Botswana Medicines Regulatory Authority

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1. Purpose

The intention and purpose of this guideline is

1. to assist a manufacturer to allocate its IVD medical device to an appropriate risk class using a set of harmonized classification principles
2. base such classification principles on an IVD medical device's intended use

2. Scope

This guideline applies to all products that fall within the definition of in vitro diagnostic medical devices.

3. Definitions and Abbreviations

3.1 Definitions

The following definitions shall apply:

3.1.1 Accessory to an IVD Medical Device

An article intended specifically by its manufacturer to be used together with an IVD medical device:

- to enable the IVD medical device to achieve its intended purpose: or
- to augment or extend the capabilities of the IVD medical device in the fulfilment of its intended purpose.

3.1.2 Calibration

An operation that, under specified conditions in a first step, establishes a relationship between the quantity values with measurement uncertainties provided by measurement standards and corresponding measurement indications with associated measurement uncertainties and, in a second step, uses this information to establish a relationship for obtaining a measurement result from an indication.

3.1.3 Calibrator

Measurement standard used in the calibration of an IVD test, instrument, or system

3.1.4 Companion Diagnostics Medical Device

An IVD medical device, which is essential for the safe and effective use of a corresponding medicinal product to: system.

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

NOTE 1: Companion diagnostics are essential for defining patients' eligibility for specific treatment with a medicinal product through the quantitative or qualitative determination of specific markers identifying subjects at a higher risk of developing an adverse reaction to the medicinal product in question or identifying patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective. Such biomarker or biomarkers can be present in healthy subjects and/or in patients.

NOTE 2: Devices that are used to monitor treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be companion diagnostics.

3.1.5 **Control Material**

Substance, material or article intended by its manufacturer to be used to verify the performance characteristics of an IVD medical device.

3.1.6 **Critical Situation**

situation or condition where accurate and/or timely diagnosis or treatment action is vital to avoid death, long-term disability or other serious deterioration of health of an individual patient or to mitigating impact to public health.

3.1.7 **Examination**

Set of operations having the object of determining the value of a property.

NOTE: In the IVD medical device industry and in many laboratories that use IVD medical devices, examination of an analyte in a biological sample is commonly referred to, as a test, assay or analysis

3.1.8 **Harm**

Injury or damage to the health of people, or damage to property or the environment

3.1.9 **Hazard**

Potential source of harm. (s).

3.1.10 **Indications for Use**

A general description of the disease or condition the medical device or IVD medical device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the medical device or IVD medical device is intended.

3.1.11 **Intended Use/ Purpose**

The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

3.1.12 **IVD Instrument**

Equipment or apparatus intended by the manufacturer to be used as an IVD medical device

3.1.13 **In vitro diagnostic devices (IVDs)**

Means a medical device , whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimen derived from the human or animal; solely or principally to provide information for diagnostic, monitoring or compatibility purposes which includes but not limited to – reagents used for IVD purposes, calibrators, control chemicals, specimen receptacles, software and related instruments or apparatus or other articles and are used for the following test purposes; diagnosis; aid to diagnosis; screening; monitoring; predisposition; prognosis; prediction; determination of physiological status.

3.1.13 **IVD Reagent**

Chemical, biological or immunological components, solutions or preparations intended by the manufacturer to be used as an IVD medical device.

3.1.14 **Lay User**
The individual that does not have formal training in a relevant field or discipline.

3.1.15 **Public Health**
The science and art of preventing disease, prolonging life and promoting human health through organized efforts and informed choices of society, organizations, public and private communities and individuals.

3.1.16 **Risk**
Combination of the probability of occurrence of harm and the severity of that harm.

3.1.17 **Self-testing IVD Medical Device**
An IVD medical device intended for use by a lay user who is responsible for collecting the data or specimen, by themselves and on themselves, relying solely on the instructions provided by the manufacturer. This use can also include performing the test and interpreting the results by themselves and on themselves.

3.1.18 **Software as a Medical Device (SaMD)**
Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.
NOTE: SaMD is a medical device and includes in-vitro diagnostic (IVD) medical device.

3.1.19 **Specimen Receptacle**:
Apparatus specifically intended by a manufacturer to obtain, contain and preserve a body fluid or tissue for in vitro diagnostic examination
NOTE 1: Includes devices intended to store a primary sample prior to examination.
NOTE 2: Includes both vacuum and non-vacuum primary sample collection devices.

3.1.20 **State of the Art:**
Developed stage of technical capability at a given time as regards products, processes and services, based on the relevant consolidated findings of science, technology and experience.

3.1.21 **Transmissible Agent**
An agent capable of being transmitted to a person, as a communicable, infectious or contagious disease.

3.1.22 **User**
The person, professional or lay user, who uses a medical device. The patient may be that user.

3.2 Abbreviations
The following abbreviations shall apply:
3.2.1 **IMDRF**- International Medical Device Regulators Forum.
3.2.2 **IVD** - In Vitro Diagnostic
3.2.3 **GHTF-** The Global Harmonization Task Force
3.2.4 **SaMD**- Software as a Medical Device

4. General Principles

Regulatory controls are intended to safeguard the health and safety of patients, users and other persons by ensuring that manufacturers of IVDs medical devices follow specified procedures during design, manufacture and marketing.

The risk presented by a particular device depends substantially on its intended use, indications for use and intended user.

The guidance documents on; essential principles of safety and performance of medical devices and IVDs medical devices and principles of labelling for medical devices and IVDs medical devices apply to all devices whatever their risk class.

Regulatory controls should be proportional to the level of risk associated with a medical device. The level of regulatory control should increase with increasing degree of risk, taking account of the benefits offered by use of the device.

The Classification of an IVD medical device is based on the following criteria:

1. the intended use and indications for use as specified by the manufacturer
2. the technical/scientific/medical expertise of the intended user (lay person or healthcare professional)
3. the importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician
4. the impact of the result (true or false) to the individual and/or to public health

5. Recommendations and Factors Influencing IVD Medical Device Classification

The determination of classification for an IVD medical device should be based on a set of rules derived from those features that create risk. This system should consist of four risk classes. This is sufficient to accommodate all IVD medical devices and allows an efficient and defined conformity assessment system.

I. The set of rules should be sufficiently clear that manufacturers may readily identify the class of their IVD medical device, subject, when appropriate, to confirmation by the Regulatory Authority of compliance to the relevant rule.

II. The manufacturer should document its justification for placing its product into a particular risk class, including the resolution of any matters of interpretation where it has asked a Conformity Assessment Body and/or Regulatory Authority for a ruling.

III. The rules should be capable of accommodating generally acknowledged state of the art.

IV. Where more than one of the classification rules applies to the IVD medical device, the device should be allocated to the highest class indicated.

V. Calibrators intended to be used with an IVD reagent should be placed in the same class as the IVD reagent.

VI. Stand alone control materials with quantitative or qualitative assigned values intended for one specific analyte or multiple analytes should be placed in the same class as the IVD reagent(s)

VII. Stand alone control materials with no assigned values intended for use with multiple or single analytes could be placed in the same or lower class as it is for corresponding IVD reagent(s).

VIII. Software as a Medical Device (SaMD) that processes output from an IVD Medical Device should be classified based on the SaMD's intended diagnostic purpose, with consideration given to provisions in the document "Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations" (IMDRF/SaMD WG/N12FINAL:2014).

6. Proposed General Classification System for IVD Medical Devices

A four-class system is proposed. An alphabetical system is used in this document to identify risk-based classes for IVD medical devices.

Table 1 indicates the four risk classes of devices. The examples given are for illustration only; the manufacturer must apply the classification rules to each IVD medical device according to its intended use.

Table 1; proposed general classification system for IVDs medical devices.

Risk Class	Risk Level	Examples
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser, general culture media, Specimen receptacle
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self-testing, Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self testing, HLA typing, PSA screening, Rubella IgM
D	High Individual Risk and High Public Health Risk	HIV blood donor screening, HIV diagnostic kit

7. Determination of Device Class

The manufacturer should:

1. Take into consideration all the rules as listed in section 8.0 in order to establish the adequate classification for the device. Where an IVD medical device has multiple intended uses, as specified by the manufacturer, which can place the device into more than one class, it will be classified in the higher class.

2. Where more than one of the classification rules applies to the IVD medical device, it should be allocated to the highest class indicated, e.g. a self-testing for HIV would be a class D under rule 1 and not a class C under rule 4

8. Classification Rule for IVD Medical Devices

7.1. Rule 1

Rule	IVD medical devices intended for the following purposes are classified as Class D • Devices intended to be used to detect the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs or any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration. • Devices intended to be used to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening, disease with a high or suspected risk of propagation.
Rationale	The application of this rule as defined above should be in accordance with the rationale that follows: Devices in this Class are intended to be used to ensure the safety of blood and blood components for transfusion and/or cells, tissues and organs for transplantation. In most cases, the result of the test is the major determinant as to whether the donation/product will be used. Serious diseases are those that result in death or long-term disability, that are often incurable or require major therapeutic interventions and where an accurate diagnosis is vital to mitigate the public health impact of the condition.
Illustrative Examples	• Tests to detect infection by HIV, HCV, HBV, HTLV; • HIV blood donor screening and HIV blood diagnostics. This rule applies to first-line assays, confirmatory assays, and supplemental assays.

7.2. Rule 2

Rule	IVD medical devices intended to be used for blood grouping, or to determine foetomaternal blood group incompatibility, or tissue typing to ensure the immunological compatibility of blood, blood grouping for cell administration, blood components, cells, tissue, or organs that are intended for transfusion or transplantation, are classified as Class C, except when intended to determine the presence of the antigen or antibody for any of the following markers: • ABO system [A (ABO1), B (ABO2), AB (ABO3)], • Rhesus system [RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e), and weak or partial Rh(D)], • Kell system [Kel1 (K)], • Kidd system [JK1 (Jka), JK2 (Jkb)]; or • Duffy system [FY1 (Fya), FY2 (Fyb)], in which case they are classified as Class D.
Rationale	The application of this rule as defined above should be in accordance with the rationale for this rule, which is as follows: A high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, places the device into Class D. The rule divides blood-grouping devices into two subsets, Class C or D, depending on the nature of the blood group antigen the IVD medical device is designed to detect, and its importance in a transfusion setting
Illustrative Examples	• HLA, Rhesus system • Duffy system (other Duffy systems except those listed in the rule as Class D are in Class C).

7.3 Rule 3

Rule	IVD medical devices are classified as Class C if they are intended for use: • in detecting the presence of, or exposure to, a sexually transmitted agent. • in detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation. • in detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested or to the individual`s offspring. • in pre-natal screening of women in order to determine their immune status towards transmissible agents. • in determining infective disease status or immune status, and where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation or severe disability for the patient or for the patient`s offspring. • in screening for selection of patients for selective therapy and management as companion diagnostics • in screening, diagnosis or staging of cancer; • in human genetic testing • to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient or for the patient`s offspring. • in the management of patients suffering from a life-threatening disease or condition. • in screening for congenital disorders in the foetus or embryo. in screening for congenital disorders in new-born babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities.

Rationale	The application of this rule as defined above should be in accordance with the rationale that follows: Devices in this Class are intended to be used to ensure the safety of blood and blood components for transfusion and/or cells, tissues and organs for transplantation. In most cases, the result of the test is the major determinant as to whether the donation/product will be used. Serious diseases are those that result in death or long-term disability, that are often incurable or require major therapeutic interventions and where an accurate diagnosis is vital to mitigate the public health impact of the condition.
Illustrative Examples	• Sexually transmitted diseases, such as Chlamydia trachomatis, Neisseria gonorrhoeae. • Neisseria meningitidis or Cryptococcus neoformans. • diagnostic assay for CMV, Chlamydia pneumoniae, Methicillin Resistant Staphylococcus aureus. • Immune status tests for Rubella or Toxoplasmosis. • Enteroviruses, CMV and HSV in transplant patients • PSA, CEA, and CA 125. • Huntington's Disease, Cystic Fibrosis. • Troponin, Cyclosporin, Prothrombin time testing. • HBV monitoring marker, HCV viral load, HIV Viral Load and HIV and HCV geno- and subtyping • Spina Bifida, Down Syndrome, Glucose-6-Phosphate Dehydrogenase Deficiency, and Tay-Sachs disease.

7.4 Rule 4

Rule	IVD medical devices intended for use by lay users (such as for self-testing or near-patient testing) are classified as Class C, except: those devices from which the result is not determining a critical situation, in which case they are classified under Class B, and those devices which are classified under Class D by Rule 1 and/or Rule 2.
Rationale	The application of this rule as defined above should be in accordance with the rationale for this rule, which is as follows: in general, these devices may be used by lay user.
Illustrative Examples	• Self-testing class C: Blood glucose monitoring. • Self-testing class B: Pregnancy self-test, fertility testing, and urine test strips.

7.5 Rule 5

Rule	The following IVD medical devices are classified as Class A: • Reagents or other articles, which possess no critical characteristics intended by the manufacturer to make them suitable for in vitro diagnostic procedures related to a specific examination; • Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures. • Specimen receptacles. NOTE 1: Any product for general laboratory use which is not specifically intended by the manufacturer to be used in in vitro diagnostic applications is not deemed to be an IVD medical device, as defined in this document. NOTE 2: In certain jurisdictions there may be differences as to whether a device classified in this rule is considered an IVD medical device
Rationale	The application of this rule as defined above should be in accordance with the rationale for this rule which is as follows: these devices present a low individual risk and no or minimal public health risk.
Illustrative Examples	• General culture media (excluding the dehydrated powders which are considered not to be a finished IVD medical device) • Wash solutions • Plain urine cup • Clinical chemistry analysers, and • Microbiological specimen collection devices. NOTE 3: The performance of software or an instrument that is specifically required to perform a particular test will be assessed at the same time as the respective reagent(s)

7.6 Rule 6

Rule	IVD medical devices not covered in Rules 1 through 5 are classified as Class B.
Rationale	The application of this rule as defined above should be in accordance with the rationale for this rule which is as follows: These devices present a moderate individual risk as they are not likely to lead to an erroneous result that would cause death or severe disability, have a major negative impact on patient outcome or put the individual in immediate danger. The devices give results that are usually one of several determinants. If the test result is the sole determinant, but other information is available, such as presenting signs and symptoms or other clinical information, which may guide a physician, classification into Class B may be justified. Other appropriate controls may also be in place to validate the results. This Class also includes those devices that present a low public health risk because they detect infectious agents that are not easily propagated in a population.
Illustrative Examples	• Blood gases, • H. pylori test • Physiological markers such as hormones, vitamins, and enzymes, metabolic markers, • Specific IgE assays and celiac disease markers, and • Tests for anti-nuclear antibody • Sex hormone-binding globulin (SHBG) • Blood urea nitrogen (BUN) • Aspartate aminotransferase (AST) • Alkaline phosphatase (ALP), creatinine and HbA1c.

7.7 Rule 7

Rule	IVD medical devices that are controls without a quantitative or qualitative assigned value will be classified as Class B.
Rationale	For such controls, the qualitative or quantitative value is assigned by the user and not the manufacturer
Illustrative Examples	• Urinalysis controls and • Chemistry controls