National Agency for Food and Drug Administration & Control (NAFDAC)

Drug Registration and Regulatory Affairs (DR & R) Directorate

NAFDAC Instruction for Compilation of a Product Dossier for Registration of In Vitro Diagnostics - IMDRF ToC

Contents

A. **Acknowledgment**

The Agency acknowledges the utilization of some documents and the technical support of the World Health Organization (WHO) as well as the International Medical Device Regulators Forum (IMDRF) in development of these Guidance document.

B. **Scope**

This Guidelines have been developed in pursuance to the NAFDAC Act Cap N1, LFN, 2004 and made to provide guidance to applicant in the organization of information to be provided to the Agency in seeking marketing authorization for in vitro diagnostics for human use. It also provides guidance to the industry on the expectation of NAFDAC as it concerns submission of technical documents.

C. **Introduction**

This document provides instructions to manufacturers on the type of information and necessary documents to be submitted in a product dossier for the purposes of regulatory assessment of IVDs (Registration process).

The regulatory assessment process allows for flexibility in a manufacturer's approach to compiling the information required for an application. Alternative approaches to both the principles, and application, of the requirements described in this document may be acceptable provided they are supported by adequate scientific justification.

NAFDAC may request, during the course of the registration process, additional information that is not specifically described in this document. This will be done in order to facilitate a clearer understanding of the quality, safety and performance of a product under assessment. The rationale for any additional requests will be clearly documented in correspondence to the manufacturer.

For the purpose of this document, the verbal forms used follow the usage described below:

- "shall" indicates that the manufacturer is required to comply with the instructions in the document below.
- "should" indicates that the manufacturer is recommended to comply with the instructions, but it is not a requirement.
- "may" indicates that the instructions are a suggested method to compile the documentation request, but it is not a requirement.

B. **Intended Audience**

This document has been prepared as guidance to manufacturers of IVDs to assist in correctly compiling a product dossier for the registration process.

NOTE: This document should be read in conjunction with all relevant IMDRF guidance documents including the following;

a. **GHTF/SG1/N71:2012 "Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device"** GHTF SG1 Definition of the Terms 'Medical Device' and 'In Vitro Diagnostics' Medical Device's (imdrf.org)

b. **In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC), IMDRF/RPS WG/N13(Edition 2) FINAL:2019**
https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-

190321-ivd-mdma-toc-n13.docx

GHTF/SG1/N70:2011 "Label and Instructions for Use for Medical Devices" GHTF SG1 - Label and Instructions for Use for Medical Devices - September 2011 (imdrf.org)

C. **The Product Dossier**

C. 1. About the product dossier

There are many terms used internationally to describe a product dossier. These terms include: *standard technical documentation*, *technical file, summary technical documentation, product summary file, product master file* and others. For the purposes of registration of IVDs, NAFDAC uses the term the *product dossier*.

NAFDAC expects a manufacturer to prepare and either hold, or provide timely access to, technical documentation that shows how its IVD is designed, developed, validated, and manufactured. This technical documentation, typically controlled in the manufacturer's quality management system (QMS), is often extensive and the documentation is revised over time to reflect any changes made during the life cycle of the IVD through normal application of the manufacturer's QMS.

The product dossier is a selection of records and documents from the entire collection of technical records and documents that a manufacturer holds for a product. Manufacturers compile a product dossier from their existing technical documentation to provide evidence that an IVD conforms to the internationally-recognized set of quality, safety and performance principles as described in the International Medical Device Regulators Forum (IMDRF) document IMDRF/GRRP WG/N47 FINAL:2018 *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices (3)* (the Essential Principles). Evidence will take the form for example, of results of testing, certifications, standard operating procedures (SOPs), systems and any other documentation necessary to support quality, safety and performance.

NAFDAC requires that a product dossier is submitted in the "Table of Contents" (ToC) format, described in the IMDRF document IMDRF/RPS WG/N13 FINAL:2019 (Edition 3)(*4*). In this document chapters 1-6 and their subheadings, as well as the corresponding chapters and subheadings of the *Product Dossier Checklist* are numbered according to IMDRF ToC format. As the IMDRF ToC is comprehensive in nature, not all subheadings are required for the purpose of registration and are therefore excluded.
NAFDAC reviews the product dossier with the purpose of:

- **assessing the product and how it performs**
- **assessing the product manufacture**

C. 2. **Submission of product dossier**

For the purpose of registration, NAFDAC requires an applicant to submit a product dossier; a product dossier should be submitted using a memory steak (pen drive) during the application process.

Note: All information submitted in the product dossier is **CONFIDENTIAL.**

Once an assessment is completed, NAFDAC reserves the right to destroy any dossier materials provided with the application. Dossier materials will not be returned.

C.3. **Product dossier clarity and completeness**

Applicants shall submit all necessary sections of a product dossier, identified both in this document and in the NAFDAC *Product Dossier Checklist.* All sections listed in this

document are required to be submitted as part of the product dossier unless indicated "if applicable".

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

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

C. 4. 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,NAFDAC requires 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.

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 characterization
- 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.

D. **Dossier Format**

D.1. **Product dossier submission format**

Submit one electronic copy using a secure file hosting device (e.g pen drive).

D.2. **Layout**

NAFDAC requires the following format for the dossier submission:

- Use the page numbers format page 1 of 2, 2 of 2, and so on.
- Clearly divide the submission into sections and subheadings, as prescribed in the *Product Dossier Checklist*, and number all pages of each section, including annexes, so that they are easily identified. Documentation for each section (chapter) may be submitted as separate file directories (folders). For example, the device description (Section 2.4.1 Comprehensive device description and principle of operation) may be provided in a file directory (folder) in the electronic submission that is named: "Section 2.4.1", or similar.
- Use the *Product Dossier Checklist* as the first page, and cross-reference all sections of the dossier, including associated annexes, to this checklist.
- Ensure that there are appropriately named tab identifiers. The names shall link directly with the sections of the dossier as outlined in this document. For example, the Labelling information shall be separated from the other documents by a tab identifier named "Section 5.2 Product/Package Labels".
- The page numbers in each section of the dossier and the page numbers summarized in the Product Dossier Checklist should correspond.
- Font sizes for text and tables are of a style and size that are large enough to be easily legible. Fonts smaller than 12 points should be avoided whenever possible, except in tables and footnotes where a font size of 10 points is acceptable.
- Depending on the level of detail, the information requested in each section may either be:
    - Provided directly in the corresponding section of the main product dossier file, preceded by an explanatory summary of the information, as appropriate, or
    - Provided in summary in the corresponding section of the main product dossier file, with the detailed information (full study validation reports, photographs, other documentation, etc.) included as annexes, duly cross-referenced both in the corresponding section of the report and the *Product Dossier Checklist*.
- Refer to related annexes in the body of the text and list them in the *Product Dossier Checklist*.

D.3. Electronic copy requirements

Portable Document Format (PDF) is the primary file format used for product dossiers. However, *do not* include any PDF that requires a password to open it. This will result in return of dossiers to manufacturers resulting in the delay of the assessment.

Use file names that are descriptive of a file's content and meaningful to dossier reviewers. The name can be up to 125 characters and can have spaces, dashes (not elongated dashes), underscores, and periods. However, the name of the file shall not contain any of the following special characters as they are not compatible with NAFDAC's storage platform:

tilde (~) apostrophe (') colon (:)

vertical bar (|)	greater than sign (>)	various other symbols
asterisk (*)	single quotation mark (‘)	(e.g., →,*,β,α,∞,±,™)
forward slash (/)	less than sign (<)	pound sign (#)
elongated dash (–)	double quotation marks (“)	
backward slash (\)	question mark (?)	

- When creating a PDF from an electronic source document (e.g. Microsoft Word document) avoid using specialist application plug-ins for capture or display data; not all dossier reviewers will necessarily have access to these plug-ins.
- As far as practicable, electronic files shall contain searchable text. Electronic files made by directly scanning paper documents are generally low quality and are difficult to read; moreover, the lack of searchable text can make dossier information difficult to readily locate and may delay assessment of the dossier.
- For any scanned document, optical character recognition (OCR) should be used to allow text to be searchable. This can be verified by: (1) highlighting an area of text and (2) using the software search function to locate a particular word or phrase. If the word or phrase is not returned in the search, then the OCR did not recognize the text and it is, therefore, not searchable.

D. 4. **Acceptance of dossier previously prepared for national regulatory**

Product dossiers should be compiled according to the WHO requirements described above. However, WHO may accept submissions previously prepared for national regulatory authorities if:

- all the information required by WHO is included
- the information is fully cross-referenced to the requirements of this document using the Product Dossier Checklist
- the information reflects current activities and practices (expired/superseded documentation shall not be used)

D.5. **Language and units of measurement**

Information in the product dossier shall be in English

Any document provided in a language other than English shall be accompanied by a certified translation that is signed and dated by the translator and where the translator has stated that it is a true and accurate translation of the original document.

All measurements units used should be expressed in the International System of Units (SI), as appropriate.

1. **Administration**

1.1. **Cover letter**

A cover letter for submission of product dossier for regulatory review addressed to the Director General, NAFDAC

Attn: Director Drug Registration and Regulatory Affairs

NAFDAC, Isolo, Lagos.

1.2. **Submission Table of Contents**

The Table of Contents [ToC] NAFDAC Product Dossier Checklist shall be included at the beginning of the product dossier. The checklist shall be signed, dated and include a declaration attesting that all the information provided in the product dossier is current and correct.

- NB: this item is a specific requirement for NAFDAC product dossiers and does not exist as a heading in the IMDRF ToC dossier format.

1.3. **List of term/Acronyms**

Abbreviations used in this submission shall be defined here.

1.4. **Application form/Administrative information**

Information that was submitted in the application for product registration on the NAPAMS portal will be considered during the review of the product dossier. Therefore, manufacturers/authorized representative shall ensure that the content of the product dossier is consistent with the information submitted in the Application form and that any changes in the information submitted in or as part of the Application Form are promptly notified in writing to NAFDAC. This may include problems identified during vetting of the product application on the NAPAMS platform.

1.5. **Listing of devices (s)**

In this section, the manufacturer shall summarize the different configurations/variants of the product that are intended to be the subject of the submission. This information shall be consistent with that provided in the application for product registration. Please note, a detailed description of configurations/variants is provided in section 2.4.1.

1.6. **QMS or other Regulatory certificates**

In this section, the manufacturer should provide evidence of a valid quality management system, such as an ISO 13485:2016 certificate issued by a Conformity Assessment Body. The product under assessment shall be within the scope of the certification.

1.7. **Free sale certificate/Certificate of Registration (Marketing Authorization)**

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.
- The evidence should clearly show that the product under assessment falls within the scope of the submitted regulatory approval.
- Copies must be certified by a notary public or by the manufacturer. The manufacturer may be asked to present the original copy at any time.

1.10. **Statements, Certificates, Declarations of Conformity**

1.12.5. **Truthful and accurate Statement**

A declaration attesting that all the information provided in the product dossier is current and correct shall be signed and date and included as part of Section 1.2 Submission Table of Contents.

2. **Submission context (Product Information)**

2.4. **Device description**

2.4.1. **Comprehensive device description and principles of operation**

The dossier should include product descriptive information sufficient to allow a dossier reviewer to understand the design applied to the product and how it functions. The instructions for use (IFU) may be used to provide some of this information, on the condition that it is clearly indicated in the dossier what information can be found in the IFU. The following information shall be provided in

this section:

- A general description of the principle of the assay method or principles of operation of the instrument.
- 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 (e.g., antibodies, antigens, nucleic acid primers).
- If applicable, a description of the various configurations/variants that will be made available for the product under assessment.
- If applicable, a description of the accessories, and other products that are intendedto be used in combination with the diagnostic.
- Photographs of the product and all of its components including all accessories and/or auxiliary components either supplied with the product or ordered separately, as well as any variants/configurations. Photographs should comprise individual components; where possible, photographs of the entire product, in its final packaging configuration, should be provided.
- A description and photographs of the specimen collection and/or transport containers/materials that are provided with the product, or descriptions of specifications recommended for use.
- A statement as to whether the product is automated, semi-automated or manually operated.
- For automated and semi-automated assays: a description of the dedicated instrumentation, or for assays that do not require dedicated instrumentation; a description of the appropriate instrumentation characteristics; and a description of the dedicated consumables.
- A statement as to whether the test output is qualitative, semi-quantitative or quantitative.
- If applicable, a description of any software to be used with the product**.**

2.4.1. (g) **Biological material**

In this section, the manufacturer shall provide a table or list of all biological components included in the product under assessment.

- The table or list shall include (as applicable):
    - The name of the biological component (i.e. material of bacterial, viral, parasitic, animal, or human origin, such as plasma, cells, tissues, or their derivatives. For example, human CD4 cells, human plasma, recombinant proteins expressed in bacteria, monoclonal antibodies from modified murine cells, bovine or other animal material, ruminant proteins (bovine, ovine, caprine), or fish proteins).
    - Details of the use of the biological component in the product.
    - A description of steps taken for the reduction of transmission or infection risk (such asinactivation or removal of infectious or transmissible agents, certification of country of origin (e.g. to indicate transmissible spongiform encephalopathy (TSE)-free herds), validation studies or risk mitigation measures).
- Provide a determination of the residual risk of transmission or infection to the user of the device from these biological agents after risk reduction methods have been applied.

- For biological material (such as serum or plasma), include a statement indicating that the material has been tested for evidence of infection (e.g. tests for specific antigens, antibodies, nucleic acids, etc.), and the results of that testing (positive or negative for each).
    - Typically, this would include, at a minimum, testing for evidence of infection with HIV, hepatitis B virus, and hepatitis C virus by the most sensitive methods available for the given analyte.
    - If there are no such methods that apply to the product, state that this is the case.
- Provide information as to how users of the device are informed of any residual risk.

2.4.2. **Material specifications**

In this section, the manufacturer shall provide details of the critical raw materials used in the product.

For each of the raw materials/ingredients, provide the formulation or composition information. For example, include information such as nucleic acid sequences for primers, ingredient lists for buffers, amino-acid sequence details for recombinant proteins, and clone and isotype of antibodies.

Depending on the intended use of the product, include a brief description of key reagents used in the test (e.g. capture antigens and/or antibodies) and how they were designed and purified (e.g. whether monoclonal antibodies were used; what epitopes are targeted).

Identify the sources of the materials from which the IVD components are constructed, which, depending on the product will include:

- Whether they are manufactured in house or purchased commercially.
- From what species they are derived.

2.4.4. History of development

In this section, the manufacturer shall provide the date of design lock down (design freeze). This is the date that final documentation is signed off, including quality control and quality assurance specifications, and the finalized method is stated in the IFU.

Where design change has occurred since the date of design lock down the manufacturer shall provide records of each such change, including:

- The reasons that each change was made.
- References to validation/verification data to support the change (this may be cross referenced to studies provided in the product dossier).
- Evidence that the product continues to comply with the Essential Principles**.**

Product related changes include but are not limited to product formulation, intended use, presentation, packaging, shelf life, manufacturing, quality control release criteria.

Where different versions and/or prototypes of the product are referred to in dossier, the manufacturer shall provide a table describing the version/name, with four columns (device name and/or version; description of changes from previous row; reason for the change; list of verification/validation activities (including clinical studies) conducted using this version). This table should also describe how the product IFU has changed between different versions of the product and make clear which versions of the IFU were used in different performance studies. This section

shall also include an explanation, with supporting evidence as appropriate, that use of earlier versions of the product in the dossier is representative of the current product.

2.5. **Indications for use and/or intended use**

Relevant WHO guidance: See TGS-5 Designing Instructions for use for IVDs *(7)* for additional detailed information regarding the content of an intended use statement.

2.5.1. **Intended use; Intended Purpose, Intended User; Indications for Use**

In this section, the manufacturer shall provide a description of both the intended use, and the intended user of the product. This section should provide sufficient detail to allow it to be understood:

- What the product is intended to detect (e.g. analyte).
- The function of the product (e.g., screening [e.g. for surveillance or safety of blood supply]; aiding the diagnosis and determination of a patient's disease course and prognosis; monitoring patient therapy or following their progress after treatment; staging or aid to determining the stage of a disease; disease differentiation or prediction; etc.).
- The clinical indication for the IVD (i.e. the specific disorder, condition or risk factor of interest that the product is intended to detect, define or differentiate), as appropriate.
- The type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine, etc.) and any additives (e.g. anticoagulants used in specimen collection).
- The intended testing population (e.g. neonates, pregnant women, symptomatic individuals, etc.).
- The intended user (e.g. laboratory professional, health care worker at point-of-care, etc.).

2.5.2. **Intended environment/setting for use**

In this section, the manufacturer shall provide a description of the intended setting of use of the product (e.g. laboratory, point-of-care setting, etc.).

2.6. **Global Market history/(Commercial History)**

2.6.1. **Global Market History**

Different regulatory requirements apply to different international markets for IVDs. Manufacturers who market their IVDs to multiple countries often alter some aspects of their products to comply with regional regulatory requirements and marketing needs (e.g., differences in design, information within the instructions for use, different intended use statements, different batch release procedures, different sites of manufacture, different information on package labels). If such various versions of a product exist, NAFDAC must have a clear understanding of precisely which version of the product the manufacturer is seeking to be registered. In this section:

- Identify if there are multiple regulatory versions of this product. If the product has multiple regulatory versions, clearly indicate which regulatory version of the product the manufacturer submitted for the purpose of registration.
- Identify the version that is being submitted for regulatory assessment. If the version has not been assessed in any jurisdiction, indicate this.
- Ensure that all documents submitted in the product dossier identify the regulatory version to which they relate. Where it is not the version submitted for regulatory assessment, a justification for its inclusion in the product dossier shall

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

- Provide a list of all countries in which the product under assessment is currently supplied and the year when supply started.

2.6.2. **Global Incident reports and recalls**

In this section, the manufacturer shall provide:

- A list of all adverse events within the last five years that did affect, or could have potentially affected, the performance of the product, safety of the person being tested, safety of users of the product, or safety of any person associated with the product. Include details of the corrective and preventive action taken.
- Details regarding any situations in which the product was rejected by a National Regulatory Authority, situations in which an application for regulatory approval was withdrawn, or situations in which regulatory approval has been withdrawn. Include details of the corrective and preventive action taken.
- A list of all events within the last five years that required field safety corrective action such as:
- Withdrawal of products from sale or distribution.
- Physical return of the product to the manufacturer.
- Product exchange.
- Destruction of the product.
- Product modification(s).
- Additional advice provision to customers to ensure that the product continues to function as intended.

2.7. **Other Submissions Context Information**

2.7.2. Training and support networks

The information provided in this section shall include:

- Detailed information about the training and support network that will be made available in-country upon granting of marketing authorization, including:
- How the users are trained in the operation of the product
- How the users of the product can contact the supplier/manufacturer for technical support
- A statement as to whether there is representative located in Nigeria that can provide technical support; and if so, how well.

3. **Non-Clinical evidence**

3.2. **Risk management**

Relevant WHO Guidance: See TGS-7 Risk Management for manufacturers of IVDs for additional detailed information.

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 and in the intended settings of use.

- 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.

3.3. Essential Principles (EP) Checklist

The product dossier will provide evidence of conformity to the "Essential Principles" as outlined in the IMDRF document IMDRF/GRRP WG/N47 FINAL:2018 Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices. (***3***)
Conformity to the Essential Principles shall be summarized in an Essential Principles Checklist, a table that includes:

- Whether each Essential Principle applies to the product and if not, a justification for why this is not the case.
- The method used to demonstrate conformity with each relevant Essential Principle, as well as the reference for the method used.
- A reference to specific technical documentation that demonstrates conformity to each relevant Essential Principle (where such documentation is specifically required for inclusion in the product dossier, its location in the product dossier shall be provided).
- Identification of specific standards or guidelines referenced, as appropriate.

Note: Annex 1 of this document contains additional information regarding the Essential Principles checklist, as well as a sample checklist. Note that Annex 1 does not show a complete list of *Essential Principles* but is meant to serve as an example. The manufacturer shall provide a complete table extracted from the IMDRF document listed above that addresses all the *Essential Principles* applicable to IVDs.

3.5. Analytical performance

Relevant WHO guidance: See TGS-3 Principles of performance studies *(6)* for additional detailed information.

3.5.1. Stability of specimen(s)

In this section, the manufacturer shall provide studies to support the stability, storage and where appropriate, transport, of all specimen type(s) identified in the labeling,

including any and all recommended additives (e.g. anticoagulants). This information, presented as described in section C.4, 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.

3.5.2. **Validation Specimens**

In this section, the manufacturer shall provide information regarding the types of specimens that can be used with the IVD.

The different specimen types that can be used with the product shall be identified, including detailed information for each matrix and anticoagulant, and whether contrived specimens have been used in the study, as applicable. The method used to generate contrived specimens shall be described. Specimen types claimed in the product dossier shall be consistent with those reported in the product IFU.

Evidence supporting claims of performance in each claimed specimen type (including anticoagulants) shall be provided as described in section C.4.

Depending on the product, information should be provided on the relationship of specimens collected by different methods (e.g., specimens that can be collected by a swab or by other means), as applicable.

The established relationship between product performance in claimed specimen types (e.g., plasma, blood, dried blood spots [DBS], etc) shall be considered in the design of subsequent studies. For example, if it is demonstrated that two or more claimed specimen types are equivalent, then not all specimen types need necessarily be tested in all subsequent studies. If there is no equivalence between claimed specimen types, then the impact that this will have on each subsequent performance claim shall be fully understood and described.

3.5.3. **Metrological traceability of calibrator and control material values**

In this section, the manufacturer shall provide detailed information about the traceability of values assigned to calibrators and trueness control materials supplied with the product (if applicable) and those used for the manufacturing process. Include, for example, methods and acceptance criteria for the traceability to reference materials and/or reference measurement procedures and a description of value assignment and validation.

Note: Precision control materials used when establishing the reproducibility of a measurement procedure do not require the assessment of traceability to reference material

3.5.4. **Accuracy of measurement**

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

3.5.4.1. **Trueness**

Trueness measures apply to both quantitative and qualitative assays only when a reference standard or method is available.

In this section, the manufacturer shall provide evidence that establishes the trueness of the product. Information shall be provided, as described in section C.4, in sufficient detail to allow an understanding of the adequacy of the approach. Where this evidence has been generated as part of other performance evaluations, this evidence should be reported in the appropriate section of the product dossier and a reference to it made here.

3.5.4.2. **Precision (repeatability and reproducibility**

In this section, 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). In addition to the information specified in section C.4, 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.

3.5.5. **Analytical sensitivity**

This section shall include 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.

For a quantitative assay, identify the following parameters and provide details as to how they were derived:

- Limit of blank (LoB): the number of standard deviations above the mean value of the specimen without analyte (measurand).
- Limit of detection (LoD): the lowest concentration distinguishable from zero, based on measurements of specimens containing analyte (measurand).
- Limit of quantitation (LoQ): the lowest concentration at which precision and/or trueness are within specified criteria.

In addition to the information described in section C.4, 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.

3.5.6. **Analytical specificity**

This section 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.

In this section, the manufacturer shall provide studies, as presented in section C.4, 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.

3.5.7. **High dose hook effect**

In this section, the manufacturer shall provide evidence, as described in section C.4, 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 registered. This second method shall be of a design not subject to prozoning.

3.5.8. **Measuring range of the assay**

Relevant WHO guidance: See TGS-6 Panels for quality assurance and quality control of in vitro diagnostic medical devices *(9)* for additional detailed information.

This section provides information regarding 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 as to 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 identified in sections C.4 that allow an understanding of the approach and its validity.

3.5.9. **Validation of assay cut-off**

In this section, 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). Evidence in this section shall be presented as described in section C.4.
For products that include the use of a test reader, the way in which the reader has been designed to differentiate reactive specimens from those that are non-reactive shall be demonstrated.

3.5.10. **Validation of the assay procedure**

In this section, 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.
Evidence in this section shall be presented as described in section C.4. These studies may be conducted as part of investigations into the robustness of the product (see

section 3.6.4 Usability/Human factors).

3.6. **Other studies**

3.6.4. **Usability/Human factors**

In this section, 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 to 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, and/or 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 requirements summarized in section C.4, 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 studies, as described in section C.4, 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.

Manufacturers are reminded to refer to the corresponding TSS to understand the requirements for usability studies relevant to their product.
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.

3.6.5. Stability of the IVD

Relevant WHO guidance: See TGS-2 Establishing the stability of an IVD (10), Annex to TGS 2 Establishing component stability for in vitro diagnostic medical devices (11) and TGS-3 Principles of performance studies (6) for additional detailed information.

This section describes 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 can be 12 months.
Each of the studies referred to in section 3.6.5 for product stability must be presented as described in section C.4. 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.

3.6.5.1. Claimed shelf life

In this section, the manufacturer shall provide information and studies that support the claimed shelf life of the product. Determination of product shelf life shall be preceded by a simulated transport challenge using storage conditions that mimic environmental conditions likely to be encountered in resource-limited Sub-Sahara Africa -Zone IVB.
The product lots used for shelf life determination shall be equivalent to routine production. Product lots shall be in their final configuration, if the product is available in different configurations, testing shall be conducted on all configurations.
The final claim of shelf life shall be based on real-time stability testing. Claims of shelf

life from accelerated studies may be accepted as preliminary estimates, provided real-time studies are underway. The method used to estimate shelf life from accelerated data shall be provided.

3.6.5.2. **In use-stability**

In this section, the manufacturer shall provide information, as described in section C.4, establishing the in-use stability of each labile component in the product. Depending on the product this may include: test cartridge, buffer, conjugate, substrate, stopping solution and other prepared, or reconstituted working reagents.

In-use stability shall reflect actual routine use of the device (real or simulated)**.** Depending on the product, this would include open vial stability and/or, for automated instruments, on-board stability. Consideration shall be given to multiple accessing of reagent bottles or plate pouches (opened several times during its use).

In the case of automated instrumentation, if calibration stability is claimed, then supporting data shall be included.

3.6.5.3. **Shipping stability**

This section describes evidence in support of claims that the product is not affected by the extremes of conditions likely to be encountered during transport to the end-user once a product has been manufactured.

It is expected that a product is subjected to a simulated shipping challenge before commencing real- time shelf life determination (see section 3.6.5.1). Consequently, a separate shipping stability study is not necessarily required in this section.

If a separate shipping stability study is provided in this section, please refer to study requirements summarized in sections C.4, 3.6.5 and 3.6.5.1.

In this section, the manufacturer shall provide information and studies that demonstrate that the product, in its final packaging, has been subjected to drop-shock testing.

3.8. **Other evidence**

3.8.1 **Testing In Performance Panels And Other TSS Specific Evidence**

Depending on the intended use of the product, the corresponding TSS may stipulate requirements for additional studies that establish particular claims for product performance. These may include studies that demonstrate antibody neutralization (e.g. for IVDs with a confirmatory function), performance at critical decision points and/or testing in performance panels, such as:

- Seroconversion panels.
- Genotype panels.
- Subtype panels.
- Mixed-titre panels.

In this section, the manufacturer shall provide information, as described in section C.4, that demonstrates performance of the product according to the specific WHO TSS requirements.

4. 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 will include claims for clinical or diagnostic sensitivity and specificity.

4.2. **Overall clinical evidence summary**

Relevant WHO guidance: See TGS-3 Principles of performance studies *(6)* for additional detailed information.

In this section, the manufacturer shall provide a brief (1-2 page) summary of the available clinical evidence being presented in support of the submission. The document should list the evidence presented, its characteristics and provide a discussion of how this is considered sufficient to support request for marketing for the requested indications. A tabular listing of clinical studies may be included in this section. This section should also include a discussion to support why the evidence presented is sufficient to support the application.

4.2.1. **Expected values/reference rangers**

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

4.2.3. **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 information described in section C.4, 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.

4.5. **Other clinical evidence**

4.5.1. **Qualification of Usability**

Depending on the intended use of the product (e.g. self-testing), the corresponding TSS may stipulatea requirement for clinical evaluation of the usability of the product. In this section, the manufacturer shall provide information, as described in section C.4, that demonstrates the performance of the product when used by observed, untrained self-testing users.

5. **Labelling and Promotional Materials**

5.2. **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 forshipping). 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 themanufacturer, on the outer package labels.
- The name of the reagent/ingredient.
- The manufacturing and expiry dates
- 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 bedisplayed).
- 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, manufacturing and expiry dates, volume, and storage conditions.
- If the product requires associated instrumentation, the requirements listed above also applyto the instrument.

5.3. Packaging insert/Instructions for use

Relevant WHO guidance: See TGS-5 Designing Instructions for use for in vitro diagnostic medical device*(7)* for additional detailed information.

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 consistentwith 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. themarker or nucleic acid sequence being detected).
  - The clinical indication for the test (e.g. if it is for a specific disorder, or a conditionor 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 (self-tester, 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 orrecommended for use.
- For instruments of automated assays: a description of the appropriate assay characteristics ordedicated 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 usedin 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 about 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.

5.6. **Technical/operators manuel**

If the product requires associated instrumentation, include a copy of the instrument manual and/or associated operator manuals.

5.8. **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.

6.A. **Quality management system procedures**

6.A.4. **Quality management system procedures**

An effective quality management system is a key consideration for all manufacturers of IVDs.
Therefore, products submitted for regulatory assessment shall be manufactured under an appropriate quality management system. The manufacturer's quality management system shall cover all sites used to manufacture this product.

The quality management standard ISO 13485:2016 Medical devices — Quality management systems

— *Requirements for regulatory purposes (12)* is a benchmark in quality management for manufacturers of IVDs for regulatory authorities throughout the world. NAFDAC bases its product dossier assessment and inspection processes on the requirements of this internationally-recognized quality management standard.

In this section, the manufacturer shall provide high level quality management system procedures for establishing and maintaining the quality management system, including a copy of the current version of the manufacturer's quality manual. The following aspects shall be addressed (or referred to) in the quality manual:

- title and scope
- table of contents
- review, approval and revision
- quality policy and objectives
- organization, responsibility and authority
- references
- quality management system description
- appendices
- document control information relevant to the quality manual, including version number, release date and approval record

Provide the documented procedure(s) relevant to risk management planning and implementation Provide a list of current quality management procedures.

6.A.6. **Resource management procedure**

In this section, the manufacturer shall provide:

- A staff organogram.
- The number of employees at the manufacturing site.

6.A.7. **Product realization procedures**

In this section, the manufacturer shall provide high level product realization procedures such as those addressing planning and customer related processes.

6.A.8. **Design and development of procedures**

In this section, the manufacturer shall provide procedures that document the systematic and controlled development of product design from initiation of a project to transfer to production, including those relevant to change control/change notifications [product and processes]). This shall include information regarding the design processes specific to the product under assessment, including a flowchart of the design process that outlines design inputs and outputs for the product. If design takes place at multiple sites, the controlling site shall be identified.

6.A.9. **Purchasing procedures**

In this section, the manufacturer shall provide procedures that document that purchased products/services conform to established quality and/or product specifications, including those relevant to the evaluation and control of key suppliers and verification of purchased product/services.

6.A.10 **Production and service controls**

In this section, the manufacturer shall provide procedures that document that 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 and shall include:

- An overview of verification, validation and quality-control activities for all stages of design and manufacture (including purchased components, in-process products, and finished products)
- A list of outsourced processes with direct product impact (e.g. outsourced manufacturing of components (conjugated antibodies, strips, reagents, etc.), outsourced laboratory testing, packaging, printing, etc.) including details of the supplier for each process
- The batch release criteria for the product under assessment as well as documented procedures for how these were determined.

6.A.12. **QMS measurement analysis and improvement procedures**

In this section, the manufacturer shall provide procedures that document monitoring, measurement, analysis and improvement to ensure the conformity of the product and QMS, and to maintain the effectiveness of the QMS, including those relevant to control of nonconforming goods/processes and complaint handling and vigilance.

6B.9 **Production and service controls information**

In this section, the manufacturer shall provide:

- A description of the manufacturing site(s), including:
  - Full address(es), including latitude and longitude of the manufacturing facility(s).
  - A site master file, with a diagram of the floor plan, highlighting production areas.
- A flow chart of the entire manufacturing process including in-process control points.
- Details of each major step (including in–process control points and final product testing and packaging) in the manufacturing process.
- An overview of verification, validation, and quality control activities for all stages of design and manufacture.
- A list of critical raw materials (including details and address of the supplier of outsourced materials and their corresponding certificates of analysis).
- A list of outsourced processes with direct product impact (e.g. outsourced manufacturing of components (conjugated antibodies, strips, reagents…), outsourced laboratory testing, packaging, printing, etc.) including details of the

supplier for each process.
- A description of any other manufacturing that occurs at each site.

7. **Contact Information**

Any inquiries regarding the dossier submission/review should be addressed to: bvmregistration@nafdac.gov.ng

8. Annex 1 - Essential Principles (EP) checklist

The EP checklist is used by manufacturers 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. More 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 is a recommended template for the EP checklist. Preparation of the EP checklist as outlined below will provide a useful overview of the manufacturer's conformity to the Essential Principles.

Note: Examples of completed EP checklists can be found in the WHO Sample Product Dossiers for WHO Prequalification, available at: https://extranet.who.int/pqweb/sample-product-dossiers
These are provided for illustrative purposes and it is important to ensure that the latest version of the IMDRF guidance document *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices* IMDRF/GRRP WG/N47 FINAL:2018 be referred to.

8.1. How to fill the checklist

8.1.1. Identity of the IVD

The manufacturer shall identify the IVD, and when applicable the various configurations/variants covered by the checklist.

8.1.2. Is the list applicable to the IVD

Is the listed Essential Principle applicable to the IVD? Here the answer is either 'Yes' or 'No'.

If the answer is 'No' this shall be briefly explained.

8.1.3 Method used to demonstrate conformity

In this column, the manufacturer shall state the type(s) of method(s) that it has chosen to demonstrate conformity e.g. the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used.

The method used to demonstrate conformity may include one or more of the following:
- conformity with recognized or other standards;
- conformity with a commonly accepted industry test method (reference method);
- conformity with appropriate in-house test methods that have been validated and verified;
- comparison to a diagnostic already available on the market.

8.1.4. **Method reference**

After having stated the method in the previous column, in this column the manufacturer shall name the title and reference the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used to demonstrate conformity. When referencing a standard, the manufacturer shall state the date of the standard and where appropriate, the clause(s) that demonstrates conformity with the relevant EP.

8.1.5. **Reference to supporting controlled documents**

This column shall contain the reference to the actual technical documentation that demonstrates conformity to the Essential Principle, i.e. the certificates, test reports, study reports or other documents that resulted from the method used to demonstrate conformity and its location within the product dossier.

Note: The table that follows is for illustrative purposes only. The *Essential Principles* listed in the first column should be extracted from the latest version of the IMDRF guidance document *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices* IMDRF/GRRP WG/N47 FINAL:2018 (***3***)

Essential Principles Checklist				
Identity of the IVD:				
Essential Principle	**Applicable to the device?**	**Method Used to Demonstrate Conformity**	**Method Reference**	**Reference to 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 points5.1.3 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.				

9. **Annex 2 Example declaration of authenticity**

This declaration should appear on the front page of the document being certified or notarized.

Declaration of authenticity

I, the undersigned, as a …….. …….. for the state of ……..,
country……..
Declare that the attached copy of the document issued by and certified by me, is a true and accurate copy of an original document presented to me for certification.

10. Reference

1. WHO document PQDx_049 *Product Dossier Checklist*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/what-we-do
2. WHO document PQDx_007 *Overview of the Prequalification of In Vitro Diagnostics Assessment*. Available at: https://extranet.who.int/pqweb/key-resources/documents/overview-who-prequalification-vitro-diagnostics-assessment
3. IMDRF document IMDRF/GRRP WG/N47FINAL:2018 *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices*. Available at: https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf
4. IMDRF document IMDRF/RPS WG/N13 FINAL:2019 (Edition 3) *In Vitro Diagnostic Medical Device Market Authorization Table of Contents*. Available at: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-ivd-mdma-toc-n13.pdf
5. WHO document PQDx_15 *Pre-Submission Form*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/procedures-and-fees-prequalification
6. WHO guidance: TGS-3 *Principles of performance studies*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/technical-guidance-series
7. WHO guidance: See TGS-5 *Designing Instructions for use for in vitro diagnostic medical devices*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/technical-guidance-series
8. WHO guidance: TGS-7 *Risk management for manufacturers of in vitro diagnostic medical devices*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/technical-guidance-series
9. WHO guidance: TGS-6 *Panels for quality assurance and quality control of in vitro diagnostic medical devices*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/technical-guidance-series
10. WHO guidance: TGS-2 *Establishing stability of in vitro diagnostic medical devices*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/technical-guidance-series
11. WHO guidance: Annex to TGS-2 *Establishing component stability for in vitro diagnostic medical devices*. Available at: https://extranet.who.int/pqweb/vitro-diagnostics/technical-guidance-series
12. ISO 13485:2016 Medical devices – Quality management systems – Requirements for regulatory purposes. Geneva: International Organization for Standardization; 2016.

Annexure

National Agency for Food & Drug Administration & Control (NAFDAC)

Drug Registration and Regulatory Affairs (DR&R) Directorate

Product Dossier Checklist for In Vitro Diagnostics

The attached Product Dossier contains information in support of the submission of in vitro diagnostics for the following product.

Product Name:		
Manufacturer Name:		

Instructions for the reader:

The information in this checklist is used in the screening for completeness and dossier review phase of the registration process. The NAFDAC requires that a product dossier is submitted in the format described in this document.

- All sections listed in the table are required to be submitted as part of the product dossier for full assessment unless indicated "if applicable".
- The requirements for an abridged dossier submission are noted in the column "Abridged requirements" (R= required, NR= not required).
- Insert Yes or No in the "Provided" column whether each section is supplied. Where information is not available or the field is not applicable, type in N/A.
- In the "Location" column, state the associated page numbers and volume or section number as required for each field.
- The manufacturer is requested to submit this form as a searchable PDF file. The Manufacturer Declaration on page 16 of this document may be signed electronically.

Dossier Content Requirement	**Provided**	**Location**
DOSSIER FORMAT		
Product Dossier Submission Format		
One electronic copy of the product dossier submitted		
Layout and Order		
Proper formatting of page numbers for example page 1 of 2, 2 of 2, etc., used		
The submission is clearly divided into sections as described and all pages are numbered		
Font sizes are easily legible		
Electronic Copy Requirements		
The electronic copy is in PDF form with no password required		
The name of the file is descriptive and doesn't contain any of the noted special characters		
Language and Units of Measurement		
English language and International System of Units of measure used		
Any translations have been carried out by a certified translator (if applicable)		
1.0 ADMINISTRATIVE		
1a. Manufacturer Information		

Name		
Address		
Contact (e-mail, website, phone number)		
Brief overview of the company (Business summary)		
1b. Local Applicant Information		
Name		
Address		
Contact (e-mail, website, phone number)		
1.1 Cover letter		
The Letter of Agreement is attached to the front page of the dossier		
The information concerning the product in the dossier provided is the same in the Letter of Agreement and the Prequalification Dossier		
1.2 Submission table of content		
This table of contents appears at the beginning of the product dossier		
Each section is numbered and named according to the Product Dossier Checklist		
The physical pages of the dossier and the page numbers in this checklist correspond		
1.3 List of terms/Acronyms		
Abbreviations and acronyms used in the submission are defined		
1.4 Application form/Administrative information		
A copy of the completed Registration Application Form to which this submission relates is included		
The information in the product dossier is consistent with the completed Application Form: if not, any differences are explained and supporting evidence provided		
1.5 Listing of devices		
A list of configurations is included, if applicable		
A list of accessories and/or other products to be used with the IVD is included, if applicable		
1.6 QMS or other regulatory certificates		
A certified copy of the manufacturer's quality management system certificate is included		
1.7 Free sale certificate/Certificate of marketing authorisation		
If applicable, a list of National Regulatory Authorities that have provided current regulatory approval for the supply of the IVD and the type of regulatory approval obtained is included		
Certificates provided by National Regulatory Authorities where the IVD is approved for use are included, if applicable		

Information relating to export-only regulatory approvals are clearly identified		
1.12 Statements/Certifications/Declarations of conformity		
1.12.5 Truthful and accurate statement		
The Manufacturer Declaration at the end of this checklist, that all the information provided in the product dossier is current and correct, has been signed and date.		
2.0**. SUBMISSION CONTEXT (PRODUCT INFPRMATION)**		
2.4 Device description		
2.4.1 **Comprehensive device description and principle of operation**		
A description of the principle of the assay method/instrument principles of operation are provided		
A description of the components and reactive ingredients are included		
Photographs of all kit components, both packaged and individual, are included		
A description and photographs of the specimen collection and transport materials are provided		
A statement as to whether the test output is qualitative, semi-quantitative or quantitative		
A statement as to whether the product is automated, semi-automated or manually operated		
For automated and semi-automated assays: a description of the dedicated instrumentation, or for assays that do not require dedicated instrumentation, a description of the appropriate instrumentation characteristics; and a description of the dedicated consumables.		
If applicable, there is a description of software to be used with the product		
2.4.1(g) **(a) Biological material**		
A table of all biological materials is provided that includes identity of each material, origin, source (e.g. blood, tissue etc) and where it is used in the product		
For each biological material, a description of the steps taken to reduce transition or infection risk is provided		
If applicable, a determination of the residual risk of transmission/infection to the user is provided and how the user is informed of any residual risk		
2.4.2 **Material specifications**		
A list of all critical raw materials and components used in the product is provided		

For each identified raw material or component, details of the formulation and composition are provided		
Sources of IVD component materials are identified		
2.4.4 **History of development**		
A table summarizing all versions of the product referred to in the dossier is provided, if applicable		
Date of design lockdown (design freeze) is provided		
Any changes to the product have been documented and supporting evidence provided		
2.5 Indications for use and/or intended use		
2.5.1 **Intended use; Intended purpose; Intended user. Indications for use**		
The intended use of the IVD, testing population, user, specimen types, analyte, and clinical indication are included		
2.5.2 **Intended environment / setting for use**		
The setting(s) where the device is intended to be used is included		
2.6 Global market history		
2.6.1 **Global market history**		
There is a list of all countries in which the product under assessment is currently supplied and the year when supply started		
All regulatory versions of the product are identified and the version being submitted for assessment is indicated		
The regulatory version to which the information in the product dossier relates is identified		
2.6.2 **Global incident reports and recalls**		
If applicable, a list of all adverse events within the last five years with details of the corrective and preventive action taken is provided		
If applicable, details are provided regarding any situations in which this product was rejected by a National Regulatory Authority or regulatory approval was withdrawn		
2.6.4 **Evaluation/inspection reports**		
The most recent full and subsequent surveillance regulatory inspection reports issued by the certification body are included		
2.7 Other submission context information		
2.7.2 **Training and support networks**		
For each country, detailed information about the training and support network is provided, including whether manufacturer representatives are located in the country		
3. NON-CLINICAL EVIDENCE		
3.2 **Risk management**		
There is a summary report of the risks identified during the risk analysis process		

A description of how risks have been controlled to an acceptable level		
A signed conclusion with evidence that the remaining risks are acceptable is presented		
There is evidence that the risk analysis is part of the manufacturer's risk management plan		
When applicable, specific standards/guidelines recommended by the WHO are identified		
3.3 **Essential principles checklist**		
A checklist in the form of a table that lists all relevant material is included		
This checklist is filled in as per the description and examples provided in the instructions and annexes		
3.5 Analytical performance		
Product performance specifications and associated validation and verification studies with the following information provided for each section: a study description, study summary, full study protocol and report		
3.5.1 Stability of specimen(s)		
Studies and required information to support stability, storage and where applicable transport condition claims for each specimen type are included		
3.5.2 Validation of specimens		
The different specimen types that can be used with the product are identified		
Studies to support each specimen type are included		
3.5.3 Metrological traceability of calibrator and control material values		
Detailed information about the traceability of values assigned to calibrators and control materials supplied with the assay (if applicable) and those used in the manufacturing process.		
3.5.4 Accuracy of measurement		
3.5.4.1 Trueness		
Studies to establish trueness of measurement are provided, where applicable		
3.5.4.2 Precision of measurement (repeatability and reproducibility)		
Studies and information needed to establish within-run variability are included		
Studies and information to establish the appropriate types of variability (between-run, -lot, -operator, -site, -instrument, etc) are included		
The use of specimens that represent the full range of expected analyte concentration are included		

If applicable, studies to establish precision undertaken by non-laboratory personnel are provided		
3.5.5 Analytical sensitivity		
Studies required to establish analytical sensitivity are included		
3.5.6 Analytical specificity		
Studies to evaluate the effects of potentially interfering and cross-reacting substances/agents on the assay are included		
3.5.7 High dose hook effect		
Studies to establish the absence of high dose hook effect are provided, if applicable		
3.5.8 Measuring range of the assay		
Studies that define the measuring range of the assay, and a description of how this was established are included, if applicable		
3.5.9 Validation of assay cut-off		
Studies on how the assay cut-off is determined are included, if applicable		
3.5.10 Validation of assay procedure		
For products where a reading interval is specified, a validation study of the critical time points is included		
3.6 Other studies		
3.6.4 **Usability / Human factor**		
The test environment and its relation to the intended environment are stated		
There is a discussion of what tests were considered for the device and why they were/were not performed		
There is a discussion to support why the evidence presented is sufficient to support the application		
If performance studies that have been conducted in other sections of the product dossier include human factors/usability end points, reference to the studies and endpoints are made		
Label comprehension study is provided, if applicable Interpretation of results study is provided, if applicable		
3.6.5 **Stability of the IVD**		
3.6.5.1 **Claimed shelf life**		
Studies supporting claimed shelf life are provided		
Testing intervals and acceptance criteria are described		
If applicable, the method used for accelerated studies is identified		
The results and conclusions clearly demonstrate that the product will be effective at the end of its claimed shelf-life after being subjected to a simulated transport challenge		
3.6.5.2 **In-use stability**		
Studies are provided for the in-use stability of each labile component		
Testing intervals and acceptance criteria are described		

The studies reflect routine use of the device (open vial stability and/or on-board stability for automated instruments, and/or multiple access of reagent bottles)		
If applicable, supporting data for calibration stability claims is provided		
Conclusions clearly identify the claimed in-use stability		
3.6.5.3 **Shipping stability**		
Studies are provided for drop-shock testing of the product		
A separate shipping stability study is not necessarily required in this section (real-time shelf-life determination shall be preceded by a simulated transport challenge; see section 3.5.1.1)		
4. CLINICAL EVIDENCE		
4.2 Overall clinical evidence summary		
4.2.1 **Expected values / reference ranges**		
The values to expect in healthy normal patients versus affected patients is provided, if applicable		
4.2.3. **IVD medical device specific clinical studies**		
All claims for clinical performance are supported by well-designed performance evaluations. These may include evaluations carried out or coordinated by the manufacturer, as well as evaluations carried out by bodies wholly independent of the manufacturer.		
Testimonials are not included as evidence of performance		
4.5 Other clinical evidence		
4.5.1 **Qualification of usability**		
A clinical evaluation of the usability of the product is provided to fulfil the product's corresponding technical specification (TSS) requirements, if applicable (i.e. observed untrained self-testing users).		
5. LABEL, LABELLING AND PROMOTIONAL MATERIAL		
5.2 **Product/package labels**		
The product dossier contains a complete set of labels associated with the product		
5.3 **Package insert/Instructions for use**		
A copy of the current instructions for use are included and these instructions include all relevant information		
5.6 **Technical / operators manual**		
If applicable, there is a copy of the instrument manual/associated operator manuals included		
5.8 **Other labelling and promotional materials**		
If applicable, copies of any other instructional materials are provided		
6A QUALITY MANAGEMENT SYSTEM PROCEDURES		
6A.4 **Quality management system procedures**		

There is a copy of the current version of the manufacturer's quality manual with all required information		
A complete list of all current quality management system procedures is included		
Documented procedure/s relevant to risk management planning and implementation are included		
6A.6 **Resource management procedures**		
Staff organogram is provided		
6A.7 **Prouct realization procedures**		
Procedures addressing planning and customer related processes are included		
6A.8 **Design and development**		
Documented procedure/s for the control of design and development changes, and change notification are included		
If design takes place at multiple sites, the controlling site is identified		
6A.9 **Purchasing procedures**		
Names and addresses of all critical subcontractors are included, where applicable		
Documented procedure/s relevant to the control of key suppliers including procedures for supplier evaluation and control, and verification of purchased product are included		
6A.10 **Production and service control procedures**		
Procedures documenting that production and services activities are carried out under controlled conditions are provided		
Documented procedures for the determination of batch/lot criteria are provided		
Batch release criteria for the product are provided		
6A.12 **Quality management system measurement, analysis and improvement procedures**		
Documented procedure/s relevant to control of nonconforming goods including, but not limited to, procedures for complaint handling, vigilance, are included		
6B.9 **Production and service controls information**		
Full addresses and contact information for all sites undertaking manufacture of the IVD are provided		
A site master file, with a diagram of the floor plan, is provided		
A flow chart of the entire manufacturing process is included		
There are details of each major step (including in–process control points and final product testing and packaging) in the manufacturing process		
List of critical raw materials is provided		
There is an overview of verification, validation, and quality control activities for all stages of design and manufacture		

List of outsourced processes with direct product impact is supplied		
A description of any other manufacturing that occurs at each site		

Manufacturer Declaration:

The undersigned authorized contact person for the Manufacturer makes the following declarations on behalf of the Manufacturer and, in signing this product dossier checklist form, declares that he/she has the authority to bind the Manufacturer.

I declare that:

- I am authorized to represent the manufacturer specified in this product dossier (the "Manufacturer") for the purposes of NAFDAC registration of In Vitro Diagnostics for the product specified in this product dossier (the "Product").
- All the information provided in this product dossier is current and correct.
- This product dossier contains all the information as is prescribed in the Instructions for Compilation of a Product Dossier.
- The Manufacturer will notify NAFDAC of all changes and variations to the Product prior to implementation of the changes.
- The Manufacturer will notify NAFDAC of any changes to the regulatory approval status for the Product, such as suspension or withdrawal of regulatory approval, in all countries of manufacture and supply.

Name of the Authorized Contact Person for the Manufacturer: _____

Signature of the Authorized Contact Person for the Manufacturer: _____

Date: _____

Please Note: The Checklist submitted to NAFDAC must be signed and date