from the USAID-funded *Envision FP* project led by FHI 360, this document was developed to address some of these gaps in knowledge and practice by outlining requirements for quality standards and providing details on technical specifications, derived mainly from the EU, US FDA and ISO 13485, to inform pregnancy test procurement and related decision-making.

Developed in consultation with key stakeholder groups and in alignment with WHO and FIND's initiatives towards the improvements of quality of malaria rapid diagnostics (MRDTs), this document identifies global standards, technical specifications encompassing performance criteria and best practices in an effort to increase access to high quality pregnancy tests in low-resource settings.

6 Intended Audience

This document has been designed to provide knowledge and guidance to procurers to understand the relevant manufacturing and product quality standards that apply to pregnancy tests, and to develop adequate specifications for their procurement related decision making.

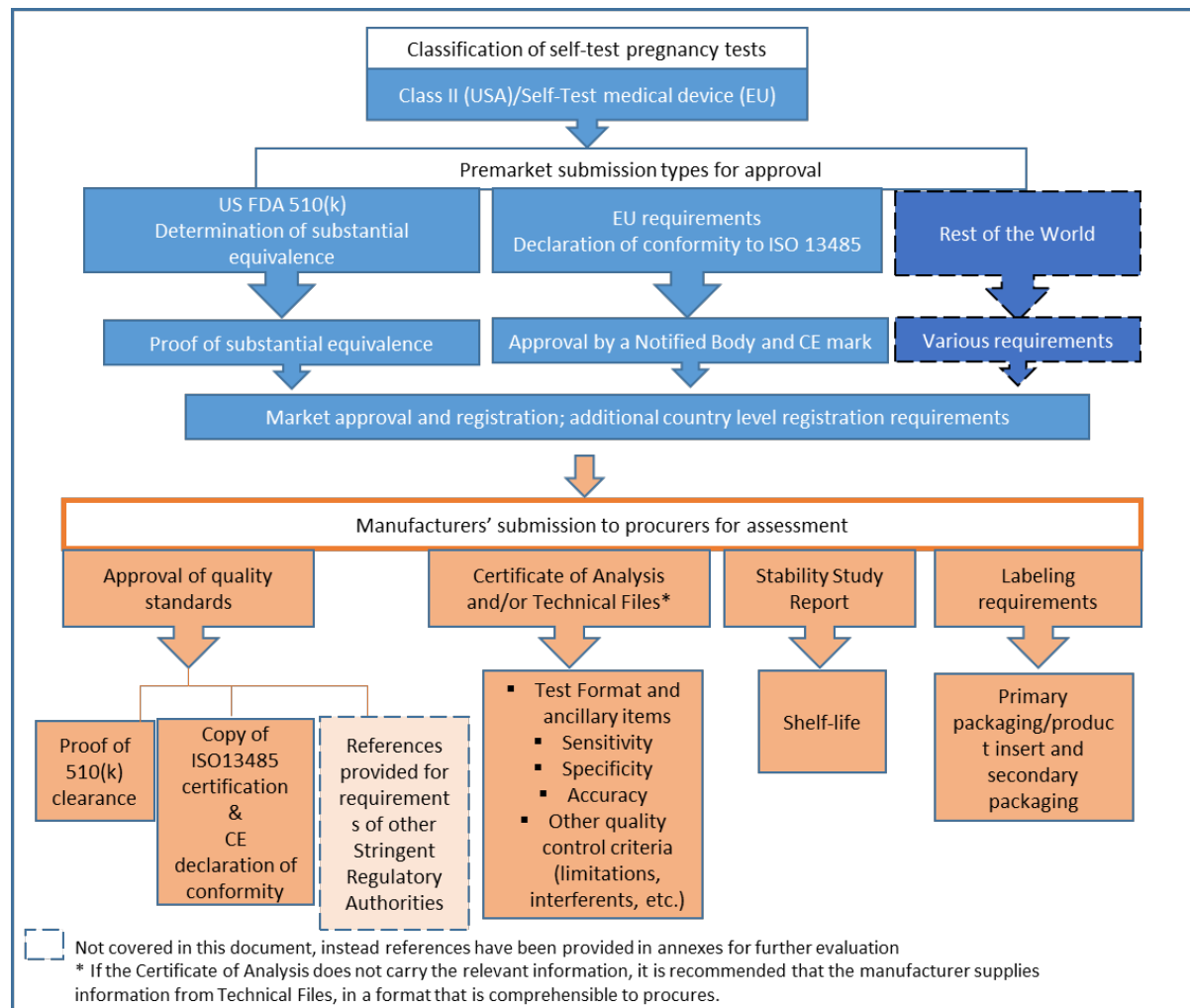
Its intended audience includes individuals responsible for the procurement, supply, and quality assurance of pregnancy tests at a global, national and/or local level including procurement officers, health officers and supply chain managers responsible for selecting, procuring or assisting in the procurement of pregnancy tests for use in the public and private sectors. In addition, the document is relevant to those manufacturers who wish to supply pregnancy tests to global and local public health programs. This document may also prove helpful to policy makers and social marketing and service delivery groups.

7 How to Use this Document

Broadly, this document provides recommendations on quality standards (section 10) and technical specifications (section 11) for self-test pregnancy tests. The areas covered are those derived from ISO 13485, US FDA and EU CE-marking, and are outlined in Figure 1. References

have been provided for other SRAs as pertinent to the rest of the world (ROW) quality standards ([Annex S2](#)).

Figure 1: Areas of guidance covered in this document



- In developing this document, careful consideration was given to the unique challenges in resource-poor settings through a consensus driven process, and the recommendations discussed within the main text of the body was considered as adoptable by most countries, regardless of the level of maturity of regulatory infrastructure. In addition, at the end of each quality criteria, 'enhanced quality practices' have been included in green boxes for consideration by those countries with more mature regulatory infrastructure; this information is also useful for awareness building within the community about additional quality practices that could bring about even better outcomes.

Enhanced quality practices

- At the end of quality criteria sections, where applicable, documents procurers are recommended to request from manufacturers are summarized in orange boxes.

Documents for procurers

- [In Annex S3](#), all the relevant details of the document have been categorized and summarized in a **checklist** form for procurers to incorporate into their workflow.
- Detailed annexes on several pertinent areas, have also been provided for those wanting more information.
- Blue call-out boxes have been used to highlight further clarifications.

- This document is not intended to replace existing guidance on procurement processes, but rather to provide quality related technical guidance specifically related to the selection of self-test pregnancy tests for procurement.
 - For recommended guidance on procurement processes and supply chain management please refer to [Annex S4](#) for a recommended reading list.
 - For information on Contraceptive Logistics Cycle and measures for monitoring and quality improvement please refer to [Annex S5](#).

Technical and quality assurance experts with specific insight into the procurement of health commodities—in particular rapid diagnostic tests—are recommended to be involved in both the selection and continuous quality monitoring of pregnancy tests procurement process.

Should you have any questions, please contact us at: EnvisionFP@fhi360.org

[This document will be housed in the following websites for free access:](#)

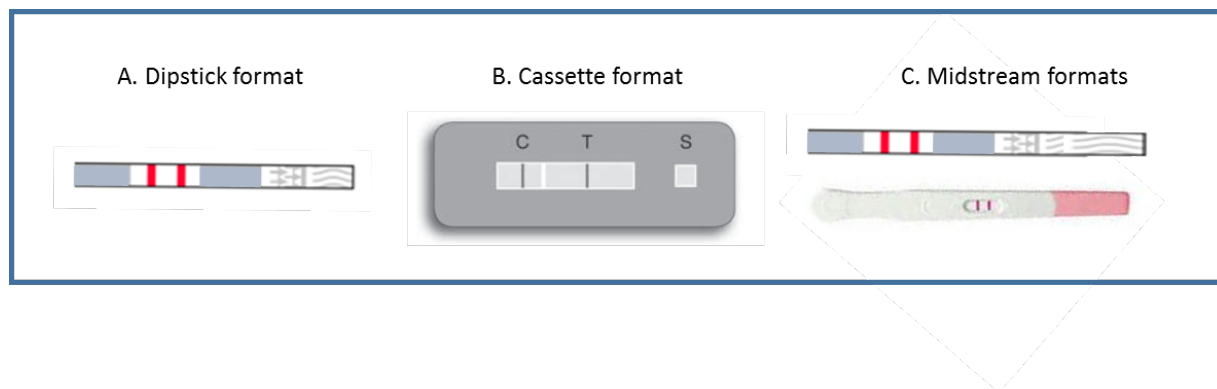


8 Applicability of Guidance

The standards and specifications described herein are applicable to three formats of self-test pregnancy tests that are designed to use urine as sample, and can be read visually

without the aid of an additional device: 1) dipstick, 2) cassette-type, or 3) midstream (Figure 2). This guidance document does not apply to blood tests that evaluate pregnancy status.

Figure 2: Three formats of self-test pregnancy tests covered in this document



9 Overview of Self-Test Pregnancy Tests

Self-test pregnancy tests are also known as ‘urine pregnancy tests,’ ‘home pregnancy tests,’ ‘hCG/HCG tests,’ and ‘over-the-counter pregnancy tests’; the term ‘point-of-care pregnancy tests’ is often used when the test is run by the provider. Typical self-test pregnancy tests are designed to provide a qualitative result indicating only a negative or positive result (yes/no result).

The most common tests come in three formats as illustrated in Figure 2: dipstick, cassette and midstream format. The principle behind this diagnosis is schematically described in [Annex S6](#). Briefly, a dipstick is assembled by careful layering of different membranes on a plastic backing. Encasement of this dipstick in different plastic housing yields a cassette or one of the midstream formats. Assay reagents constituting various antibody preparations are then deposited on the test strip in specific regions. Upon addition of the urine sample, labeled antibodies are directionally mobilized through capillary action. The presence of the pregnancy hormone, human chorionic gonadotrophin (hCG), leads to localization of the labeled antibody to the test line yielding a positive signal. The localization of labeled antibody to the control line is independent of hCG, and should yield a positive signal validating that the assay and the reagents are operating as expected. If the test is positive for pregnancy, then the test and control line should develop; if the test is negative for pregnancy, then only the control line should develop.

Approximately 6-12 days after fertilization of an egg, the woman's body begins to produce the hCG hormone; hCG levels continue to rise as the pregnancy progresses and plateaus around 45 days post-conception. Ninety-eight percent of women who have conceived have a urine concentration of hCG > 25 mIU/mL by the day of their next expected period (). Due to natural fluctuations in menstrual cycles and quality issues with pregnancy tests, pregnancy diagnosis prior to a week or two after the missed period remains challenging.⁶

Providers can be reasonably sure a woman is pregnant before a missed period by using the **Pregnancy Checklist**, which has been endorsed by the WHO, USAID and a number of country governments. The Pregnancy Checklist and pregnancy tests are complimentary tools as there are times when both tools will not be effective at ruling out pregnancy. More information about the Checklist is available in [Annex S7](#).

10 Quality Standards

This document briefly discusses quality standards applicable to *in vitro* diagnostics as detailed out in ISO 13485, US FDA and CE-marking directives. The demonstration of compliance to these quality standards involves a choice of testing pathways that is dependent on the **classification** of the medical device. Based on perceived risk associated with the device to the user, US FDA has classified self-test pregnancy test as a **Class II device** (medium risk), while the EU has classified it as a **self-test** under **Class I devices** (low risk). The conformance criteria relevant to self-test pregnancy tests are discussed below based on their applicability to manufacturer (party taking responsibility for compliance) and product.

10.1 Standards Applicable to Manufacturer

The manufacturing site is recommended to be in compliance with the quality management system regulation standard **ISO 13485:2003** and later ⁷, which is a globally recognized system in many countries, or 21 CFR part 820 **cGMP/QSR**, which is the US FDA requirement for medical devices. A well established and compliant quality management system is instrumental to manufacturing of high quality pregnancy tests.

⁶ If using highly sensitive pregnancy tests (limit of detection 25 mIU/ml), pregnancy can be detected as early as first day of missed menses. If using tests with lower sensitivity (\geq limit of detection 50 mIU/ml), it is recommended to wait till about 10 days after expected date of menses (Pregnancy tests for family planning, 2013).

⁷ ISO 13485: 2003 will be valid until 2019 followed by ISO 13485:2016.

Documents for Procurers: It is recommended that the procurer requests a copy of the manufacturer's ISO 13485 certification at the time of assessment. The validity of the certificate can be checked by consulting the body that issued it, and it is recommended that the renewal date be added to the supplier's records. It is important that the scope of the ISO 13485 certificate is checked so that the production of the pregnancy tests fall within the issuance of the certificate.

- The industry standard for overall quality management, ISO 9001, should not be confused with the quality system standard ISO 13485:2003. Proof of compliance with ISO 9001 alone, as commonly seen with self-test pregnancy tests, is not adequate for compliance with ISO 13485.

ISO 9001: This standard sets out the requirements for a quality management system. It helps businesses and organizations to be more efficient and improve customer satisfaction (22).

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 requirements of ISO 13485:2003 are specific to organizations providing medical devices, regardless of the type or size of the organization (23). This standard is required as the basis for quality assurance management of *in vitro* diagnostic devices for their registration and regulatory control in many places.

10.2 Standards Applicable to Products





The pregnancy test is recommended to carry the **CE marking** as per *in vitro* Diagnostic Directive (IVDD) 98/79/EC for EU ([Annex S8](#)), or be **US FDA-approved** as per 510(k) (9,10). Approval from other SRAs could also be considered, subject to procurer's understanding and knowledge of these groups. [Annex S2](#) provides a list of SRAs with links to their websites.

10.2.1 CE Marking

- IVDD 98/79/EC 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
- The CE marking should be in compliance with the schematics indicated in Figure 3 and elaborated in [Annex S8](#), and must be accompanied by the identification number of the Notified Body (usually a 4-digit number). 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 selection of products carrying nonconforming CE marking, as indicated below in Figure. 3 (11).

Figure 3. Comparison of CE marking of conformity and nonconformity

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

- The manufacturer is recommended to draw up the Declaration of Conformity (DoC) to declare sole responsibility for the conformity to the relevant directive. The DoC should detail out manufacturer's name and address, essential characteristics of the product, the identification number of the Notified Body, as well as a legally binding signature on behalf of the organization. The DoC is recommended to be made available to the procurers at the time of tender or supplier selection.

Documents for Procurers: It is recommended that the procurer request a copy of CE Declaration of Conformity from the manufacturer at the time of assessment.

10.2.2 US FDA approval/510(k) clearance

A manufacturer who intends to market a self-test pregnancy test in the U.S. is required to submit a 510(k) application, also known as a Premarket Notification (PMN). 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 process is known as demonstration of 'substantial equivalence' (30). Once the manufacturer receives written notification of FDA clearance confirming 'substantial equivalence' to a legally marketed

product, the test can be marketed in the U.S. Please note that the FDA clearance is not indicated on the package labeling.

510(k) clearance is required only for pregnancy tests intended for sale in the US market. For international procurers of pregnancy tests considering products claiming to be US FDA-approved, it is highly recommended to:

- 1) confirm that the manufacturer holds 510(k) clearance by visiting the 510(k) premarket notification site;
(US FDA home page → Medical Devices Tab → Medical Device Database (under Tools & Resources) → select the 'Premarket Notifications (510(k)' database → type 'LCX' under 'product code' → Search for the product of interest)
Please refer to [Annex S9](#) for a screenshot of the FDA website to check for the 510(k) clearance status of the pregnancy test.
- 2) confirm with the manufacturer that the test of interest is manufactured to the same standard as that cleared for the US market.

Documents for Procurers on US FDA Approval: Check for 510(k) clearance on the US FDA website, and confirm with manufacturer that the same quality standards have been applied to the manufacturing process for pregnancy test being evaluated.

10.3 Rest of the World Regulatory Approvals and Country Registrations

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) may also be required. However, in a number of countries, regulations applicable to diagnostics are generally weak to non-existent. Therefore, given the lack of regulatory oversight for diagnostics in many countries, an assessment by a SRA is often used as an alternative or complementary strategy for national approval. Global efforts towards harmonization of regulatory approaches have led to internationally accepted standards for a risk-based approach for the pre-market assessment of safety, quality and performance of diagnostics – these include a number of SRAs that are founding members of the Global Harmonization Task Force -i.e., EU, US FDA and other SRAs ([Annex S2](#)) (31).

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 these guidelines. The landscape is changing rapidly and different NRAs will have different requirements. Prior to purchasing pregnancy tests for specific markets, procurers are advised to check the regulatory requirements of the country in question. The Contraceptive Technology Innovation (CTI) Exchange is a useful website with [links](#) to a number of regulatory agencies and regulatory information.

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'. Given the differences in regulatory requirements, manufacturers will often supply different regulatory versions of the 'same diagnostic' versions for markets with stringent regulatory controls, and versions for markets with little or no regulatory control, often referred to as 'rest of the world' regulatory versions. Therefore, though a manufacturer may manufacture a stringent regulated version of the product, they may equally supply a less-regulated or un-regulated version of the same product without any assurance that the same quality controlled components and procedures were used to manufacture the product. Usually regulatory requirements for 'export only' products are 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 (). It is therefore crucial that procurers request supportive documentation to verify the exact regulatory status of the product to be procured.

Documents for Procurers on other Regulatory Approvals:

- It is recommended that procurers check the regulatory requirements of the country in question, prior to purchasing pregnancy tests.
- For pregnancy tests that have been approved by other SRAs, it is recommended that procurers verify regulatory statutes applicable to the pregnancy test being evaluated.

11 Technical Specifications

Technical specifications are instrumental in the decision-making process involving identification of effective pregnancy tests that will meet programmatic needs. For example, it would be helpful to know the analytical sensitivity of a pregnancy test so that service providers have a handle on capability of the test to diagnose early pregnancy. This information is usually included in the Certificate of Analysis (COA), product insert, Technical File and/or on product labels, as applicable. Many of the recommended criteria in this section are based on the WHO and FIND's efforts to standardize and harmonize malaria rapid diagnostic tests (MRDTs), which follows the same assay principle as pregnancy tests.

Prior to selecting pregnancy tests for procurement, it is recommended that procurers request a dossier of technical product information (Technical Files) from the manufacturer. This dossier provides product specifications, including detailed information for each of the following technical categories, evidence that supports performance studies, and a copy of the COA for recent batches.

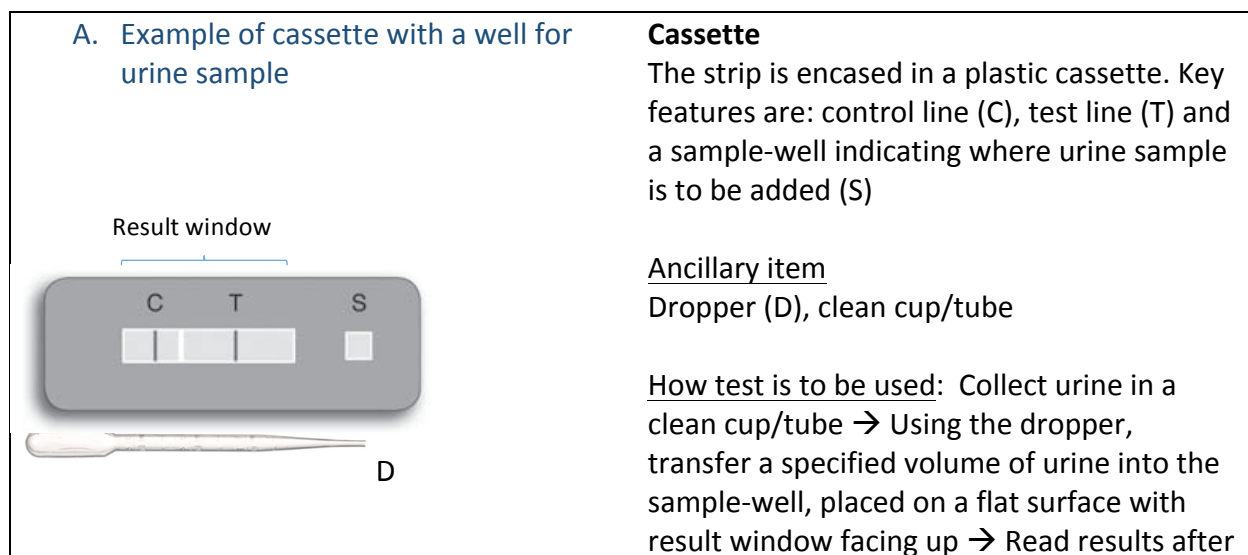
11.1 Test Format and Ancillary Items

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

11.1.1 Components of a pregnancy test

Pregnancy tests usually come in three formats: cassette-type, dipsticks or midstream test strips. Note that ancillary items such as the droppers and the urine collection cup, as shown in Figure 4, may not be included with the tests. Therefore, the procurer is recommended to determine the need for these items and include them in the requirements of the tender, as appropriate.

Figure 4. Example of the three pregnancy test formats and their usage⁸

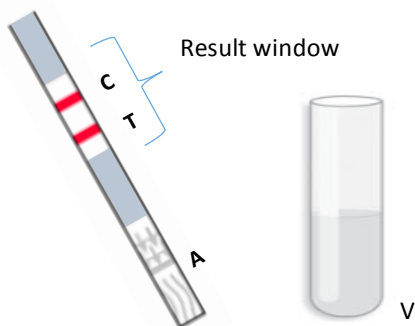


⁸ Diagrams have been adapted from Malaria rapid diagnostic test performance: Results of WHO product testing of malaria RDTs: Round 6 (2014-2015). (n.d.). Retrieved August 31, 2016, from <http://www.who.int/malaria/publications/atoz/9789241510035/en>

the specified period of time.

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

B. Example of dipstick



Dipstick

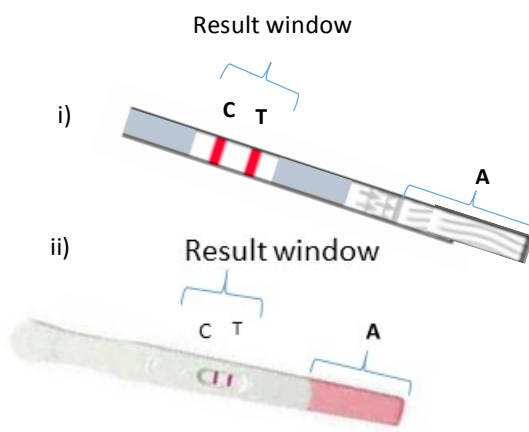
The strip is mounted on a laminated strip. Key features are: control line (C), test line (T), and absorbent pad to wick the urine (A)

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 of time for results to develop

C. Example of a midstream test strip



Midstream test strip

i) 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).

ii) Alternative format of midstream test where the dipstick is encased in plastic. Encasing prevents the urine from wetting areas other than that intended to capture and absorb urine.

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 of time for results to develop

11.1.2 The test line and control line

Self-test pregnancy tests usually have two lines: one control line and one test line (Figure 4 A, B&C). The product insert is recommended to include information on exact labeling of these lines per their orientation. Although not common in resource poor settings, some pregnancy tests may have a 'plus' sign or the word 'positive' if positive for pregnancy.

11.2 Analytical and Diagnostic Performance of Self-Test Pregnancy Tests

The specifications and test panels recommended below have been derived from literature reviews, and are based on sound scientific evidence, best practices, and high quality pregnancy test evaluations (9,17-19). Manufacturers' inclusion of these performance metrics in the COA or Technical Files will aid the decision-making process of procurers.

11.2.1 Target antigen/analyte

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

11.2.2 Recommended analytical sensitivity (also known as detection limit or cut-off)

While some pregnancy tests are more or less sensitive than others, it is recommended to use 25 mIU/ml as the criteria for analytical sensitivity (17-19); 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. If validated clinical evidence exists, the manufacturer may state the number of days after the missed period/menses that will yield a positive test result (US FDA).

11.2.3 Recommended 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 testing are: hLH300-mIU/ml, hFSH-1000 mIU/ml, hTSH-1000 mIU/mL (32).

Documents for Procurers: It is recommended that procurers request manufacturer's Certificate of Analysis containing technical specifications inclusive of analytical sensitivity and specificity. If the Certificate of Analysis does not contain this information, manufacturer may obtain this information from the technical files and provide them in a format that is easy to interpret.

Enhanced Quality Practices on Test Performance: Include a list of interfering agents and % accuracy

11.2.4 Interfering agents

Details of any substances that have been tested and shown to cause interference with test performance: 1) analyte-independent interferences caused by agents such as caffeine, glucose, hemoglobin, albumin, bilirubin and 2) analyte-dependent interferences/cross-reactivity caused by disease states, such as rheumatoid arthritis and syphilis, should be stated. Commonly used medications, such as pain relievers, antibiotics and contraceptives, should not interfere with test performance and evidence should be provided to support claims (9,10, 24).

11.2.5 Recommended % Accuracy

This value should not exceed 99%. Statements such as '100% accurate, virtually 100% accurate, nearly 100% accurate,' must always be proven by detailed clinical evidence (performance evaluation) (9)

11.3 Declared Reading Time and Stability of Results

The time period between addition of urine sample to reading of results is defined as the 'declared reading time'. Depending on the product, this time typically varies (e.g., 5, 10 or 15 minutes). As it may not be possible to read a result at an exact moment, especially in a point of care setting, manufacturers may provide this information in the form of a time range, as in minimum time to results and maximum reading time or as a recommended reading time. Time range should be included on the product label and in the package insert.

Upon the use of a pregnancy test, the test and control lines fade and change in intensity over time. The rate at which this fading takes place depends on the product/manufacturer. It is important that the manufacturer displays the 'reading window', which is the time range within which the test results should be read, on the product label and in the package insert. While there is some overlap between declared reading time and stability of results, it is important to make the user understand that beyond a certain time limit, the results should not be read or interpreted.

11.4 Shelf-Life

Shelf-life is the period of time, during which the test in its original packaging, maintains its performance characteristics under the storage conditions specified by the manufacturer (WHO). It is the responsibility of the manufacturer to ensure that all claims made regarding shelf life are supported by evidence. It is recommended that manufactures follow ISO 23640⁹ when designing their shelf-life studies.

- Recommended storage conditions and shelf life should be clearly indicated on the product label.
- Pregnancy tests are recommended to be stable for storage up to 30°C, with stability claims supported by evidence. Although submission of evidence is not always required by SRAs, the US FDA requires that supporting documents remain on file for evaluation upon request (9). Procurers of pregnancy tests are encouraged to request real-time experimental stability studies¹⁰ undertaken on batches per a prescribed protocol from manufacturers to assess heat compatibility, based on climate conditions of the region. Real time stability should be conducted over a period longer than the stated shelf life of the pregnancy test.
- Upon receipt by the procurer, the product is recommended to still have no less than 5/6th of its effective life (29).

Documents for Procurers on Shelf-Life: It is recommended that procurers request evidence of real time experimental stability studies indicating evidence for heat stability testing of the pregnancy test.

Enhanced Quality Practices for Shelf-Life:

A Transport Validation Document stating minimum and maximum transport temperatures and durations should be made available

For countries that experience high temperatures and humidity, procurers are encouraged to request supporting data demonstrating product stability up to 35-40 °C

WHO recommends heat stability testing at 35 °C and 40 °C for MRDTs as these tests may be subject to extreme temperatures during transport. Compromised performance of some

⁹ Current version is ISO 23640:2013

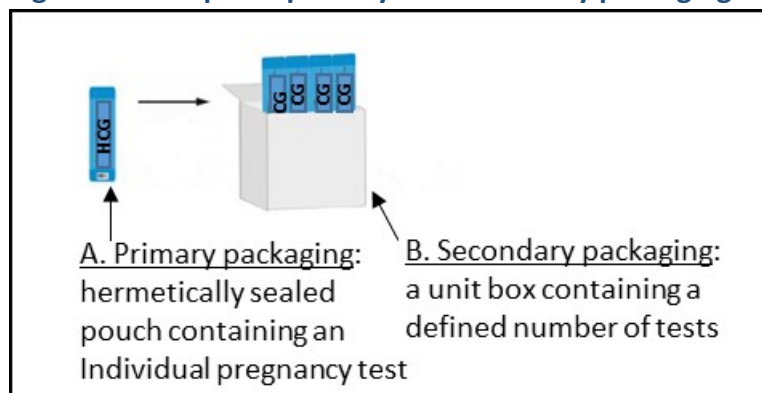
¹⁰ Accelerated stability studies are usually not sufficient to support a shelf-life claim

MRDT products exposed to high temperatures has been documented. (28). As noted earlier, the assay principle for MRDTs and pregnancy tests is the same. It is recommended that procurers request pregnancy test manufacturers to provide supporting documentation to demonstrate a heat stability profile within this recommended range if applicable.

11.5 Packaging and Kit Content

- **Primary packaging** – individually sealed pouches containing pregnancy tests (Figure 5A)
- **Secondary packaging** – a unit box containing defined number of pregnancy tests (Figure 5B)

Figure 5: Example 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 their supply chain path (i.e., from manufacturing site, through transport, storage and to point-of-use.)
- Based on WHO recommendations for MRDTs and CE guidelines for packaging, addition of desiccants inside primary packaging of pregnancy tests is strongly recommended to preserve the performance of the test (11). Please refer to [Annex S10](#) for additional details.

Enhanced Quality Practices for Packaging and Kit Content: Include humidity-indicator desiccant in each individual test pouch, in correct packaging with adequate labeling.

11.6 Recommended Labeling Requirements for Secondary Packaging (Cartons and Boxes)

The large carton containing smaller boxes, as well as the smaller boxes containing pregnancy tests, are recommended to have the label information listed below. [Annex S110](#) provides an illustration of recommended labeling for primary and secondary packaging using established symbols as per ISO 15223-1(ref).

- Name of the test
- Batch/lot number
- Expiry date
- Name and address of manufacturer (or authorized representative if applicable)
- CE marking (if applicable) accompanied by identification number of Notified Body

Enhanced Quality Practices for Labeling of Secondary Packaging:

- **Catalog number of pregnancy test**
- **Date of manufacture**
- **Recommendations for transport and storage: keep dry, keep away from sunlight/heat**
- **Clear indication of *in vitro* diagnostic status**
- **Storage/handling conditions**

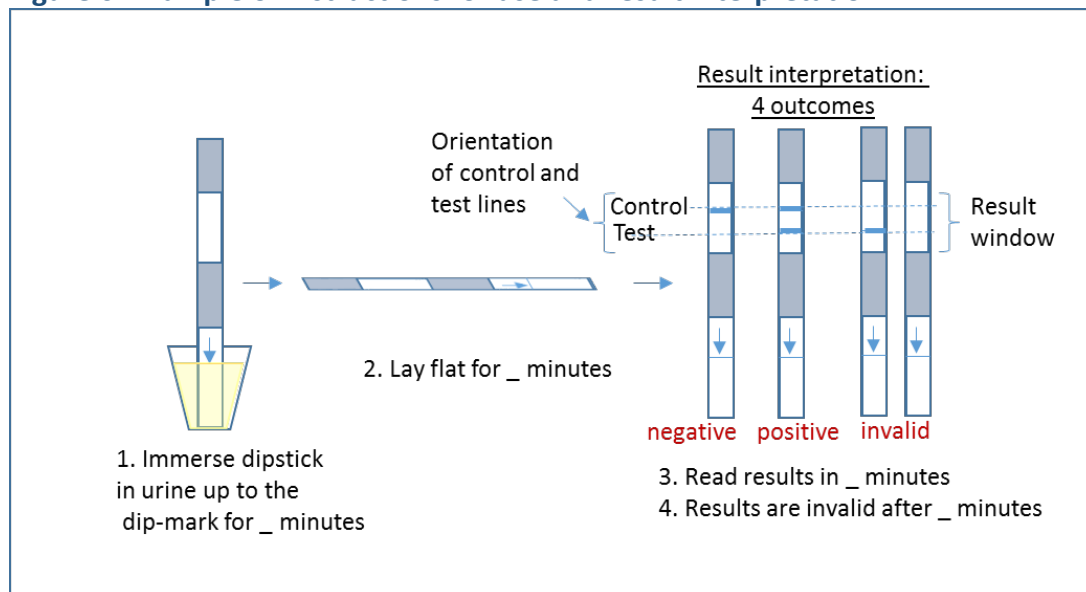
11.7 Recommended Labeling Requirements for Primary Packaging and/or Product Insert

Product information should be concise, contain clear illustrations and be easy to understand. In developing countries, most self-test pregnancy tests have this information printed directly on the primary packaging. Inclusion of this same information as a product insert (printed copy inside the pouch) is a slightly costlier alternative, but widely practiced in the developed world. At a minimum, the following label information is recommended:

- Legal name and address of legal manufacturer (or, if applicable, authorized representative)
- Batch/lot number
- Expiry date
- CE marking (if applicable) accompanied by identification number of Notified Body
- Intended use

- Performance characteristics: analytical sensitivity and specificity
- Materials: both materials provided and those required but not provided, such as the urine collection cup
- Product support contact information (i.e. for manufacturer or local agent/marketing authorization holder).
- Step-by-step instructions from collection of urine sample to reading the results. As indicated in Figure 6, it is important to specify time period required for each of the 4 steps of the test procedure.
 - Step 1: Time to keep the dipstick immersed in urine, or if using a midstream test strip, time to hold the dipstick in urine stream
 - Step 2: Time to test, flat on a surface, for the results to develop. Applicable to all 3 tests formats
 - Step 3: Time to read the results
Declared reading time (the time from adding the urine sample to reading the results; details in section 11.3): Minimum time to reading results or both minimum and maximum time to reading results should be provided by the manufacturer. Applicable to all 3 test formats.
 - Step 4: Time beyond which test results should not be read
Since the stability of the positive lines decrease over time, results should not be read beyond a certain time (see section 11.3 for details). It is recommended that manufacturer provide this time beyond which the results are not stable.
Applicable to all 3 test formats.
- Instructions for interpreting results: Figure 6 illustrates four possible result outcomes. Note: the exploratory evaluation of pregnancy tests illustrated that 'invalid results' are commonly represented only by the presence of test line turning positive; it is important to include the other invalid result option of a blank result window, which is indicative of failure of either the performance or the procedure of the test ([Annex S1](#)).

Figure 6: Example of instructions for use and result interpretation



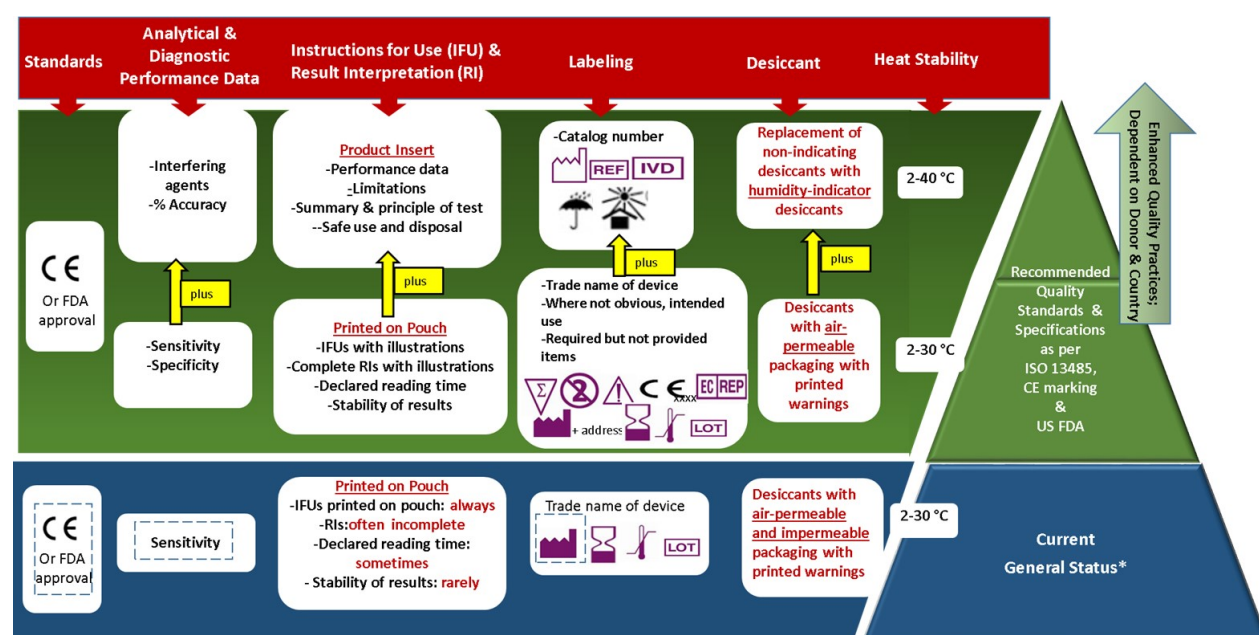
Enhanced Quality Practices for primary packaging labeling requirements, preferably as a product insert:

- Description/summary of the test
- Principle of the procedure
- Description of the procedural/reagent/sample volume control in the test
- Limitations of the procedure: notice that the test cannot be reused and should not be used past the expiration date; health conditions that can cause a false or irregular results; opportunities for false negative results; importance of adherence to instructions for use
- Known interfering agents/results from studies with interfering agents
- Instructions for use in national language (could be stapled on to the primary packaging)
- Safe use and disposal information

12 Summary of Current, Recommended and Enhanced Quality 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 quality practices, recommendations, and enhanced quality practices. The differentiation between recommendations and enhanced quality practices were made through consensus from stakeholders.

Figure 7: Summary of current, recommended and enhanced quality practices relevant to pregnancy tests¹¹



* Based on an in-house evaluation of 16 pregnancy tests; results are summarized in Annex S1
□ Indicates minimal practice, as observed with the in-house pregnancy test evaluation.

¹¹ Please refer to [Annex S10](#) for definitions of the symbols

13 Pre- and Post-Shipment Testing for Analytical Performance

Goal: to develop work instructions for QA of specificity, sensitivity, accuracy, and package seal integrity

Intended audience: any laboratory interested in evaluating pregnancy tests (i.e., Africa, Asia, and South America)

Sources: Information obtained from publicly available sources, and not from proprietary sources (i.e., manufacturers / suppliers)

Content:

- Sampling plans / criteria for different scenarios:
- product qualification
- pre-shipment testing
- post-shipment testing
- stability study evaluations

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31. Manual for procurement of diagnostic and related laboratory equipment

32 Accutest

33.http://apps.who.int/prequal/info_applicants/Guidelines/2014/ANNEX-6_SRA-Guide_DRAFT.pdf

15 Annexes

15.1 Annex S1: Exploratory analysis of pregnancy tests purchased from the developing world to identify prevailing quality gaps

To gain a preliminary understanding of quality status of pregnancy tests in the developing world, an in-house assessment of 16 pregnancy tests collected over a 2-year period, from a mix of low- and middle-income countries in the African region was carried out. These pregnancy tests were purchased from pharmacies as individually packaged items. These tests were benchmarked against 27 relevant criteria compiled from normative documents that have been used to compile this guidance document.

Table 1: Prevailing quality status of 16 pregnancy tests from developing countries

Criteria used for benchmarking	Number of conformant tests (n=16)	% of conformant tests
International quality standards		
Indicates a accepted quality mark (ISO 13485, CE-marking or US FDA clearance)	7	44%
Of those carrying a CE marking, products that indicate a conformant CE marking symbol	3	43%
Of those carrying a CE marking, products that indicate a Notified Body number	5	71%
Packaging/labeling/insert information		
Indication of a lot number	15	94%
Indication of a manufacturer	14	88%
Indication of a contact information of a manufacturer	7	44%
Indication of date of manufacture	7	44%
Indication of date of expiry	15	94%
Indication of temperature limitations	15	94%
Indication of number of units/pkg	8	50%
Indication of intended use	13	81%
Indication of IVD status	12	75%
Indication of 'do not reuse'	5	31%
Inclusion of any form of desiccants	ND	ND
Safety warnings	1	6%
Disposal instructions	0	0%
Indication of instructions for use	15	94%
Inclusion of illustrations for instructions for use	14	88%
Indication of 'declared reading time'	12	75%
Indication of stability of test result	6	38%
Indication of result interpretation	15	94%
Indication of incomplete result interpretation conditions (most commonly observed is exclusion of a blank window outcome, which renders the test invalid)	7	44%
Test performance criteria		
Indication of analytical sensitivity of test	2	13%
Indication of analytical specificity of test	0	0%
Indication of accuracy of test	1	6%
Indication of limitations of test	0	0%
Indication of interfering agents	0	0%

15.2 Annex S2: Quality approval of other Stringent Regulatory Authorities (SRA) for consideration in the procurement of self-test pregnancy tests

SRA is a regulatory authority (in case of the EU both EMEA and national competent authorities are included) which is (a) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH (as specified on its website: www.ich.org); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic, Health Canada and WHO (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time) (33).

Country	Institution	Website
Australia	Therapeutic Goods Administration	https://www.tga.gov.au/
Canada	Health Canada	http://www.hc-sc.gc.ca/index-eng.php
Europe	European Medicines Agency ¹²	http://www.ema.europa.eu/ema/
Iceland	Iceland Medicines Agency	http://www.ima.is/ima/about_ima/
Japan	Pharmaceutical and Medical Device Agency	https://www.pmda.go.jp/english/
Norway	Norwegian Medicines Agency	http://www.legemiddelverket.no/English/about-norwegian-medicines-agency/Sider/default.aspx
Switzerland	Swiss Agency for Therapeutic Goods	https://www.swissmedic.ch/index.html?lang=en
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
United	Food and Drug	http://www.fda.gov/

¹² Includes the following European Member States: Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom

For links to individual European country websites please refer to :
<https://www.ispor.org/HTARoadMaps/HealthAuthorityEurope.asp> and <https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/global-regulatory-authority-websites>

15.3 Annex S3: Checklist to be used for quality assurance of pregnancy tests by procurers

Procurers may use this checklist to verify manufacturer's compliance with recommended standards as part of the product selection process. Items shaded in green are those listed under 'enhanced quality practices', and therefore, are recommended to adopt as the country regulatory infrastructure improves or at procurer's discretion based on organizational risk analysis.

Commercial name of pregnancy test				
Manufacturer				
Lot number				
Date of assessment				
Name of assessor				
	Yes	No	NA	Comments/problems
List of Documents to be Provided by Manufacturer				
1. ISO 13485 certification				
2. CE Declaration of Conformity (if applicable)				
3. FDA 510 Clearance Status (if applicable)				
4. Product Stability Documentation				
5. Certificate of Analysis				
6. Technical File				
7. Test results from independent Quality Control Tests for pre- and post-shipment testing (if applicable)				
Quality Standards				
8. Manufacturer compliant with ISO 13485: _____				
9. Compliant with a different standard (state the standard under comments)				
10. Product is CE marked				
11. CE mark is accompanied by the identification number of the notified body				
12. CE-marking is conformant				
13. Product is US FDA regulated				
14. Product is regulated by another Stringent Regulatory Authority (state the authority in the comments column)				
Labeling/Marking on Secondary Packaging (Carton and Boxes)				
15. Commercial name of the test included				

16. Batch/lot number included				
17. Expiry date/shelf-life included				
18. Name and address of manufacturer included				
19. Contact details of a 'local authorized person' included (if applicable)				
20. CE-marking is conformant				
21. Identification number of notified body is present				
22. Catalog number included				
23. Manufacturing date included				
24. Storage/handling conditions are included				
25. Clear indication of in vitro diagnostic status included				
Packaging and Kit Content				
26. The secondary packaging/box containing tests, is in good condition and are not torn, wet or with illegible writing				
27. Pregnancy tests are in individually sealed pouches and are intact				
28. Shelf-life indicated on the product label				
29. The product has not exceeded 1/6 th of its effective shelf-life				
30. The tests are stable up to 30 °C				
31. Recommend storage conditions indicated on the product label				
32. The tests are stable up to 40 °C (if required by country setting) and supporting documentation is available)				
Test format and ancillary items				
33. If the test is in <u>cassette</u> format: -The control and test lines are clearly marked on the cassettes -A device for transfer of urine to cassette is included				
34. Desiccant is present in each individually sealed pouch containing a pregnancy test				
35. Desiccant is packaged in material that is permeable to air				
36. Desiccant packaging has adequate labeling				

37. Desiccant is of humidity-indicator type				
Product Information for Users/Product Insert				
38. Product information is included (printed or as a product insert)				
39. The product information is for the correct product				
40. Instructions for use is provided				
41. Declared reading time is provided (time to read results)				
42. Interpretation of results is explained with illustrations displaying 4 possible outcomes				
43. Materials provided and materials required but not provided is included				
44. Analytical performance information is included (sensitivity and specificity)				
45. Stated analytical sensitivity is 25 mIU/mL ¹³ and/or				
46. Sensitivity is stated in number of days following the days of missed period/menses				
47. Specificity results indicated (reactivity with FSH, TSH, LH)				
48. Where not obvious, intended use, 'for pregnancy testing', is clearly indicated				
49. Local product support contact details included				
50. Additional analytical performance info (accuracy and interfering agents) is included				
51. % Accuracy is <99%				
52. Interference substances indicated				
53. A summary of the test is included				
54. Principle of the procedure is included				
55. Quality control measures are included				
56. Product information is in national language				
57. Disposal instructions included				
58. Limitations of the procedure are included:				

¹³ Several studies have demonstrated that by the day of the expected period, 98% of women who have conceived would have a urinary concentration of hCG \geq 25 mIU/mL (references).

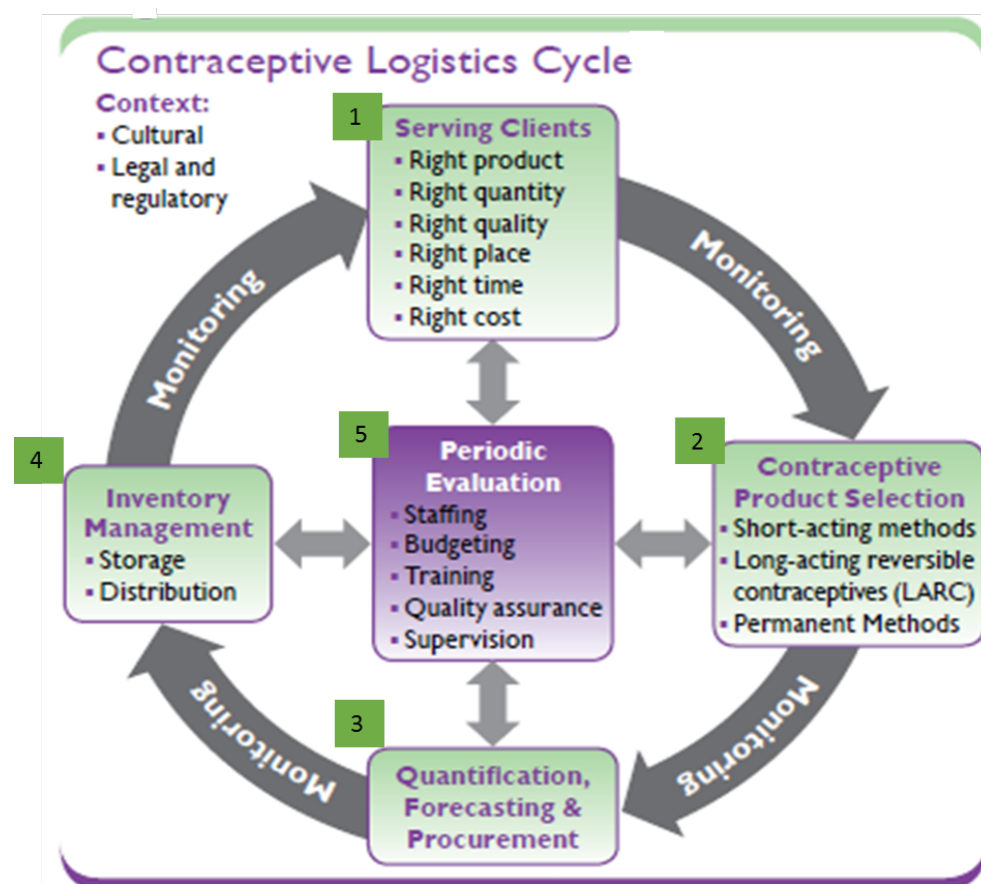
<ul style="list-style-type: none">-The test cannot be reused-Do not use past the expiration date-Certain health conditions can cause false positive result-The instructions and testing procedure should be followed precisely for accurate results-A false negative result could result if the urine is too dilute or with very early stage pregnancy. If pregnancy is strongly suspected, repeat test with first-morning urine				

15.4 Annex S4: List of recommended procurement guidance documents on procurement process and supply chain management

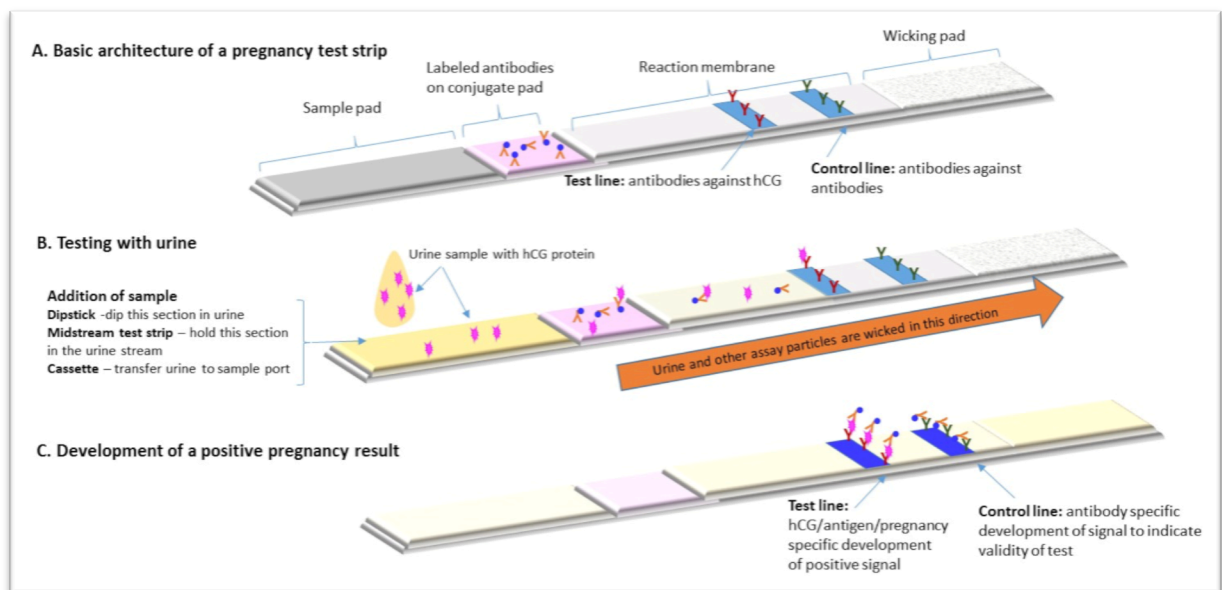
1. A Model Quality Assurance System For Procurement Agencies; WHO, UNICEF, UNDP, UNFPA & World Bank.
<http://www.who.int/medicines/publications/ModelQualityAssurance.pdf>
2. Guidelines for the Storage of Essential Medicines and Health Commodities;
http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/GuidStorEsse_Pock.pdf
3. Guidelines for Warehousing Health Commodities, USIAID Deliver, March 2014.
http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/GuidWareHealComm.pdf
4. Managing Access to Medicines and Health Technologies (MDS-3).
<http://www.msh.org/sites/msh.org/files/mds3-fm-revised-nov2012.pdf>
5. Manual for procurement of diagnostics and related laboratory items and equipment.
http://www.who.int/diagnostics_laboratory/procurement/130627_manual_for_procurement_of_diagnostics-001-june2013.pdf
6. Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies, PATH.
http://www.path.org/publications/files/RH_proc_cap_toolkit_v2.pdf
7. The Logistics Handbook: A Practical Guide for the Supply Chain Management of Health Commodities.
https://www.k4health.org/sites/default/files/LogiHand_0.pdf
www.deliver.jsi.com

15.5 Annex S5: Contraceptive Logistics Cycle

Illustrated below is a conceptual framework, adapted by The Partnership for Maternal, Newborn and Child Health, for contraceptive supply chain management. Improving access to family planning requires a robust supply chain constituting of 1) Contraceptive Product Selection 2) Quantification, Forecasting and Procurement 3) Inventory management and 4) Periodic Evaluation, with continuous monitoring (Rectangles 2-5). These components should strive to 'Serve Client' by incorporating the "Six Rights": 1) Right Product 2) Right Quantity 3) Right Quality 4) Right Place 5) Right time and 6) Right Cost (Rectangle 1).



15.6 Annex S6: Assay principle of self-test pregnancy test



A. Basic architecture of a pregnancy test strip: a typical rapid tests consist of several components adhered to an inert backing 2) sample pad for the application of sample 2) conjugate pad where dried labeled antibodies are deposited 3) reaction membrane with test line carrying pregnancy specific antibodies and a control line carrying antibodies capable of recognizing antibodies 4) wicking pad is designed to draw the sample across the reaction membrane. **B. Testing with urine:** Upon addition of urine, the liquid moves due to capillary action, hydrating labeled antibodies and enabling their migration across the membrane towards the test and control strips. During this process, the hCG proteins bind the labeled antibodies as well as those on the test strip as they are specific for hCG. **C. Development of a positive result:** Recruitment of labeled antibodies to the test line occurs dependent of hCG, and the accumulation of these labeled antibodies result in the development of a positive line. Recruitment of labeled antibodies to the control line is independent of hCG, and results in the development of a control line indicating that the reagents and the assay has operated as expected.

15.7 Annex S7. Use of pregnancy tests in family planning for optimal effectiveness and efficiency

Prior to initiation of hormonal contraceptives and intra uterine devices (IUD), pregnancy has to be ruled out to avoid possible harm to the fetus. Family planning providers currently use the pregnancy checklist and pregnancy tests to rule out pregnancy among clients who are not menstruating at the time of the visit. While each approach has its advantages and limitations, both tools have to be used under certain circumstances to rule out pregnancy. Currently, as there is no guidance on the usage of these tools to complement one another, FHI 360 is in the process of developing a protocol to rule out pregnancy in three mutually exclusive categories: 1) Amenorrheic (e.g., due to lactation or recent use of progesting-only injectable contraception) 2. Between menses 3) has missed her period.

	Hormonal Methods	Intrauterine Devices (IUDs)
Amenorrhea	Take history using pregnancy checklist. • If pregnancy ruled out, provide method. • If pregnancy not ruled out, use pregnancy test if available. • If the test is negative (or not available), provide the method, but schedule a follow-up pregnancy test in 3-4 weeks.	Take history using pregnancy checklist. • If pregnancy ruled out, provide method. • If pregnancy not ruled out, a pregnancy test should be used. If negative, advise woman to use a barrier method or abstain for 3-4 weeks, then repeat pregnancy test. • If the test is still negative, provide an IUD.
Between Menses	Do not use pregnancy test (it is too early for it to be effective). Take history using pregnancy checklist. • If pregnancy ruled out, provide method. • If pregnancy not ruled out, do not provide implant, but "Quick Start" (explained below) is acceptable for pills and injectables (pregnancy assessment recommended if next menses are delayed).	Do not use pregnancy test (it is too early for it to be effective). Take history using pregnancy checklist. • If pregnancy ruled out, provide method. • If pregnancy not ruled out, do not provide IUD. Advise woman to use barrier method or abstain and return for IUD insertion within 12 days of onset of next menses.
Missed Period	History not necessary; use pregnancy test. • If using highly sensitive pregnancy test (e.g., 25 mIU/ml) and it is negative, provide desired method. • If using test with lower sensitivity (e.g., 50 mIU/ml) and it is negative, wait and reassess at least 10 days after expected date of menses. If test is still negative, provide desired method.	

→ Recommend usage of pregnancy test
 → Avoid usage of pregnancy test

How to be Reasonably Sure a Client is Not Pregnant

Ask the client questions 1–6. As soon as the client answers YES to any question, stop, and follow the instructions.

NO	1. Did your last menstrual period start within the past 7 days?*	YES
NO	2. Have you abstained from sexual intercourse since your last menstrual period or delivery?	YES
NO	3. Have you been using a reliable contraceptive method consistently and correctly since your last menstrual period or delivery?	YES
NO	4. Have you had a baby in the last 4 weeks?	YES
NO	5. Did you have a baby less than 6 months ago, are you fully or nearly fully breastfeeding, and have you had no menstrual period since then?	YES
NO	6. Have you had a miscarriage or abortion in the past 7 days?*	YES

* If the client is planning to use an IUD, the 7 day window is expanded to 12 days.

If the client answered NO to all of the questions, pregnancy cannot be ruled out using the checklist.† Rule out pregnancy by other means. Give her condoms to use until pregnancy can be ruled out.

If the client answered YES to at least one of the questions and she is free of signs or symptoms of pregnancy, you can be reasonably sure she is not pregnant.

† If the client is concerned about an unintended pregnancy, offer emergency contraception if more appropriate and not since last menses occurred within the last 5 days.



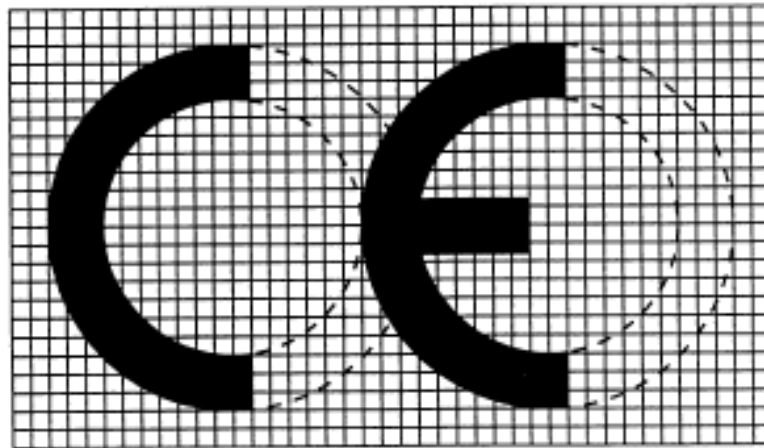
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The pregnancy checklist

This job aid was created in 1990 by FHI 360, and is designed to rule out pregnancy with six simple criteria presented in question form. If a woman answers 'yes' to any of the six questions, then pregnancy can be ruled out with reasonable degree of certainty. It is important to note that this job aid cannot be used to rule out pregnancy among amenorrheic women.

15.8 Annex S8: CE marking of conformity as specified in the directive 98/79/EC of the European Parliament and of the Council

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



- If the marking is reduced or enlarged the proportions given in the above graduated drawing must be respected,
- the various components of the CE marking must have substantially the same vertical dimension, which may not be less than 5 mm. This minimum dimension may be waived for small-scale devices.

15.9 Annex S9: A Screenshot of FDA Premarket Notifications (510(k) clearance webpage that will direct procurers to identify the 510(k) clearance status of the pregnancy test being evaluated confirm that the manufacturer holds 510 (k) clearance by visiting the 510(k) premarket notification site

(US FDA home page → Medical Devices Tab → Medical Device Database (under Tools & Resources) → select the 'Premarket Notifications (510(k))' database → type 'LCX' under 'product code' → Search for the product of interest)

Current website URL: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>

The screenshot shows the FDA's Premarket Notifications (510(k)) database search interface. The page is titled "510(k) Premarket Notification" and includes a navigation bar with links to Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, and Animal. A sidebar on the left contains a "510(k) Premarket Notification" section with a brief description of the submission process and a "Learn more..." link. The main content area features a "Search Database" form with various search criteria: 510K Number, Center, Applicant Name, Device Name, Panel, Decision, Decision Date, and Sort by. There are also checkboxes for "Product Code", "Combination Products", "Cleared/Approved In Vitro Products", "Redacted FOIA 510(k)", "Third Party Reviewed", and "Clinical Trials". A "Quick Search" button is located at the bottom of the form. The footer of the page includes the FDA logo and links to Accessibility, Contact FDA, Careers, FDA Basics, FOIA, and No FEAR Act.

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

U.S. Department of Health & Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal

510(k) Premarket Notification

FDA Home Medical Devices Databases

A 510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR §807.62(a)(3)) that is not subject to premarket approval.
[Learn more...](#)

Search Database Help Download Files

510K Number Type [Product Code](#)

Center

Applicant Name

Device Name

Panel

Decision

Decision Date to

Sort by

[Quick Search](#) [Clear Form](#) [Search](#)

Page Last Updated: 10/10/2016
Note: If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#)

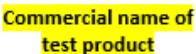
















FDA Accessibility Contact FDA Careers FDA Basics FOIA No FEAR Act

15.10 Annex S10: Desiccants and their recommended usage

Item	Purpose of use/criteria to meet	Recommendation
Desiccant	<ul style="list-style-type: none"> Protects the test from exposure to humidity Humidity has been shown to decrease analytical performance of RDTs 	Recommended
Desiccant with humidity indicator	<ul style="list-style-type: none"> Indicates if the 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 due to demonstrated adverse health issues 	Enhanced quality practices
Material of desiccant package should be permeable to air	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Aids safe and easy visualization of color change in desiccant 	Enhanced quality practice
Warning message indicating not to eat desiccant	<ul style="list-style-type: none"> Desiccant could be harmful if swallowed and should be kept away from children 	Recommended
Sachet with desiccant should carry instructions for: interpretation of color changes <ul style="list-style-type: none"> Steps to follow if test is exposed to humidity Safe disposal of desiccants 	<ul style="list-style-type: none"> Enables appropriate decision making for accurate and safe outcomes 	Enhanced quality practice

15.11 Annex S11: Example of recommended labeling on primary and secondary packaging ^(25,26)

For the safe and effective use of medical devices, ISO 15223-1:2012 has identified the symbols used below for use in labelling, in combination with applicable ISO standards. This information is provided as a source of information for interpreting the meanings of symbols as they appear in various packaging, as well as enhanced quality practices to aspire towards.

Information, symbols and their definitions		
 Commercial name of test product	 CE logo	 Do not reuse
 Catalog number	 Identification number of the notified body	 Consult instructions for use
 Batch number or lot number	 Name and address of authorized representative in the European Community	 Temperature limitations
 Manufacturer	 Caution, consult accompanying documents	 In vitro diagnostic medical device
 Date of manufacture	 Keep dry	 Contains sufficient for <n> tests
 Use by YYYY-MM-DD or YYYY-MM	 Keep away from sunlight/heat	Content and required but not provided items