Annex III

EAST AFRICAN COMMUNITY

SUMMARY TECHNICAL DOCUMENTATION (STED) FOR IN VITRO DIAGNOSTIC MEDICAL DEVICES DOSSIER

JUNE 2020

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1.0 Compilation of the dossier

Applicants are required to arrange the application dossier in the format described below:

i. Application form

ii. Device Details

iii. Summary technical documentation

iv. Labelling information

v. Essential requirement checklist

NOTE: Failure to arrange the application dossier accordingly will lead to rejection of the application.

1.1 Evidence of Compliance with QMS

For the IVD medical devices with higher risks the pre-registration GMP inspection or Quality System audit will be conducted to verify their compliance. The audit will be conducted on risk basis, however in most cases evidence of compliance to GMP or Quality Management System for IVD provided by manufacturer will be adequate.

For IVDs that require evidence of compliance to Quality Management System, a CE certificate issued by a Notified Body designated in Europe for the purposes of the In Vitro Diagnostic Medical Devices Directive (98/79/EC) (IVDD) will be accepted. (May also be referred to as an EU Certificate, an EC certificate or an EEC Certificate) ISO 13485 certificates issued by Notified Bodies designated in Europe for the purposes of the IVDD will also be accepted.

CE and ISO 13485 certificates will only be accepted if they include acceptable evidence of good manufacturing practice (GMP) for IVDs:

- full legal name of the manufacturer of the goods, including trading names if appropriate.
- street address of the manufacturing site (PO box is not acceptable)
- date of the last audit/inspection.
- standard of manufacture with which the manufacturer of the product(s) complies.
- product(s) or type(s) of product(s) in sufficient detail to determine if the scope of the certificate is relevant to the IVD to be supplied
- date of issue
- period of validity or expiry date (must be current)
- Notified Body number
- Notified Body name

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2. DEVICE DETAILS

2.1 Name(s)

State the generic and brand name of the IVD medical device.

2.2 Description

Provide a general description on design, characteristics and performance of the IVD medical device. The description should also include information on device packaging.

2.3 Category

State the class of the IVD medical device and the applicable classification rule as appended in **annex IV** of these guidelines.

2.4 Intended Use/Indication

State the intended use of the IVD medical device and/or provide a general description of the disease or condition that the device will diagnose, treat, prevent, or mitigate. The description of the target patient population for which the device is intended should also be included, whether it is automated or not, whether it is qualitative or quantitative; type of specimen it requires (serum, plasma, urine) and what the assay type is e.g. immunoassay, chemistry, cyto-chemistry, image analysis should be stated.

2.5 Instruction of Use

Give a concise summary of information for safe use of the device including procedures, methods, frequency, duration, quantity and preparation to be followed.

2.6 Contraindications

State conditions under which the IVD medical device should not be used. For example, a limitation of an assay using specimens from patients who have received preparations of mouse monoclonal antibodies for therapy when tested with assay kits which employed mouse monoclonal antibodies. It may show either false elevated or depressed values.

2.7 Warnings

State the specific hazard alert information that a user needs to know before using the IVD medical device. E.g. for products containing biological material, radioactive material, explosive material and any other hazardous material, safety warnings must be included.

2.8 Precautions

State briefly precautions to be taken and any special care necessary for the safe and effective use of the IVD medical device.

2.9 Adverse Effects

Describe all adverse and side effects associated with the IVD medical device under normal conditions of use.

2.10 Alternative Use

Describe any alternative practices or procedures for diagnosing, treating, or mitigating the disease or condition for which the IVD medical device is intended.

2.11 Storage conditions

State the storage conditions for the IVD medical device.

2.12 Recommended shelf-life (where applicable)

State the recommended shelf-life of the IVD medical device.

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3. SUMMARY TECHNICAL DOCUMENTATION

3.1 Device description and features

Provide a detailed description of the device attributes that are necessary to explain how the device functions. These details should include:

(a) Intended use of the diagnostic. This may include:

(i) What is detected

(ii) The function of the IVD medical device (e.g. screening, monitoring, diagnostic or aid to diagnosis, staging or aid to staging of disease);

(iii) The specific disorder, condition or risk factor of interest that is intended to detect, define or differentiate;

(iv) Whether the product is automated or not;

(v) Whether the test is qualitative or quantitative.

(vi) The type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine)

(vii) The intended testing population (e.g. neonates, antenatal women)

(b) The intended user (laboratory professional and/or at point-of-care);

(c) A general description of the principle of the assay method or instrument principles of operation.

(d) A description of the components of the assay (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).

(e) A description of the specimen collection and transport materials provided with the product or description of specifications recommended for use.

(f) For instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays.

(g) For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation.

(h) If applicable, a description of any software to be used with the product.

(i) If applicable, a description or complete list of the various configuration/variants of product that will be made available. For example a family of pregnancy rapid test can consist of device available in different configurations, such as test strip or in a cassette.

(j) If applicable, a description of the accessories, and other non IVD products that is intended to be used in combination with the diagnostic.

(k) Risk class and the applicable classification rule for the IVD medical device according to GHTF guidelines.

The instruction for use may be used to provide some of this information on the condition that a cross-reference to the different requirements is supplied in conjunction with the instructions-for-use.

3.2 Evidence of Conformity to Essential Principles

Provide evidence of conformity to Essential Principles of Safety and Performance (EPSP) by completing the checklist appended as Annex III.

Note:

(i) Manufacturer should identify the essential principles of safety and performance that are applicable to the device and the general methods used to demonstrate conformity to each applicable Essential Principle. The methods that may be used include:

(a) Conformity with a recognized or other standard(s)

(b) Conformity with a commonly accepted industry test method (reference method)

(c) Conformity with appropriate in-house test methods that have been validated and verified;

(d) Comparison to a diagnostic already available on the market.

(ii) When the manufacturer uses national, international or other standards to demonstrate conformity with the Essential Principles, full title of the standard, identifying numbers, date of the standard and the organization that created the standard should be provided. (Essential Principles of Safety and Performance of Medical Devices http://www.ghtf.org).

The IVD device, to which the Essential Principles (EP) conformity checklist is applicable, should be identified by the brand name, common name and risk class on the checklist itself. The columns of the checklist should be completed as follows:

a) Applicable to the IVD device?

Either a “Yes” or “No” answer is required. If the answer is “No” there should be a brief explanation.

b) Method of conformity

State the title and reference of the standard(s), industry or in-house test method(s), comparison study(ies) or other methods to demonstrate compliance. For standards, this should include the date of the standard and where a standard is referred to more than once in the checklist, the reference number and date can be repeated.

c) Identity of specific documents

The column should contain the reference to the actual technical documentation that demonstrates compliance to the EP, i.e. the certificate number(s), test reports, study reports or other documents that resulted from the method used to demonstrate compliance, and its location within the technical documentation or dossier.

3.3 Risk Analysis

Provide a summary of the risks identified during the risk analysis process and how such risks have been controlled to an acceptable level. Preferably, the risk analysis should be based on recognized standards and be part of the manufacturer's risk management plan.

The summary should address possible hazards for the IVD medical device such as the risk from false positive or false negative results, indirect risks which may lead to erroneous results, or from user-related hazards, such as reagents containing infectious agents.

The results of the risk analysis should provide a conclusion with evidence that remaining risks are acceptable when compared to the benefits.

3.4 Design and Manufacturing Information

3.4.1 Product design

Provide information such as to give a general understanding of the design applied to the IVD medical device. It should include a description of the critical ingredients of an assay such as antibodies, antigens, enzymes and nucleic acid primers provided or recommended for use with the IVD medical device.

i. For **instruments** include a description of major subsystems, analytical technology (e.g. operating principles, control mechanisms), dedicated computer hardware and software.

ii. For **instruments and software**, give an overview of the entire system, including an Architecture Design Chart which is typically a flowchart of the relationships among the major functional units in the software, including relationships to hardware and to data flows such as networking.

iii. For **standalone software**, include a description of the data interpretation methodology (i.e. algorithms).

iv. For self-testing devices the design should include a description of the design aspects that make it suitable for lay person use.

v. If design takes place at multiple sites, a controlling site must be identified.

3.4.1.1 Formulation and composition

Provide formulation/composition for each of the ingredients;

(a) Materials

Provide complete details of material specifications, including raw materials;

(i) All components of the IVD medical device should be listed and chemically and biologically characterized, including antibodies, antigens, and assay controls, substrates used to detect antigen-antibody complexes, and test reagents. Appropriate references should be cited.

(ii) If synthetic peptides are used, the peptide sequence should be provided.

(iii) If components are of biological origin or recombinant, the source must be indicated and details on production must be provided. These details would include the strain of the virus, the cell line for cultivation of the virus, sequences of relevant nucleic acids and amino acids, etc., used in the manufacturing process of viral lysate, purified proteins, recombinant and synthetic proteins.

(iv) If applicable, process validation results to be provided to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents. This also includes inactivation of infectious organisms in reagents and the production of reagents.

(v) If applicable, information to be provided on irradiating components, non-ionising or ionizing (e.g. Iodide- 131 in the Radioimmunoassay kit, radio-labelled Phosphorus-32 DNA probes in Southern blots)

(vi) If applicable, information to be provided on the poison or controlled substance (e.g Buprenorphine in drug assay kit)

(vii) Give the nature and specification of the packaging material(s) including complete chemical and physical characterization of the packaging material making either direct or indirect contact with the IVD device.

Identify the sources of the materials from which the components are constructed.

(a) Biological Safety

List all biological components included in the IVD device to include material of bacterial, viral, parasitic, animal, or human origin or their derivatives where applicable. Indicate the name of the biological component, details of its use in the product and description of steps taken for the reduction of transmission or infection risk.

(c) Documentation of design change

Provide records of each design change, if any, with reasons for these changes along with associated validation/verification data. Include evidence that the change achieves the desired effect, and that the product continues to comply with the Essential Principles of Safety and Performance.

3.4.2 Manufacturing Processes

3.4.2.1 Overview of Manufacturing Process

Provide information on the manufacturing process, which may be in form of a process flow chart, showing an overview of production including technologies used, assembly and packaging of the finished IVD device. Include details of any in-process and final product testing (e.g. the manufacturer's QC release program).

3.4.2.2 Sites of Manufacture

Provide the following information;

i. Name of site,

ii. Physical address of the site,

iii. Description of the component manufacture/stage of manufacturing process carried out at the site,

iv. A simple sight plan highlighting production areas and number of employees at the site,

v. A description of any other manufacturing that occurs at the site;

For all the critical manufacturing sites that are involved in the manufacture of this product (i.e. including design, warehousing and quality control stages of manufacture).

3.4.2.3 Key Suppliers

Provide a list of key suppliers of ingredients/products/services for the manufacture of the IVD device, indicating the;

i. Name of the supplier,

ii. Supplier's manufacturing site physical address

iii. A description of the ingredient/product/service supplied

iv. Evidence of purchasing and verification procedures for the ingredients/products/services sourced from these suppliers

3.5 Device Specifications

Describe functional characteristics and technical performance specifications for the device including as relevant, accuracy, sensitivity, specificity of measuring and other specifications including chemical, physical, mechanical, electrical and biological.

A list of the features, dimensions and performance characteristics of the IVD medical device its variants and accessories should be provided in the dossier and also made available to the end user.

3.5.1 Device Verification and Validation

Summarize the results of verification and validation studies undertaken to demonstrate compliance of the IVD medical device with Essential Principles that apply to it. Whenever applicable the information should cover:-

i. The complete study protocol,

ii. The method of data analysis,

iii. Complete study report,

iv. The study conclusion,

v. Any published literature regarding the device or substantially similar devices.

vi. Summaries or reports of tests and evaluations based on other standards, manufacturer methods and tests or alternative ways of demonstrating compliance. Declarations/certificate of compliance to a recognized standard as applied by the manufacturer should be provided.

When a recognized standard exists that contains the protocol and the method of data analysis, this information can be substituted by a declaration/certificate of conformity to the recognized standard. However, a summary of the data and conclusions should be provided. Where appropriate actual test results summaries with their acceptance criteria should be provided and not just pass/fail statements.

3.5.2 Specimen type

This section should describe the different specimen types that can be used, including their stability (and storage) conditions and is typically applicable to all systems and assay types.

i. Stability includes storage and where applicable transport conditions. Storage includes elements such as duration, temperature limits and freeze/thaw cycles.

ii. Summary information for each matrix and anticoagulant when applicable, including a description of the measurement procedure for comparison or

determination of measurement accuracy. This includes information such as specimen type tested, number of samples, sample range (using spiked samples as appropriate) or target concentrations tested, calculations and statistical methods, results and conclusions.

3.6 Analytical performance characteristics

3.6.1 Accuracy of measurement

Provide information to describe both trueness and precision studies.

3.6.1.1Trueness of measurement

Provide information on the trueness of the measurement procedure and summarize the data used to establish the trueness measures for both quantitative and qualitative assays.

(a) Precision of measurement

Provide information to describe repeatability and reproducibility studies.

(i) Repeatability

Provide detail on repeatability estimation and information about the studies used to estimate, as appropriate, within-run variability. Repeatability data is obtained for instrumentation in conjunction with an appropriate assay.

(ii) Reproducibility

Provide information on reproducibility estimates and information about the studies used to estimate, as appropriate, variability between days, runs, sites, lots, operators and instruments. Such variability is also known as “Intermediate Precision”.

3.6.2 Analytical sensitivity

Provide information about the study design and results. Give a detailed description of specimen type and preparation including matrix, analyte (measured) levels, and how levels were established. The number of replicates tested at each concentration should also be provided as well as a description of the calculation used to determine assay sensitivity. For example:

(i) Number of standard deviations above the mean value of the sample without analyte (measurand), commonly referred to as ‘limit of blank’ (LoB).

(ii) Lowest concentration distinguishable from zero, based on measurements of samples containing analyte (measurand), commonly referred to as ‘limit of detection, (LoD).

(iii) Lowest concentration at which precision and/or trueness are within specified criteria, commonly refereed to as ‘limit of quantitation’ (LoQ).

3.6.3 Analytical specificity

Give information to describe interference and cross reactivity studies to determine the analytical specificity, 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 sample.

Provide information on the evaluation of potentially interfering and cross reacting substances/agents on the assay. Information should be provided on the substance/agent type and concentration tested, sample type, analyte (measurand) test concentration, and results.

Interferents and cross reacting substances/agents, which vary greatly depending on the assay type and design, could derive from exogenous or endogenous sources such as:

Substances used for patient treatment (e.g. therapeutic drugs, alcohol, vitamins, foods, etc.), substances added during sample preparation (e.g. preservatives, stabilizers), substances encountered in specific specimen types (e.g. haemoglobin, lipids, bilirubin, proteins), and; 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: test specimens negative for hepatitis A virus, but positive for hepatitis B virus)

3.6.4 Metrological traceability of calibrator and control material values

Where applicable, summarize the information about metrological traceability of values assigned to calibrators and trueness control materials. Include, for reference materials and/or reference measurement procedures and a description of value assignment and validation.

3.6.4.1 Measuring range of the assay

Provide a summary of studies which define the measuring range (linear and non-linear measuring systems) including the limit of detection and describe information on how these were established. The summary should include a description of specimen type, number of samples, number of replicates, and preparation including information on matrix, analyte (measurand) levels and how levels were established. If applicable, add a description of high dose hook effect and the data supporting the mitigation (e.g. dilution) steps.

3.6.4.2 Validation of assay cut-off

Provide a summary of analytical data with a description of the study design including methods for determining the assay cut-off, including: the population (s) studied, method or mode of characterization of specimens and statistical methods e.g.

Receiver Operator Characteristic (ROC) to generate results and if applicable, define gray-zone/equivocal zone.

3.7 Stability (excluding specimen stability)

Describe claimed shelf life, in use stability and shipping studies.

3.7.1 Claimed shelf life

Provide information on stability testing studies, to support the claimed shelf life, performed on at least three different lots manufactured under conditions that are essentially equivalent to routine production conditions (these lots do not need to be consecutive lots). The summary should include:

i. The study report (i.e. protocol, number of lots, acceptance criteria and testing intervals),

ii. When accelerated studies have been performed in anticipation of the real time studies, the method used for accelerated studies;

iii. Conclusion and claimed shelf life.

Note:
Shelf life can be derived from the lot with the longest real time stability data as long as accelerated or extrapolated data from all three lots are comparable.

3.7.2 In use stability

Provide information on in use stability studies for one lot reflecting actual routine use of the device (real or simulated). This may include open vial stability and/or, for automated instruments, on board stability.

In case of automated instrumentation if calibration stability is claimed, supporting data should be included sufficient to describe: the study protocol (i.e. protocol, acceptance criteria and testing intervals), conclusions and claimed in use stability.

3.7.3 Shipping stability

Provide information on shipping stability studies for one lot to evaluate the tolerance of products to the anticipated shipping conditions, describing the study report(i.e. protocol, acceptance criteria), method used for simulated conditions, conclusion and recommended shipping conditions.

Shipping studies can be done under real and/or simulated conditions and should include variable shipping conditions such as extreme heat and/or cold.

3.8 Software Verification and Validation (if applicable)

Provide information on the software design and development process and evidence of the validation of the software, as used in the finished device. This information should typically include the summary results of all verification, validation protocol and report and testing performed both in-house and in a simulated or actual user environment prior to final release. It should also address all of the different hardware configurations and, where applicable, operating systems identified in the labelling.

3.9 Clinical Performance

Provide evidence of assessment and analysis of data generated from the clinical use of the product sufficient enough to verify the clinical safety of the IVD device. Include claims for clinical/diagnostic sensitivity and specificity. All claims should be supported by well-designed performance evaluations which should include:

(a) A detailed written plan and protocol of the evaluation study

(b) Dates on which the study was performed and by which site

(c) A written report on the outcome of the study; all anomalous results should be explained and justified. The report outline should contain,

i. The technology on which the medical device is based, the intended use of the device and any claims made about the device's clinical performance or safety.

ii. The nature and extent of the clinical data that has been evaluated; and,

iii. How the referenced information (recognized standards and/or clinical data) demonstrate the clinical performance and safety of the device in question.

(d) Details of the IVD device lots/batches used for the evaluation including lot number date of expiry, and the storage conditions of the product prior to and during study.

(e) The clinical evaluation report should be signed and dated by evaluator(s) and accompanied by manufacturer's justification of the choice of evaluator.

The clinical evaluation report should be summarized as per required information elaborated above.

4. LABELLING REQUIREMENTS

Labelling information shall be in English and/or Kiswahili and shall be expressed in a legible, permanent and prominent manner that can be easily understood by the intended user.

Provide a complete set of labeling associated with the IVD medical device including immediate and outer container labels on the IVD medical device, instructions for use. The labeling should contain the final content as determined by the manufacturer.

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Depending on the type of device, the following minimum information should be provided on the label:-

(a) The name of the IVD medical device shall be indicated. If the name does not uniquely identify the IVD medical device, an additional means of identification shall also be provided.
Examples: Catalogue number, commodity number

(b) the name and address of the manufacturer

(c) the identifier of the device, including the identifier of a device that is part of a system, test kit, or IVD medical device class.

(d) batch or lot number

(e) Contents : if the contents are not readily apparent, an indication of what the package contains, expressed in terms appropriate to the device, such as size, net weight, length, volume or number of units, volume after reconstitution shall be indicated

(f) the words “Sterile” if the manufacturer intends to sell the IVD medical device in a sterile condition

(g) the word “For Single Use Only” shall be included if the IVD medical device is intended for single use

(h) In vitro diagnostics use: The In vitro diagnostics use of the device shall be indicated e.g. “For In vitro diagnostics use” or graphical symbol: “In vitro diagnostic medical device”.

(i) The Expiry date: An expiry date based upon the storage instructions shall be indicated and shall follow the requirements of ISO 8601. Expiry dates shall be expressed as the year, the month and where relevant, the day. E.g. “YYYY-MM-DD” or “YYYY-MM”.

(j) unless self-evident to the intended user, the medical conditions, purposes and uses for which the device is manufactured, sold or represented, including the performance specifications of the device if those specifications are necessary for proper use

(k) the directions for use, unless directions are not required for the device to be used safely and effectively

(l) Warning and precautions: If an IVD device is considered hazardous, the outer container label shall include the appropriate danger wording or symbol(s) e.g. chemical, radioactive and biological hazards

(m) Storage and Handling conditions: The storage conditions necessary to maintain the stability of the reagents, calibrators, control materials in the unopened state and other IVDs shall be indicated. If there are any other conditions that may affect the handling or storage of the reagents, calibrators, control materials and other IVDs shall be specified e.g. Fragile

(n) Intended use: If the intended use is not indicated by the name of the IVD medical device, then an abbreviated intended use statement shall be given or included in the instruction for use. e.g. For measurement of plasma glucose concentration

In case the device is intended to be sold to the general public, labeling information:-

i. Shall be set out on the outside of the package that contains the device; and be visible under normal conditions of sale
ii. where a package that contains a device is too small to display all the information in accordance with (a-k) above, the directions for use shall accompany the device but need not be set out on the outside of the package or be visible under normal conditions of sale.

Specimen label(s), promotional material(s) and user manual(s) should be provided.

Note:
Requirements that have been described in a respective standard should also be followed when labelling a device.