ETHIOPIAN FOOD AND DRUG AUTHORITY

GUIDELINE FOR REGISTRATION REQUIREMENTS OF IN VITRO DIAGNOSTIC MEDICAL DEVICES

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ACRONYMS

EFDA	Ethiopian Food and Drugs Administration
CAPA	Corrective Action and Preventive Action
CSDT	Common Submission Dossier Template
EU	European Union
GMDN	Global Medical Device Nomenclature
IMDRF	International Medical Device Regulators Forum
MDUFA	Medical Device User Fee Amendments
NB	Notified Body
SUD	Single Use Device
TGA	Therapeutic Goods Administration - Australia
USFDA	United States Food and Drug Administration
IRB	Institutional Review Board
IVD	In Vitro Diagnostic Devices
Non-IVD	Non-In Vitro Diagnostic Devices

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- Daniel Takele (BSc in Biomedical Engineering), Medical Device Registration Dossier Assessor, currently head of Medical device Evaluation and Marketing Authorization department at EFDA.
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1. INTRODUCTION

Ethiopian Food and Drugs Authority is the national regulatory authority responsible to regulate food, medicines, medical devices, cosmetics and other health products mandated by Ethiopian Food and Medicine Administration Proclamation No: 1112/19. The regulated products including medical devices follow various regulatory processes from their premarket assessment to post-market control in order to protect the public health by ensuring the safety, performance and quality of the products. One of the EFDA's premarket assessments is to evaluate the product dossiers of the medical devices. This guideline is therefore intended to provide a comprehensive and well-organized structure for premarket In Vitro Diagnostic Medical device submissions that assists the manufacturers to submit uniform registration dossier when registering their products.

This document provides harmonized, modular, format for use when filing In Vitro Diagnostic medical device submissions to EFDA for market authorization.

The outline of documentation is to support a smooth documentation process. It remains the applicant's responsibility to ensure all regulatory requirements are met, and that clear and transparent evidence of conformity to these requirements are provided.

Manufacturers of all classes of medical device are expected to demonstrate conformity of the device to the Essential Principles of Safety and Performance (EPSP) through collection and examination of evidence of conformity in technical documentation that shows how each medical device was developed, designed and manufactured together with the descriptions and explanations necessary to understand the manufacturer's determination with respect to such conformity. This technical documentation must be updated as necessary to reflect the current status, specification and configuration of the device.

The evidence of conformity of medical device to the EPSP must be compiled and submitted as per the requirements set in this guideline for the purpose of conformity assessment and submission of application for medical device registration. The compiled documents need to be kept in the premise for audit or inspection purposes.

The EFDA will monitor the use of these structures and work to continually improve the documents at appropriate intervals based on sufficient use and experience.

2. SCOPE

This Guideline is applicable for registration of In-vitro diagnostic Medical devices. This guideline does not apply to medical devices listed under the "*Guideline for Premarket Notification of Low Risk Medical Devices*". The Medical devices other than In Vitro diagnostic medical devices are also not in the scope of this guideline as these devices have separate guideline stipulating requirements for their registration.

3. PURPOSE

The purpose of this guideline is to provide guidance on requirements for In Vitro Diagnostic medical devices registration in Ethiopia.

4. DEFINITIONS

Sponsor- Means any individual, company, institution or organization which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation;

Single-use device- Means a device that is intended to be used on one individual during a single procedure;

Performance- Means the ability of a device to achieve its intended purpose as stated by the manufacturer;

Compatibility- Means the ability of a device, including software, when used together with one or more other devices in accordance with its intended purpose, to: (a) perform without losing or compromising the ability to perform as intended, and/or (b) integrate and/or operate without the need for modification or adaption of any part of the combined devices, and/or (c) be used together without conflict/interference or adverse reaction.

Interoperability- Means the ability of two or more devices, including software, from the same manufacturer or from different manufacturers, to: (a) exchange information and use the information that has been exchanged for the correct execution of a specified function without

changing the content of the data, and/or (b) communicate with each other, and/or (c) work together as intended.

Cyber-security: Means a state where information and systems are protected from unauthorized activities, such as access, use, disclosure, disruption, modification, or destruction to a degree that the related risks to confidentiality, integrity, and availability are maintained at an acceptable level throughout the life cycle.

Reprocessing- Means a process carried out on a used device in order to allow its safe reuse including cleaning, disinfection, sterilization and related procedures, as well as testing and restoring the technical and functional safety of the used device;

Conformity assessment- Means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled;

CE marking of conformity or 'CE marking'- Means a marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in the European Union Medical Devices Regulation and other applicable Union harmonization legislation providing for its affixing;

Clinical evaluation- Means a systematic and planned process to continuously generate, collect, analyze and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer;

Clinical investigation- Means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device;

Clinical data- Means information concerning safety or performance that is generated from the use of a device and is sourced from the following:

- clinical investigation(s) of the device concerned,
- clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,
- reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,
- clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up;

Clinical evidence- Means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer;

Informed consent- Means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorization or agreement from their legally designated representative to include them in the clinical investigation;

Adverse event- Means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device;

Submission – Means a regulatory submission can be any type of information related to a medical device regulatory process. This includes but is not limited to a request for approval/authorization to market a device, any communications relating to the original submission, and any request for modification to an existing approval.

Medical Devices other than In Vitro Diagnostic Devices: Means all medical devices including Active implantable devices, Anesthetic and respiratory devices, Dental devices, Electro mechanical medical devices, Hospital hardware, Non-active implantable devices, Ophthalmic and optical devices, Reusable devices, Single use devices, Assistive products for persons with disability, Diagnostic and therapeutic radiation devices, Complementary therapy devices, and Biological-derived devices that do not take human samples and perform in vitro analysis for screening, diagnosis or monitoring of diseases.

In vitro diagnostic devices: Means reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.

Authority- Means Ethiopian Food and Drug Authority

5. GENERAL GUIDANCE AND PRINCIPLES

The content of this Guideline should be read in conjunction with relevant information described in other existing International Medical Devices Regulators Forum (IMDRF) reference documents and WHO IVD prequalification product dossier requirements.

The quality and performance of the intended product to be registered should not be inferior to the available options.

Alternate approaches to the principles and practices described in this Guideline may be acceptable provided they are supported by adequate scientific justification. It is important to note that the Authority may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, performance, and quality of a medical device prior to and after approval.

General format and guidance for preparation of dossiers

Well-organized and compiled documents will facilitate the evaluation process and decrease the delay in the screening time. In contrast, poorly compiled documents may lead to unnecessary loss of time, both for the applicant and the Authority. Therefore, documents should have unambiguous contents: title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check.

Formats of all the files to be submitted:

1. Paper size is A4; top, bottom, header, and footer margins are 12.5 mm; left and right margins are 25mm
2. Single-spaced paragraphs
3. Times New Roman font, 12-point; letter space 0%.
4. The weight of the font should be legible when copied.
5. The attached data and documents should appear in the English language.
6. Any abbreviations should be clearly defined.

Applications submitted for registration will be screened chronologically by the date of submission to the Authority, and the applicant will be notified of the evaluation results.

Some products are given assessment priority and they are listed in the “Medical Device Fast-track Directive”.

A request to add supplemental materials must be submitted within six months of being notified of missing elements and/or clarification. If the supplemental submission is not implemented within that time period, urge to be supplemented within 15 days shall follow.

If the supplemental document is not submitted within the urge period, or the contents of the replenishment is inappropriate, the speculation shall be clarified and the document shall be returned and/or rejected. However, if the applicant calls for an extension, the submission period shall be determined based on the speculation.

The agent or the manufacturer should appoint a technical person who is able to understand this and related guidelines of the Authority, who is familiar with the registration process of the products, and who can freely communicate with the assessors should clarification be needed (product-related or administrative) on queries raised by the Authority.

The Authority will not accept applications for registration by different applicants or local agents for the same product manufactured by the same manufacturer and/or subsidiaries of one manufacturer.

If the manufacturer of a medical device has one or more subsidiaries, the applicant is responsible for submitting the technical documents of each specific product under registration from each of the subsidiaries and/or from the site where the file is kept.

If the medical device use accessory and/or consumable (such as reagents, controls, etc.) which is manufactured by a company‘s subsidiary, the free sale certificate should indicate the same and/or a separate free sale certificate should be a part of the document.

If the medical device use accessory and/or consumable (such as reagents, controls, etc.) which is manufactured by an independent manufacturer, information regarding the manufacturer and the technical documents should be submitted. The authority will review on a case-by-case basis.

A medical device that an applicant has registered with the USFDA, Health Canada, European Union, Ministry of Health, Labour and Welfare (Japan), Therapeutic Goods Administration (Australia), or WHO Prequalification Programme is considered to be registered with Stringent Regulatory Authority approved devices registration procedures.

All the required documents should be attached at its respective attachment spaces in PDF format.

The application shall be made online through the Authority's regulated products registration platform (www.eris.efda.gov.et) after obtaining the username and password from the concerned authorized person of the Registration department of the Authority.

6. PRODUCT DOSSIER CLARITY AND COMPLETENESS

Applicants shall submit all necessary sections of a product dossier, identified in this guideline.

Not providing the required information may result in the Authority not accepting the dossier, significant delays in the assessment process, or cancellation of the registration request.

Manufacturers should make every effort to ensure that their product dossier is clear and well-organized. Poorly prepared dossiers are an obstacle to efficient market authorization assessment and may be rejected without full review.

Do not duplicate files, even if it is possible to include the same evidence under multiple subheadings. Provide the evidence under one appropriate subheading and then make specific references (including both section and page numbers) to that material in any subsequent sections that appear relevant. Be specific: references to specific sections or pages of a document should be provided when possible.

7. APPLICABILITY OF SUPPORTING EVIDENCE TO THE PRODUCT UNDER REVIEW

The manufacturer shall carry out relevant investigations to support the intended use, such as analytical and clinical sensitivity and specificity, accuracy, repeatability, reproducibility, linearity, detection limits, and traceability, as appropriate. In addition, the Authority require investigations to assess the potential effects of interfering factors and claims of reagent and product stability. Studies in support of the intended use should consider the intended user and the intended setting of use.

The manufacturer shall provide the appropriate technical specifications and the minimum performance requirements that shall be met by a product to ensure that it is safe and performs optimally.

The analytical and clinical performance characteristics described in chapters 3 and 4 of this guideline may not necessarily apply to all types of products submitted for registration assessment.

For each performance study submitted in a product dossier, the following shall be provided:

- **Study Description**: A description of the study that includes information to facilitate record traceability: study identifier, product identifier (for example, lot numbers), IFU version used, the date of initiation and the date of completion. All data shall be clearly labelled, and clearly linked to the study report.
- **Study summary**: A summary of the study findings including a conclusion that clarifies how the study objectives have been met
- **Full study protocol and report**: The study protocol and full report, which incorporates at a minimum, the following information:
    - study objectives, study design, the methodology used and data collected the site(s) where the study was performed (for example, manufacturers R&D laboratory, hospital laboratory, health care clinic)
    - operator(s) of the assay
    - the reference standard/method, if applicable
    - specimen acceptance/selection criteria, specimen characterisation
    - specimen type(s) (e.g. serum, plasma, finger stick whole blood, venous whole blood) and numbers of each type
    - actual test result summaries with their acceptance criteria and not just pass/fail statements
    - results that are reported in sufficient detail to allow the detection of potential differences in performance between the conditions being investigated (e.g. depending on the product this might require the use of either a semi-quantitative scoring system or a calibrated, graduated colour chart to record line intensity)
    - the numbers of invalid tests observed
    - photographs of all test results, wherever possible
    - details of statistical methods, estimations and calculations applied
    - the study conclusion

- when performed by a party other than the manufacturer, details of this third party and the relationship to the manufacturer as well as copy of the contract between the manufacturer and the third party identifying roles and responsibilities of each party

CHAPTER ONE

ADMINISTRATIVE

1.1. Cover Letter

The cover letter should state applicant (Local agent), Manufacturer and License holder and/or their authorized representative name and full address.

It should also state the type of registration (application), the common name of the device, device trade name or proprietary name (both of the base device and a new name if one is given to the new version/model of the device) and include the purpose of the application.

The cover letter should be stamped and signed by a person authorized by the applicant.

1.2. Agency Agreement

The local agent/representative and the license holder shall have an agreement of distribution as per the requirements set in Medical device Marketing Authorization Directive.

1.3. Evidence for registration application fee

Each application should be accompanied by a relevant service fee for registration.
Applicants are advised to consult the current rates of service fees regulation of the authority for the amount to be paid for application and contact the authority for details of mode of payment.

1.4. Quality Management System, Full Quality System

The Manufacturer shall have valid and genuine certificates confirming the implementation of good quality management system in the device's production process.

One of these certificates to be considered is ISO 13485 certificate in case it is issued by another Notified Body or registrar, CE full quality system certificates (QMS and annex II.3 MDD) covering the scope of products when issued by another Notified Body.

1.5. Good Manufacturing Practice (GMP) Certificates

For applicable high-risk medical devices, the copy of valid Certificate of compliance to Medical device Good Manufacturing Practice shall be provided.

1.6. Free Sale Certificate/Certificate of Marketing Authorization

Certificate issued by the National Regulatory Authority where the medical device is marketable, attesting that the device is marketable, without any restriction at their jurisdiction shall be submitted. This certificate shall indicate the name and full address of the manufacturer, the name(s) of the device(s) (with model if applicable) and explains whether the products are freely sold in the country of origin; if not, the reasons thereof should be clearly stated with appropriate justification. If the manufacturer of the medical device has subsidiaries, a free sale certificate should indicate the name and address of the subsidiaries with the name of the device they manufacture, and/or a separate free sale certificate should be submitted for each subsidiary. The certificate should be original, and valid.

In this section, the manufacturer shall provide (if applicable):

- List the National Regulatory Authorities that have provided current regulatory approval for the supply of this product in their country/region of authority
- Provide details of the type of regulatory approval obtained from each National Regulatory Authority
- Provide current evidence of the regulatory approval, such as certificates provided by the National Regulatory Authority.
    - The evidence should clearly show that the product under assessment falls within the scope of the submitted regulatory approval.
    - Copies can be certified by a notary public. The manufacturer may be asked to present the original copy at any time.
- Information relating to export-only regulatory approvals should be clearly identifiable as export-only approvals.

1.7. Declarations of Conformity

As part of the conformity assessment procedures, the manufacturer of a medical device is required to make a Declaration of Conformity that declares that the device complies with:

a) The applicable provisions of the Essential Principles/Requirements

b) The classification rules

c) Generic name, trade name and models (if applicable) of the device(s).

d) An appropriate conformity assessment procedure

The declaration must include the following information:

- Date from which the Declaration of Conformity is valid;
- Name and address of the device manufacturer; and,
- The name, position, and signature of the responsible person who has been authorized to complete the Declaration of Conformity on behalf of the manufacturer.

CHAPTER TWO

SUBMISSION CONTEXT

2.1. General Summary of Submission

a) Statement of the device type (e.g. Tacrolimus test system, blood specimen collection device, calibrator) and name (e.g. trade name, proprietary name), its general purpose, and a high-level summary of key supporting evidence (i.e. studies that are unique to the risks of this device type)

b) Summary of submission, including

i. The type of submission (e.g. new, amendment, change of existing application, renewal);

ii. Any high-level background information or unusual details that the manufacturer wishes to highlight in relation to the device, its history or relation to other approved devices or previous submissions (provides context to submission).

2.2. Device Description

2.2.1. Comprehensive Device Description and Principle of Operation

a) A general description of the device, including:

i. A statement of the device name.

ii. What does it detect?

iii. Who uses it and for what? (high level statement)

iv. Where to use it? (Places/environment where the device is intended to be used)\

v. General description of the principle of the assay method or instrument principles of operation

vi. Description of the components (e.g. reagents, assay controls and calibrators) and where appropriate, a description of the reactive ingredients of relevant components (such as antibodies, antigens, nucleic acid primers).

vii. If applicable, labelled pictorial representation (diagrams, photos, drawings).

viii. If system, how the components relate?

ix. If applicable, identify if the device incorporates software/firmware and its role.

b) Product specification, including:

i. Physical characteristics of relevance to the end user (dimensions, weight)

ii. If applicable, technical features and operating modes

iii. If applicable, operating specifications and performance characteristics (e.g. electrical power requirements, settings and associated allowable ranges/limits, temperature and humidity limits, number of tests per hour, sensitivity/specificity)

iv. If applicable, a complete list of the configurations/models of the devices and a summary of the differences in specifications (comparison table and/or pictures/diagrams with supporting text).

c) If applicable, engineering diagrams/prints/schematics of the device.

d) Describe the different specimen types that can be used for this device (e.g. serum, plasma, urine, cerebrospinal fluid), including any additives that are required (e.g. anticoagulant).

e) Describe the use of controls. If applicable, a list of compatible control materials or control material specifications.

f) Description of the accessories, other IVD or non-IVD medical devices and other products, which are intended to be used in combination with the IVD medical device.

g) If approved by the regulator, provide the approval number and identification for each of the accessories, other IVD or non-IVD medical devices and other products, which are intended to be used in combination with the IVD medical device.

h) If applicable, indication of biological material or derivate used in the medical device, including: origin (human, animal, recombinant or fermentation products or any other biological material) and source (e.g. blood, bone, heart, any other tissue or cells). Where a significant risk is identified, a brief summary of evaluations performed to minimize biological risks, in particular, with regard to viruses and other transmissible agents.

i) If the device contains an active pharmaceutical ingredient (API) or drug, an indication of the substance, should be provided. This should include its identity and source, and the intended reason for its presence and its primary mode of action.

j) Description of the collection and/or transport container(s) provided with the IVD medical device or a description of specifications or recommended collection and/or transport container(s).

k) If applicable, a listing of assays that are compatible with the instrument. l) If applicable, a listing of compatible instruments.

m) A list of any software to be used with the IVD medical device and a description of its role in the delivery of the intended purpose

NOTE: The sponsor/applicant should explicitly address any existing regional regulatory guidance related to the comprehensive device description and principles of operations provided in this section regarding the subject device.

2.2.2. Description of Device Packaging

a) Information regarding the packaging of the devices, including, when applicable, primary packaging, secondary and any other packaging associated;

b) Specific packaging of accessories marketed together with the IVD medical devices shall also be described;

c) If the user needs to package the IVD medical device or its accessories before they perform sterilization, information about the correct packaging (e.g. material, composition, dimension) should be provided.

2.2.3. History of Development

For any device versions/prototypes referenced in the evidence presented in the submission, a table describing the version/name, with 4 columns (Device Name and/or Version; Description of changes from previous row; motivation for the change; list of verification/validation activities, including clinical studies, conducted using this version).

For any design verification or validation activities presented in this submission (including clinical studies) performed on any earlier versions of the subject device, include a justification for why the changes do not impact the validity of the data collected under those activities in supporting the safety and performance of the final IVD medical device design.

2.2.4. Reference and Comparison to Similar and/or Previous Generations of the Device

a) A list of the similar devices (available on local and international market) and/or previous generation of the devices (if existent) relevant to the submission. This should include any similar/previous generation devices that were previously reviewed and refused by the subject regulator.

b) Description of why they were selected.

c) A key specification comparison, preferably in a table, between the references (similar and/or previous generation) considered and the device.

2.2.5. Substantial Equivalence

a) Identify the predicate device(s), and optionally reference devices

i. trade name and model number

ii. Ensure the identified predicate device(s) is consistent throughout the submission

b) Include a comparison of indications for use and the technology (including features materials and principles of operation) between the predicate device(s) and subject device(s).

c) Include an analysis of why any differences between the subject device(s) and the predicate device(s) do not render the subject device(s) Not Substantially Equivalent, affect safety or effectiveness or raise different questions of safety and effectiveness.

2.3. Indications for Use and/or Intended Use and Contraindications

2.3.1. Intended Use; Intended Purpose; Intended User; Indications for Use

This section should include, as appropriate:

a) Intended Use: The statement of intended use should specify the therapeutic or diagnostic function provided by the device and may describe the medical procedure in which the device is to be used.

b) Intended Purpose: What is expected with the use of this medical device? Which results are expected?

c) Intended user and skills/knowledge/training that the user should have to operate or use the device.

d) Identify if the device is intended for single or multiple use

e) Indications for Use:

i. Disease or medical condition that the device will diagnose, parameters to be monitored and other considerations related to indication for use.

ii. If applicable, information about patient selection criteria.

iii. If applicable, information about intended patient population (e.g. adults, pediatrics or newborn) or a statement that no subpopulations exist for the disease or condition for which the device is intended.

NOTES:

i. The statements of intended use and purpose and the intended user and indications for use must be as presented in the labeling.

ii. If more than one device is included, the information should be provided for each device.

2.3.2. Intended Environment/Setting for use

a) The setting where the device is intended to be used (e.g. domestic use, hospitals, medical/clinical laboratories, ambulances, medical/dental offices). Multiple options can be indicated.

b) If applicable, environmental conditions that can affect the device's safety and/or performance (e.g. temperature, humidity, power, pressure, movement).

2.3.3. Pediatric Use

a) Description of any pediatric subpopulations that suffer from the disease or condition that the device is intended diagnose.

b) The number of affected pediatric patients, as a whole and within each pediatric subpopulation.

OR

c) Statement that no pediatric subpopulation exists for the disease or condition for which the device is intended.

2.3.4. Contraindications for Use

If applicable, specify the disease or medical conditions that would make use of the device inadvisable due to unfavorable risk/benefit profile.

NOTE: The statement if contraindications for the device must be as presented in the labeling.

2.4. Global Market History

2.4.1. Global Market History

a) Up to date indication of the markets (all countries or jurisdictions) where the device is approved for marketing, including any marketing under compassionate use regulations.

b) Should include history of the marketing of the device by any other entity in as much detail as possible, acknowledging that detailed information may not be available in all cases.

c) If the subject device is different in any way (e.g. design, labeling, specifications) from those approved or marketed in other jurisdiction, the differences should be described.

d) The month and year of market approval in each country or jurisdiction where the device is marketed. If the device has been marketed for greater than 10 years, a statement of greater than 10 years can be made.

e) For each of the markets listed in (a) above, and statement of the commercial names used in those markets OR a clear statement that the commercial names are the same in all jurisdictions.

f) State the date of data capture for the market history data.

g) If the subject device has been the subject of any previous compassionate use and/or clinical trials this should be identified and, if applicable, relevant reference numbers provided.

2.4.2. Global Incident Reports and Recalls

a) List adverse events/incidents associated with the device and a statement of the period associated with this data.

b) If the number of adverse events is voluminous, provide a summary by event type that state the number of reported events for each event type.

c) List of the medical device recalls and/or advisory notice, and a discussion of the handling and solution given by the manufacturer in each case.

d) A description of any analysis and/or corrective actions undertaken in response to items listed above.

2.4.3. Sales, Incident and Recall Rates

a) A summary of the number of units sold in each country/region and a statement of the period associated with this data.

b) Provide the rates calculated for each country/region, for example:

i. Incident rate = # adverse events/incidents divided by # units sold x 100

ii. Recall rate = # recalls divided by # units sold x 100

Rates may be presented in other appropriate units such as per patient year of use or per use. In this case, methods for determining these rates should be presented and any assumptions supported.

c) Critical analyses of the rates calculated (e.g. why are they acceptable? How do they break down in terms of incidents? Is there some outlier data that has driven the rates up? Are there any trends associated with any sub-groups of the devices that are subject of the submission (e.g. size, version)?).

NOTES

i. Sales in this context should be reported as the number of units sold.

ii. The summary of sales should be broken down by components when appropriate.

2.4.4. Evaluation/Inspection Reports

Copies of Evaluation/Inspection Reports from other parties (e.g. Notified Body inspection reports).

CHAPTER THREE

ANALYTICAL PERFORMANCE AND OTHER EVIDENCES

3.1. Risk Management

A risk analysis shall be undertaken to identify and address all known or foreseeable hazards related to the product, taking into account such aspects as the user(s) of the device, and the technology involved.

The information provided in this section shall contain:

- A summary report of the risks identified during the risk analysis process, including, but not limited to:
  - Risk to the patient arising from false positive or false negative results
  - Indirect risks that may result from product-associated hazards, such as instability, which could lead to erroneous results
  - The risk of delays in availability of results
  - User-related hazards, such as reagents containing infectious agents
  - Production-related risks
  - Risks arising from the use of the product by users with minimal skills, training or experience.
- A description of how these risks have been controlled to an acceptable level. This may be demonstrated by provision of documented evidence using risk assessment tools such as failure modes and effects analysis (FMEA), failure reporting and corrective action system (FRACAS), fault tree analysis (FTA) or other methods.
- Measures to inform users of any residual risks.
- A conclusion with evidence that the remaining risks are acceptable when compared to the benefits. This conclusion shall be dated and signed by senior management.
- Evidence that the risk analysis is part of the manufacturer's risk management plan (inclusion of documented evidence in this regard).
- Where a standard has been followed, identify the standard

3.2. Essential Principles (EP) Checklist

a) An EP checklist (see Annex-I) established for the IVD medical devices, information about method(s) used to demonstrate conformity with each EP that applies, references for the method adopted and identification of the controlled document with evidence of conformity with each method used.

b) For the controlled documents indicated which are required for inclusion in the submission: a cross-reference of the location of such evidence within the submission.

c) If any EP indicated in the checklist does not apply to the device: a documented rationale of the non-application of each EP that does not apply.

NOTE:

Methods used to demonstrate conformity may include one or more of the following:

a) Conformity with recognized or other standards;

b) Conformity with a commonly accepted industry test method(s);

c) Conformity with an in-house test method(s);

d) The evaluation of pre-clinical and clinical evidence;

e) Comparison to a similar device already available on the market.

3.3. Standards

a) List the standards that have been complied with in full or in part in the design and manufacture of the device.

b) At a minimum should include the standard organization, standard number, standard title, year/version, and if full or partial compliance.

c) If partial compliance, a list the sections of standard that

i. Are not applicable to the device, and/or

ii. Have been adapted, and/or

iii. Were deviated from for other reasons – discussion to accompany

3.4. Analytical Performance

3.4.1. Stability of Specimen(s)

The manufacturer shall provide studies to support the stability, storage and where appropriate, transport, of all specimen type(s) identified in the labelling, including any and all recommended additives (e.g. anticoagulants). This information shall include:

- Storage conditions (lower and upper limits of claimed temperature range, duration at each temperature, variation in humidity, freeze/thaw cycles)
- Transport conditions, where applicable
- How the storage conditions, as well as the maximum allowable time between specimen collection and its processing, or addition to the IVD, takes into consideration the settings of intended use
- Details of the specimen collection media, collection devices and transfer devices, whether these contain anticoagulants and whether they can be sealed, if applicable.

3.4.2. Validation of Specimens

The manufacturer shall provide studies to support the validity of specimen type(s) used in the analytical and clinical studies as representative of all of the sample type(s) identified in the labeling, including any and all recommended additives (e.g. anticoagulants), as well as contrived specimens used in certain analytical studies. This should include:

a) A list of the specimen type(s) used, including any additives (e.g. anticoagulants), in each of the analytical performance studies. If the same specimens are used for all analytical studies, this can be stated and the specimen type identified.

b) For any or all of the analytical and clinical studies, if a particular specimen type(s) including additives (e.g. anticoagulants), has been chosen as representative of other specimen types identified in the labeling, this should be described and supported.

c) If the preparation of the specimen has not followed the protocol described in the current labeling, this should be identified and validated.

d) A justification of the selection of the studies performed.

e) Provide summary of the evidence that falls within this category

3.4.3. Metrological traceability of calibrator and control material values

The manufacturer shall provide evidences that support the metrological traceability of values assigned to calibrators and trueness control materials. This should include:

a) A description of all calibrators and trueness control materials associated with the system.

b) A justification of the selection of the studies performed.

c) Provide summary of the evidence that falls within this category, including for example, methods and acceptance criteria for the metrological traceability to reference materials and/or reference measurement procedures and a description of value assignment and validation.

NOTE: Precision control materials used during analytical studies to establish the reproducibility of a measurement procedure do not require the assessment of metrological traceability to a reference material or a reference method.

3.4.4. Accuracy of Measurement

While measurement trueness, affected by systematic error, is normally expressed in terms of bias, measurement precision, affected by random error, is naturally expressed in terms of standard deviation. Accuracy is affected by a combination of systematic and random effects that contribute as individual components of the total error of measurement.

3.4.4.1. Trueness

The manufacturer should provide a summary of information and evidence relating to the trueness of the measurement procedure. Trueness measures apply to both quantitative and qualitative assays only when a reference standard or method is available. This should include:

a) A rationale for the reference standard or method(s) used

b) A summary of the evidence that falls within this category

3.4.4.2. Precision (Repeatability and Reproducibility)

The manufacturer shall provide evidence supporting claims for the precision of the product: i.e. repeatability (e.g. within-run variability) and reproducibility (e.g. between-run, -lot, -day, -operator, -site etc. variability, as appropriate). The studies provided in this section shall include:

- Estimation of precision for each analyte for which detection is claimed. A justification shall be given if this is not provided.
- Testing in a panel of specimens that reflects the main specimen types intended for use with the IVD.

For products that will be used at point-of-care, testing is likely to be undertaken by users who represent a diversity of skills, training and experience. This section should include studies where operator-to-operator variability has been investigated using representative of likely end-users of the product (e.g., non-laboratory trained personnel: healthcare workers and trained lay providers) using only those materials provided with the IVD (e.g. instructions for use, labels and other instructional materials) who have undertaken the testing unassisted, following only those instructions provided with the product. Personnel shall be selected who reflect the diversity of intended users and operational settings so as to challenge the usability of the product.

3.4.5. Analytical Sensitivity

The manufacturer shall provide evidence that demonstrates the analytical sensitivity of the product. Analytical sensitivity shall be determined for each claimed variant, type and/or subtype, where a suitable biological reference material exists. Depending on the intended use of the product, this may include studies that establish limit of detection (LoD): the lowest concentration of analyte (measurand) in a specimen that can be reliably detected.

The studies that establish analytical sensitivity shall include:

- A description of specimen type and preparation, including the matrix used, the amount of analyte in each specimen and how this was established. Analytical sensitivity shall be demonstrated in a clinical sample matrix and shall use the entire assay system from sample preparation to interpretation
- The number of replicates tested at each concentration
- A description of the calculation used to determine assay sensitivity

3.4.6. Analytic Specificity

The manufacturer shall provide validated data that describes interference and cross reactivity studies to determine the analytical specificity of the product. Analytical specificity is defined as the ability of a measurement procedure to detect or measure only the analyte (measurand) to be detected, in the presence of other substances/agents in the specimen.

Substances with the potential to cause interference or cross-reactivity will vary depending on the assay type and design and may arise from either exogenous or endogenous sources. Typically, interference and cross-reactivity studies involve adding the substance under evaluation to the specimen and determining any bias of the test parameter relative to the control specimen to which no such substance has been added.

Analytical specificity shall be evaluated in relation to the potential not only to cause false positive results (using specimens that do not contain the analyte) but also to cause false negative results (using specimens with the analyte at or added to a low level of reactivity on the product).

Substances for which the potential for interference or cross-reactivity can be reasonably expected should be identified as part of a risk assessment for the product, taking into consideration the populations and settings in which the product will be used.

Common interferants and cross-reacting substances/agents may include, as appropriate:

- Substances used for patient treatment (e.g. therapeutic drugs, anticoagulants, etc.)
- Substances ingested by the patient (e.g. over the counter medications, alcohol, vitamins, foods, etc.)
- substances added during specimen preparation (e.g. preservatives, stabilizers)
- substances encountered in specific specimen types (e.g. haemoglobin, lipids, bilirubin, proteins)
- analytes of similar structure (e.g. precursors, metabolites) or medical conditions unrelated to the test condition, including specimens negative for the assay but positive for a condition that may mimic the test condition (e.g. for a hepatitis A assay: specimens negative for hepatitis A virus, but positive for hepatitis B virus)
- specimens from unrelated infections that cause false negative results

- substances used in, or related to, the design of the product: e.g. biotin and/or avidin; interference from human antibodies to components of the vector used for expression of product reagents

The manufacturer shall provide studies that evaluate the effects on the product of potentially interfering and cross-reacting substances/agents. These studies shall include:

- The substance/agent type, numbers of each corresponding specimen, and concentration tested
- Specimen type
- Measurand (e.g. Analyte concentration)
- Test results that are reported with respect to each condition (and analyte, as appropriate) and not reported as an aggregate of the total number of specimens tested in the study
- Evidence that any observed interference or cross-reactivity is reported as a limitation of performance in the product IFU.
- A study design that includes appropriate interferents and cross-reacting substances/agents.

3.4.7. High dose hook effect

The manufacturer shall provide evidence that supports the absence of high-dose hook, or prozone effects (if applicable). Specimens used to investigate high dose hook effect shall be chosen that have a high analyte concentration, as determined using a method other than the product intended to be prequalified. This second method shall be of a design not subject to prozoning.

3.4.8. Measuring range of the assay

The manufacturer shall provide information on studies that define the measuring range of the assay (linear and non-linear measuring systems), including the lower and upper limits of quantification (LLoQ and ULoQ), as appropriate, and describes information on how this has been established. The extent of correlation of quantitation with a suitable reference test shall also be determined.

In this section, the manufacturer shall provide the studies and information that allow an understanding of the approach and its validity.

3.4.9. Validation of assay cut off

The manufacturer shall provide an explanation, with supporting evidence describing how the assay cut-off (or the algorithm/method for determining a cut-off for different assay runs) has been established (if applicable). Depending on the intended use of the product, this may require an explanation of the statistic approach (e.g. use of Receiver Operator Characteristics [ROC] curve). This section shall include study description, study summary as well as full study and report. For products that include the use of test reader, the way in which the reader has been designed to differentiate reactive specimens from those that are non-reactive shall be demonstrated.

3.4.10. Validation of the assay procedure

The manufacturer shall provide a demonstration of how the assay procedure was validated, with regard to important reaction conditions (e.g. reaction times, reaction temperature, reagent volume, reading time,) and validation of controls (if applicable).

For example, for products where a reading interval is specified (i.e. time when result can first be read; time beyond which result should not be read), validation of critical time points shall be provided.

This section shall include study description, study summary as well as full study and report. These studies may be conducted as part of investigations into the robustness of the product.

3.5. Other Studies

3.5.1. Electrical Systems: Safety, Mechanical and Environmental Protection, and Electromagnetic Compatibility

The manufacturer shall provide evidence supporting electrical safety, mechanical and environmental protection, and electromagnetic compatibility.

This should include:

a) A justification of the selection of the studies performed.

b) A summary of the evidence that falls within this category

c) A discussion and a conclusion to support why the evidence presented is sufficient to support the application.

3.5.2. Software/Firmware

The manufacturer shall provide studies and supporting information on the software design, development process and evidence of the validation of the software, as used in the finished IVD medical device. It should also address all of the different hardware configurations and, where applicable, operating systems identified in the labeling.

3.5.2.1. Software/Firmware Description

a) Specify the name of the software

b) Specify the version of the software - The version tested must be clearly identified and should match the release version of the software, otherwise justification must be provided.

c) Provide a description of the software including the identification of the IVD medical device features that are controlled by the software, the programming language, hardware platform, operating system (if applicable), use of Off-the-shelf software (if applicable), a description of the realization process.

d) Provide a statement about software version naming rules, specify all fields and their meanings of software version, and determine the complete version of software and its identification version used for release.

3.5.2.2. Hazard Analysis

The Hazard Analysis should take into account all device hazards associated with the IVD medical device’s intended use, including both hardware and software hazards.

NOTE:

i. This document can be in the form of an extract of the software-related items from comprehensive risk management documentation, described in ISO 14971.

ii. Hazard analysis, should address all foreseeable hazards, including those resulting from intentional or inadvertent misuse of the IVD medical device.

3.5.2.3. Software Requirement Specification

The manufacturer shall provide the Software Requirements Specification (SRS) that documents the requirements for the software. This typically includes functional, performance, interface, design, developmental, and other requirements for the software. In effect, this document describes what the Software Device is supposed to do. For example, hardware requirements, programming language requirement, interface requirements, performance and functional requirements,

3.5.2.4. Architecture Design Chart

The manufacturer shall provide the detailed depiction of functional units and software modules. This may include state diagrams as well as flow charts.

3.5.2.5. Software Design Specification

The manufacturer shall provide the Software Design Specification (SDS) that describes the implementation of the requirements for the Software Device. The SDS describes how the requirements in the SRS are implemented.

3.5.2.6. Traceability Analysis

The manufacturer shall provide a Traceability Analysis that links together your product design requirements, design specifications, and testing requirements. It also provides a means of tying together identified hazards with the implementation and testing of the mitigations.

3.5.2.7. Software Life Cycle Process Description

The manufacturer shall provide a summary describing the software development life cycle and the processes that are in place to manage the various life cycle activities.

3.5.2.8. Software Verification and Validation

a) Include an overview of all verification, validation and testing performed both in-house and in a simulated or actual user environment prior to final release.

b) Discussion to support why the evidence presented is sufficient to support the application.

3.5.2.9. Revision Level History and Unresolved Anomalies (Bugs or Defects)

Revision history log, including release version number and date.

All unresolved anomalies in the release version of the software should be summarized, along with a justification for acceptability (i.e. the problem, impact on safety and performance, and any plans for correction of the problems).

3.5.2.10. Cybersecurity

The manufacturer should provide evidence to support the cybersecurity. These evidences include, but not limited to:

a) Cybersecurity vulnerabilities and risks analysis

b) Cybersecurity controls measures

c) Traceability matrix linking cybersecurity controls to the cybersecurity vulnerabilities and risks

3.5.3. Cleaning and Disinfection Validation

The manufacturer shall provide data that contains information on the validation of cleaning and disinfection instructions for reusable devices, including evidence to support maintenance of performance when subject to this procedure over a number of cycles that is representative of the IVD medical device's expected useful life. Information to be included in this section includes:

a) If applicable, a discussion of how the number of cycles that is representative of the IVD medical device's expected useful life has been determined.

b) A justification of the selection of the studies performed.

c) A summary of the evidence that falls within this category

NOTES:

This applies most typically in near patient testing involving whole blood.

3.5.4. Usability/Human factors

The manufacturer shall provide studies that specifically assess the robustness of the product, a term that denotes a product's resilience to variations in either its environment or its usage.

Robustness (flex) studies consider the labelling and/or design of the product with respect to the potential impact of human behaviour, abilities, limitations and other characteristics on the ability of the product of fulfil its intended use. The impact of reagent variations is also considered.

Robustness studies should challenge the product under conditions of stress that allow an understanding of any potential product deficiencies, including where and how a product might fail. The manufacturer shall consider multiple skill levels of users, as well as potential instrument and reagent problems.

Depending on the intended use of the product, the influence of the following factors should be included in this section:

- Operator error/ human factors, including use of incorrect specimen type, Incorrect application of the specimen to the device (e.g., incorrect placement, incorrect volume), incorrect handling of reagents including those in self-contained unitized test devices, incorrect placement of device (e.g., non-level surface), incorrect placement of reagents, including strips, or other components that contain reagent, use of incorrect reagents (for example, reagents that are not specific for the particular device or lot or generic reagents), incorrect order of reagent application, use of incorrect amount of reagent, incorrect timing of procedures (e.g., specimen application, running the test, or reading results), incorrect reading of test results, incorrect reading due to color blindness, etc..
- Specimen integrity and handling including errors in specimen collection, clotted specimens, error in specimen handling, incorrect specimen transport and/or storage, presence of bubbles in the specimen etc.
- Reagent integrity (Reagent viability) including use of improperly stored reagents, use of outdated reagents, use of improperly mixed reagents, use of contaminated reagents, etc..
- Hardware, software, and electronics integrity including power failure, power fluctuation, incorrect voltage, repeated plugging and unplugging of the device, hardware failure, software failure, electronic failure, physical trauma to unit, etc..

- Stability of calibration and internal controls including factors that affect calibrator and calibration stability, factors that may interfere with calibration.
- Environmental factors including impact of key environmental factors (temperature, relative humidity, barometric pressure changes, altitude (if applicable), sunlight, surface angle, device movement, etc.) on reagents, specimens, and test results, impact of key environmental factors (including changes in parameters such as pH or temperature) etc.

In addition to the description, summary and detail and report, the studies in this section shall include:

- A summary of the evidence that falls within this category
- Testing in specimens that represent all relevant test results and/or interpretations (e.g. reactive and non-reactive; enzyme deficiency at key decision points, etc)
- Details of the test environment and relation to the intended use environment
- A discussion of what tests were considered for the device and why they were or were not performed
- A discussion to demonstrate why the evidence presented is sufficient to support the application

Depending on the product (e.g. products likely to be used in point-of-care settings by users with limited training, skills and/or experience) this section shall include complete studies that demonstrate:

- Label comprehension - Questionnaire-based testing of subjects representative of end users undertaken to assess the ability of intended users to correctly comprehend key messages from packaging and labelling.
- Interpretation of results – Testing to assess the ability of subjects to correctly interpret contrived test results.

If a clinical study has been conducted that includes usability/human factor endpoints (e.g. for self-testing), reference to the studies and endpoints shall be made in this section but full results do not need to be repeated here and shall be included in Chapter 4 – clinical evidence.

3.5.5. Stability of the IVD

This section shall describe in detail the claimed shelf life (including transport stability) as well as in-use stability of a product.

Claims for stability shall be based on the second-last successful data point from the least stable lot. For example: for testing conducted at 3, 6, 9, 12 and 15 months, if stability was observed at 15 months, then the maximum stability claim shall be 12 months.

Each of the studies referred to in this section for product stability must be presented with the study description, protocol, full study report and conclusion. In addition to specifying acceptance criteria, the study protocol must specify appropriate testing intervals and ensure that testing extends beyond the projected claim of shelf life.

3.5.5.1. Claimed Shelf-life

This section shall contain details and evidence supporting the claimed shelf-life of the IVD medical device components (e.g. reagents, calibrators/reference materials, control material, any other components susceptible to degradation).

Information provided in this section should include:

a) A description of recommended environmental conditions for storage of the IVD medical device (e.g. temperature, pressure, humidity, light conditions).

b) A statement of the claimed shelf-life indicated as a period of time or any other means of appropriate quantification.

c) An indication of the packaging used in any studies conducted in support of the shelf- life. If the packaging used in the studies differs from the final device packaging, a discussion of why the evidence can be considered valid in support of the claimed shelf life.

d) A description of the simulated transport conditions that the IVD was exposed to before the start of shelf-life studies.

e) A justification of the selection of the studies performed.

f) A summary of the evidence that falls within this category

g) A discussion and a conclusion to support why the evidence presented is sufficient to support the claimed shelf-life.

OR

h) A rationale that, for an indefinite period, the storage conditions could not affect IVD medical device safety or performance.

3.5.5.2. In Use Stability

This section shall contain details and evidence supporting the stability during actual routine use of the IVD medical device (real or simulated), including all applicable components (e.g. reagents, reaction cartridges). This may include open vial stability and/or, for automated instruments, onboard stability. Information provided in this section should include:

a) A description of recommended environmental conditions for use of the IVD medical device (e.g. temperature, pressure, humidity, light conditions).

b) A justification of the selection of the studies performed.

c) A summary of the evidence that falls within this category

d) A discussion and a conclusion to support why the evidence presented is sufficient to support the application.

OR

e) A rationale that, for an indefinite period, the storage conditions could not affect IVD medical device safety or performance.

3.5.5.3. Shipping Stability

This section shall contain details and evidence supporting the tolerance of IVD medical device, or if provided separately, the components (e.g. reagents, calibrators/reference materials) to the specified or expected shipping conditions. Information provided in this section should include:

a) An indication of environmental conditions for correct shipment of the IVD medical device (temperature, pressure, humidity, light conditions, mechanical protection etc.).

b) A justification of the selection of the studies performed.

c) A summary of the evidence that falls within this category

d) A discussion and a conclusion to support why the evidence presented is sufficient to support the application.

OR

e) A rationale that, for an indefinite period, the storage conditions could not affect IVD medical device safety or performance.

CHAPTER FOUR

CLINICAL EVIDENCE

4. Clinical Evidence

4.1. Overall Summary of Clinical Evidence

Clinical evaluation is the assessment and analysis of data generated from the clinical intended use of the product in order to verify the clinical safety and performance of the device. Clinical evidence is the combined information from the clinical data and its evaluation. A manufacturer shall have clinical evidence to support any clinical claims. This shall include claims for clinical or diagnostic sensitivity and specificity.

4.2. Expected values/reference ranges

If applicable, the manufacturer shall provide in this section information on what values to expect in healthy individuals versus those in individuals affected by a corresponding infection, disease and/or condition.

4.3. IVD medical device specific clinical studies

All claims for the clinical performance of the product shall be supported by well-designed performance evaluations. These may include evaluations that have been carried out or coordinated by the manufacturer, as well as evaluations carried out by bodies wholly independent of the manufacture. In addition to the detail description, full reports and information, clinical evaluation studies provided in this section shall include:

- Any anomalous results, or results that are not within predetermined specifications, shall be clearly explained or justified. All invalid results shall be recorded and evaluated in comparison to the reference result. Invalid results shall not be excluded from estimates of sensitivity or specificity.
- Estimates of diagnostic/clinical sensitivity and specificity shall be reported with 95% confidence intervals

- Where an IVD is intended to detect multiple analytes without differentiating which analyte is detected, specimens chosen for the testing panel shall comprise those that are reactive only for each individual analyte.
- Results shall be reported with respect to each study site and not be reported as an aggregate of the total number of specimens tested to establish these characteristics
- Details of the product lots/batches used for the evaluation, including lot number, date of expiry, and the storage conditions of the product before and during the study
- Details of the geographical region, clinical status, age and sex, as appropriate, of the subjects from which specimens have been drawn for the clinical evaluation
- Full details of the method used to select specimens for testing that would allow it to be understood that selection biases have been either minimized or eliminated. This shall include any acceptance/exclusion criteria as well as details of any specimens that were excluded from selection using these criteria
- Full details of the methods used to define the clinical status of the subjects and to characterize the specimens
- Evidence that the outcomes of the performance studies have been reviewed by the manufacturer's management and accepted for implementation.
- All abbreviations used in reports and on data records shall be explained and clearly defined
- If the study has been published in peer-reviewed scientific literature, provide publication details for the study
- Testimonials from hospitals, laboratory staff, product users, patients, or testimonials of any other kind are not considered to be evidence of performance. Testimonials shall not be included in the dossier as they will not be considered during review

4.4. Qualification of Usability

In this section, the manufacturer shall provide information that demonstrates the performance of the product when used by observed, untrained self-testing users.

CHAPTER FIVE

LABELLING AND PROMOTIONAL MATERIAL

5. Labelling Requirements

5.1. Product/package labels

In this section, the manufacturer shall provide all packaging labels used in the product. This includes primary and secondary labelling of all devices, accessories and components (but exclusive of labels for shipping). Labels shall include at least the following information:

- The product name and product identification number (product code/catalogue number)
- The name and contact details of the manufacturer, or an authorized representative of the manufacturer, on the outer package labels
- The name of the reagent/ingredient
- The expiry date (or a statement as to where and how this will be displayed)
- An indication of any special storage and/or handling conditions that apply
- The warnings and precautions
- The lot/batch and/or serial number (or a statement as to where and how this will be displayed)
- The information regarding product conditions such as product sterility
- The names of all included reagents in each box on the outer package label, where possible
- If a component is too small to contain all the above information, it shall at a minimum contain the name, lot number expiration date, volume, and storage conditions.
- If the product requires associated instrumentation, the requirements listed above also apply to the instrument.

5.2. Package insert/ Instructions for use

In this section, the manufacturer shall provide the current product instructions for use (IFU). The information provided in a product IFU shall be clear, correct, suitable for intended users and consistent with that provided in the product dossier.

The product IFU shall at a minimum include the following information:

- Product identification (name of the product and variants and corresponding product codes)
- A clearly stated intended use, including:
    - what is detected by the assay (that is, the analytical use of the assay e.g. the marker or nucleic acid sequence being detected)
    - the clinical indication for the test (e.g. if it is for a specific disorder, or a condition or risk factor of interest that the test is intended to detect, define or differentiate)
    - the function of the product (screening, monitoring, diagnostic or aid to diagnosis, staging or aid to staging of disease)
    - the intended user (laboratory professional and/or at point-of-care)
    - the intended testing population (e.g. neonates, antenatal women)
    - the type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine)
    - whether the assay is automated
    - what the instrument is intended for
    - whether the test is qualitative or quantitative
    - an indication that the product is for in vitro use
- A general description of the principle of the assay method or instrument principles of operation
- A description of all components of the assay (e.g. reagents, assay controls and calibrators) and a description of the reactive ingredients of relevant components (e.g. antibodies, antigens, nucleic acid primers etc.)
- A description of the specimen collection and transport materials provided with the product or recommended for use
- For instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays
- For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation

- If applicable, a description of any software to be used with the product
- If applicable, a description or complete list of the various configurations/variants of product that will be made available
- If applicable, a description of the accessories, and other products that are intended to be used in combination with the product but are not provided with the product
- Storage conditions, including storage conditions and stability of both the unopened and opened product, and working solutions. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, and other pertinent factors
- Specimen exclusion criteria (e.g. specimens with visual evidence of hyperlipidaemia or haemolysis, excessive specimen age, excessive number of freeze/thaw cycles).
- If the test kit includes sterile accessories, an indication of that condition and any necessary instructions in the event of damage to sterile packaging
- If the test kit includes accessories that have been specified by the manufacturer as intended for single-use only, an indication of that status
- Clear instructions on how to perform the assay, including instructions on specimen collection, handling, preparation and storage of reagents, the use of assay calibrators and controls as well as the reading and interpretation of test results
- Recommendations for quality control procedures
- Clear instructions on the correct usage of any equipment or software that is required for the performance of the assay
- Any warning and precautions to be considered related to the use of the assay including but not limited to interpreting the results, the disposal of the assay and/or its accessories (e.g. lancets), to any consumables used with it (e.g. reagents) that may be carcinogenic, mutagenic or toxic, or to any potentially infectious substances of human or animal origin
- Any residual risks
- Precautions and measures to be taken in the event of performance changes or product malfunction
- Limitations of the assay, including information on interfering substances that may affect the performance of the assay
- Performance characteristics including diagnostic sensitivity and specificity, seroconversion sensitivity, accuracy, dynamic range, lower limit of detection, and

reproducibility, as appropriate, and any other performance aspects that are relevant to the product

- Any requirements for special training or particular qualifications of the assay user
- Any requirements for routine maintenance. Include details of frequency of maintenance and who should perform this maintenance (for example: the user, a representative of the manufacturer, or a third party)
- Where relevant, a bibliography
- Document control details, such as a document version number and release date
- Definition of terms and abbreviations (if applicable)
- The name and contact details of the manufacturer or an authorized representative of the manufacturer, in order for the user to obtain assistance.

5.3. Technical/operators manual

If the product requires associated instrumentation or the requested product for registration itself is instrument, the manufacturer shall provide a copy of the instrument's manual and/or associated operator manuals.

5.4. Other labelling and promotional materials

Provide copies of any other instructional materials that are provided to the user such as job aids, information resources on a website, CD-ROM etc.

5.5. e-labeling

For eligible medical devices and stand-alone software, the manufacturer shall identify which form of e-labeling is being used in case of e-labeling (e.g. electronic storage system or built-in system, website). The manufacturer shall also provide details of risk management in relation to e-labeling. If this is part of the overall risk management, refer to it here.
A description of the procedure and operations on providing IFU's when requested.
The manufacturer also need to submit a written information for user Information on webpage where IFU and further information can be found in relevant languages. Description on how the requirements detailed for the website have been met should also be provided.

CHAPTER 6A

QUALITY MANAGEMENT SYSTEM PROCEDURES

6A.1. Administrative

Administrative information needed to evaluate the premarket submission related to the QMS.

6A.1.1. Product Descriptive Information

Abbreviated description of the device, operating principles and overall manufacturing methods

6A.1.2. General Manufacturing Information

a) Address and contact information for all sites where the device or its components are manufactured.
b) Where applicable, addresses for all critical subcontractors, such as outsourced production, critical component or raw material production (e.g. animal tissue, drugs), and sterilization will need to be provided.

6A.2. Quality management system procedures

High level quality management system procedures for establishing and maintaining the quality management system such as the quality manual, quality policy, quality objectives, and control of documents and records ISO 13485 Elements– SOPs to satisfy clause 4.

6A.3. Management responsibilities procedures

Procedures that document the management commitment to the establishment and maintenance of the QMS by addressing quality policy, planning, responsibilities/authority/communication and management review.
ISO 13485 Elements – SOPs implementing clause 5.

6A.4. Resource management procedures

Procedures that document the adequate provision of resources to implement and maintain the QMS including human resources, infrastructure and work environment. ISO 13485 Elements – SOPs implementing clause 6.

6A.5. Product realization procedures

High level product realization procedures such as those addressing planning and customer related processes
ISO 13485 Elements – SOPs implementing sub clause 7.1 and 7.2.

6A.5.1. Design and Development Procedures

Procedures that document the systematic and controlled development of the device design from initiation of the project to transfer to production. ISO 13485 Elements – SOPs for implementing sub clause 7.3.
This section should include the following information:

a) Design Control Procedure(s) b) Design & Development Planning Procedure(s) c) Design Input Procedure(s) d) Design Output - Procedure(s) e) Design Review Procedure(s) f) Design Verification Procedure(s) g) Design Validation Procedure(s) h) Risk Analysis Procedure(s) i) Design Transfer Procedure(s) j) Design Changes Procedure(s) k) Design History File Procedure(s).

6A.5.2. Purchasing Procedures

Procedures that document that purchased products/services conform to established quality and/or product specifications.
ISO 13485 Elements – SOPs to implement sub clause 7.4.

6A.5.3. Production and service controls procedures

Procedures that document the production and service activities are carried out under controlled conditions. These SOPS address issues such as cleanliness of product and contamination control;

installation and servicing activities; process validation; identification and traceability; etc. ISO 13485 Elements – SOPs implementing sub clause 7.5.

6A.5.4. Control of monitoring and measuring devices procedures

Procedure that document that monitoring and measuring equipment used in the QMS is controlled and continuously performing per the established requirements.
ISO 13485 Element- SOPs for implementing sub clause 7.6.

6A.6. QMS measurement, analysis and improvement procedures

Procedures that document how monitoring, measurement, analysis and improvement to ensure the conformity of the product and QMS, and to maintain the effectiveness of the QMS. ISO 13485 Element – SOPS for implementing clause 8.

This section should:
a) Explain how complaint handling ties to MDR procedures b) Explain how risk management is tied to the CAPA activities c) CAPA Subsystem Procedures d) Nonconforming Product Procedure(s) e) Complaint Handling Procedures f) Quality Audit Procedures.

CHAPTER 6B
QUALITY MANAGEMENT SYSTEM DEVICE SPECIFIC INFORMATION

6B.1. Quality management system information

Documentation and records specific to the subject device that results from the high level quality management system procedures for establishing and maintaining the quality management system such as the quality manual, quality policy, quality objectives, and control of documents, noted in Chapter 6A.
ISO 13485 Elements – documentation specific to the subject device for the implementation of clause 4.

6B.2. Management responsibilities information

Documentation and records specific to the subject device that result from the implementation the management responsibilities procedures noted in Chapter 6A. ISO 13485 Elements – documentation specific to the subject device for the implementation of clause 5.

6B.3. Resource management information

Documentation and records specific to the subject device that result from the implementation the resource management procedures noted in Chapter 6A.
ISO 13485 Elements – documentation specific to the subject device for the implementation of clause 6.

6B.4. Product realization information

Documentation and records specific to the subject device that results from the implementation of the high level product realization procedures noted in Chapter 6A. ISO 13485 Elements – documentation specific to the subject device for the implementation of sub clause 7.1 and 7.2.

6B.4.1. Design and development information

Documentation and records specific to the subject device that results from the implementation of the design and development procedures noted in Chapter 6A. NOTE: The source of this information is the Design and Development Records (e.g. DHF - Design History File). ISO 13485 Elements – documentation specific to the subject device for the implementation of sub clause 7.3.

6B.4.2. Purchasing information

Documentation and records specific to the subject device that results from the implementation of purchasing procedures noted in Chapter 6A ISO 13485 Elements – documentation specific to the subject device for the implementation of sub clause 7.4.
List of suppliers of goods or services that affect product conformity with requirements (critical suppliers) and a description of how purchasing requirements are fulfilled for these suppliers.

6B.4.3. Production and service controls information

a) Detailed Manufacturing Flow Diagram
b) Summary of in-process acceptance activities for subject device
c) Process Validation Master Plan
d) List of processes that have not be validated
e) For each process validation considered critical to the safety and effectiveness of the device:
    i. Protocols/Procedures for the validated process
    ii. Process validation report
    iii. The procedures for monitoring and controlling the process parameters of a validated process should be fully described.
    iv. State the frequency of re-validation.

6B.4.4. Control of monitoring and measuring devices information

Documentation and records specific to the subject device that results from the implementation of the control of monitoring and measuring device procedures noted in Chapter 6A.

ISO 13485 Elements – documentation specific to the subject device for the implementation of sub clause 7.6.

6B.5. QMS measurement, analysis and improvement information

Documentation and records specific to the subject device that results from the implementation of the QMS measurement, analysis and improvement procedures noted in Chapter 6A. ISO 13485 Elements – documentation specific to the subject device for the implementation of clause 8.

ANNEX ONE

CHECKLIST FOR ESSENTIAL PRINCIPLES OF BASIC SAFETY AND ESSENTIAL PERFORMANCE OF IVD MEDICAL DEVICES

The manufacturer shall use the EP checklist to readily understand how the manufacturer demonstrates compliance to the Essential Principles for a particular IVD. The EP checklist also allows easy identification of relevant documents and data for conformity assessment purposes. The contents of the checklist vary among products. Many complex products are more likely to reference a larger number of standards, test reports and documents. The EP checklist in those cases might be many pages long.

The following table is a recommended template for the EP checklist.

Ethiopian Food and Drug Authority, In Vitro Diagnostic Medical Device Registration Requirements-
Checklist for Essential Principles of Safety and Performance Requirements

Name of the Manufacturer:			**Date:**
Address of the Manufacturer:			
Name of the IVD device:			
List of Accessories:			
Essential Principles	**Applicable to the device?**	**Method of conformity**	**Reference to the supporting controlled documents**
General Requirements			
5.1.1 Medical devices and IVD medical devices should achieve the performance intended by their manufacturer and should be designed and manufactured in such a way that, during intended conditions of use, they are suitable for their intended purpose. They should be safe and perform as intended, should have risks that are acceptable when weighed against the benefits to the patient, and should not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons.			
5.1.2 Manufacturers should establish, implement, document and maintain a risk management system to ensure the ongoing quality, safety and performance of the medical device and IVD medical device. Risk management should be understood as a continuous iterative process throughout the entire lifecycle of a medical device and IVD medical device, requiring regular systematic updating. In carrying out risk management manufacturers should: a) establish and document a risk management plan covering each medical device and IVD medical device; b) identify and analyze the known and foreseeable hazards associated with each medical device and IVD medical device; c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse; d) eliminate or control the risks referred to in point (c) in accordance with the requirements of points 5.1.3 and 5.1.4 below; e) evaluate the impact of information from the production and postproduction phases, on the overall risk, benefit-risk determination and risk acceptability. This evaluation should			

include the impact of the presence of previously unrecognized hazards or hazardous situations, the acceptability of the estimated risk(s) arising from a hazardous situation, and changes to the generally acknowledged state of the art. f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of points 5.1.3 and 5.1.4 below.			
5.1.3 Risk control measures adopted by manufacturers for the design and manufacture of the medical device and IVD medical device should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, manufacturers should control risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers should, in the following order of priority: a) eliminate or appropriately reduce risks through safe design and manufacture; b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and c) provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.			
5.1.4 The manufacturer should inform users of any relevant residual risks.			
5.1.5 In eliminating or reducing risks related to use, the manufacturer should: a) appropriately reduce the risks related to the features of the medical device and IVD medical device and the environment in which the medical device and IVD medical device are intended to be used (e.g. ergonomic/usability features, tolerance to dust and humidity) and b) give consideration to the technical knowledge, experience, education, training and use environment and, where applicable, the medical and physical conditions of intended users.			
5.1.6 ---------- etc. ----------			