



IMDRF International Medical
Device Regulators Forum

PROPOSED DOCUMENT

Title: Principles of In Vitro Diagnostic (IVD) Medical
Devices Classification

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Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world. The document has been subject to consultation throughout its development.

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1.0 Introduction

The objective of the International Medical Device Regulators Forum (IMDRF) is to encourage convergence at the global level in the evolution of regulatory systems for medical devices in order to facilitate trade whilst preserving the right of participating members to address the protection of public health by regulatory means considered to be most suitable.

The primary way in which the IMDRF achieves its goals is through the production of harmonized guidance documents suitable for implementation or adoption by member Regulatory Authorities, as appropriate taking into account their existing legal framework, or by nations with developing regulatory programmes.

This guidance document is one of a series that together describe a global regulatory model for medical devices. Its purpose is to assist a manufacturer to allocate its In Vitro Diagnostic (IVD) medical device to an appropriate risk class using a set of harmonized principles. Regulatory Authorities have the responsibility of ruling upon matters of interpretation for a particular medical device.

This document should be read in conjunction with the GHTF document “Principles of Conformity Assessment for IVD medical devices” that recommends conformity assessment requirements appropriate to each of the four (4) risk classes proposed herein. The link between new document on classification and conformity assessment is important to ensure a consistent approach across all countries/regions adopting the global regulatory model recommended by the IMDRF, so that premarket approval for a particular device may become acceptable globally. Regulatory Authorities who may have different classification procedures are encouraged to adopt this IMDRF guidance as the opportunity permits.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities, Conformity Assessment Bodies and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health.

Regulatory Authorities that are developing classification schemes or amending existing ones are encouraged to consider the adoption of the system described in this document, as this will help to reduce the diversity of schemes worldwide and facilitate the process of harmonization.

This document supersedes an earlier version produced under the Global Harmonization Task Force (GHTF) with the same title dated February 19, 2008 (GHTF/SG1/N045:2008).

2.0 Rationale, Purpose and Scope

2.1 Rationale

This guidance document is one of a series that together describe a global regulatory model for medical devices. It provides guidance on the principles of classification of IVD medical devices.

Since the inter-relationship between device class and conformity assessment is critical in establishing a consistent approach to premarket approval across all countries/regions, it should be read in conjunction with the GHTF document on *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices* that recommends procedures that may be used to demonstrate that an IVD medical device conforms to the *Essential Principles of Safety and Performance for Medical Devices and IVD Medical Devices*.

2.2 Purpose

The purpose of this document is to

- assist a manufacturer to allocate its IVD medical device to an appropriate risk class using a set of harmonized classification principles;
- base such classification principles on an IVD medical device's intended use;
- allow Regulatory Authorities to rule upon matters of interpretation for a particular IVD medical device, when appropriate.

Subsequently, such classification will determine the conformity assessment route as described in the GHTF document on *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*.

2.3 Scope

This document applies to all products that fall within the definition of an IVD medical device.

NOTE: International reference materials (e.g. WHO) and materials used for external quality assessment schemes are excluded.

3.0 References

GHTF/SG1/N046:2008 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*

IMDRF/GRRP WG/N47FINAL:2018 *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices*

IMDRF/GRRP WG/N52FINAL:2019 *Principles of Labelling for Medical Devices and IVD Medical Devices*

IMDRF/SaMD WG/N10FINAL:2013 *Software as a Medical Device (SaMD): Key definitions*

IMDRF/SaMD WG/N12FINAL:2014 *Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations*

GHTF/SG1/N044:2008 *Role of Standards in the Assessment of Medical Devices*

GHTF/SG1/N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*

GHTF/SG5/N8:2012 *Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices*

Regulation (EU) 2017/746 *of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU*

ISO/IEC Guide 51:2014 *Safety aspects – Guidelines for their inclusion in standards*

ISO 18113-1:2009 *In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) – Part 1: Terms, definitions and general requirements.*

4.0 Definitions

Accessory for an IVD Medical Device: accessory for an *in vitro* diagnostic medical device' means an article which, whilst not being itself an *in vitro* diagnostic medical device, is intended by its manufacturer to be used together with one or several particular *in vitro* diagnostic medical device(s) to specifically enable the *in vitro* diagnostic medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the *in vitro* diagnostic medical device(s) in terms of its/their intended purpose(s).
(Adapted from Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices)

Calibration: 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.
(ISO 18113-1:2009)

Calibrator: measurement standard used in the calibration of an IVD test, instrument or system.
(ISO 18113-1:2009)

Companion Diagnostics Medical Device: an IVD medical device, which is essential for the safe and effective use of a corresponding medicinal product to:

- (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 with a view to monitoring 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.

(Adapted from Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices)

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

(ISO 18113-1:2009)

Critical Situation: situations or conditions 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.

(IMDRF/SaMD WG/N12FINAL:2014)

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.

(Adapted from ISO 18113-1:2009)

Harm: physical injury or damage to the health of people.

(Modified from ISO/IEC Guide 51:2014)

Hazard: potential source of harm.

(ISO/IEC Guide 51:2014)

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.

(IMDRF/GRRP WG/N47FINAL:2018)

Intended User: the person, professional or lay user, who uses a medical device. The patient may be that user.

(IMDRF/GRRP WG/N47FINAL:2018)

IVD Instrument: equipment or apparatus intended by the manufacturer to be used as an IVD medical device.

(Adapted from ISO 18113-1:2009)

IVD Medical Device: a device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or

principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles

NOTE 1: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.

NOTE 2: In some jurisdictions, certain IVD medical devices may be covered by separate other regulations.

(GHTEF/SG1/N071:2012)

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

(IMDRF/GRRP WG/N47FINAL:2018)

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.

(Adapted from European Observatory on Health Systems and Policies Glossary)

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

(Adapted from ISO 18113-1:2009)

Risk: combination of the probability of occurrence of harm and the severity of that harm.

(ISO/IEC Guide 51:2014)

Self-testing IVD Medical Device: an IVD medical device intended for used 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.

(IMDRF/GRRP WG/N47FINAL:2018)

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.

(IMDRF/SaMD WG/N10FINAL: 2013)

Specimen Receptacle: apparatus specifically intended by an IVD 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.

(Adapted from Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices)

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.

(IMDRF/GRRP WG/N47FINAL:2018)

Transmissible agent: an agent capable of being transmitted to a person, as a communicable, infectious or contagious disease.

(GHTF/SG1/N045:2008)

5.0 General Principles

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

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

The IMDRF guidance documents *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices* and *Principles of Labelling for Medical Devices and IVD 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. At the same time, the imposition of regulatory controls should not place an unnecessary burden on regulators or manufacturers.

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

- the intended use and indications for use as specified by the manufacturer
- the technical/scientific/medical expertise of the intended user (lay person or healthcare professional)
- 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
- the impact of the result (true or false) to the individual and/or to public health

6.0 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.

- 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.
- 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.
- The rules should be capable of accommodating generally acknowledged state of the art.
- Where more than one of the classification rules applies to the IVD medical device, the device should be allocated to the highest class indicated.
- Calibrators intended to be used with an IVD reagent should be placed in the same class as the IVD reagent.
- 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).
- 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).
- Software as a Medical Device (SaMD) for IVD should be classified based on its 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).

Decisions on final classifications, which deviate from the initial rules-based classification, should be weighed against the disadvantages of disharmonized international classification.

7.0 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.

Figure 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.

Figure 1: Proposed general classification system for IVD medical devices.

		PUBLIC health risk		
		<i>Low</i>	<i>Moderate</i>	<i>High</i>
INDIVIDUAL health risk	<i>Low</i>	A	N/A*	N/A*
	<i>Moderate</i>	B	B or C	C or D
	<i>High</i>	C	C	D

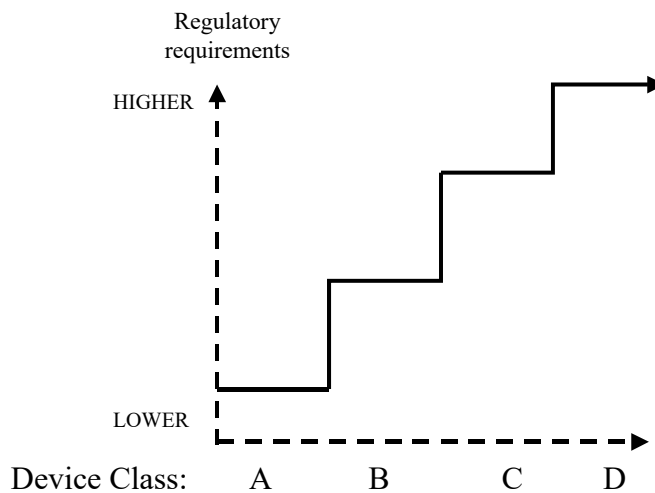
*N/A means there is no such IVD medical device

Figure 2 shows a conceptual illustration of increasing levels of regulatory requirements as the device risk class increases. These may include, for example:

- operation of a quality system (recommended for all devices);
- documentation of clinical evidence to support the manufacturer’s specified intended use;
- the need for technical data;
- product testing using in-house or independent resources;
- the need for and frequency of independent external audit of the manufacturer’s quality system; and
- independent external review of the manufacturer’s technical data.

The concept is expanded in the GHTF guidance document entitled *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*.

Figure 2: Conceptual illustration of regulatory requirements increasing with device risk class.



8.0 The Determination of Device Class

The manufacturer should:

1. Decide if the product concerned is an IVD medical device based on the intended use and the indications for use using the definition in section 4.0 of this document.
2. Take into consideration all the rules as listed in section 9.0 in order to establish the proper classification for the device. Where an IVD medical device has multiple intended uses as specified by the manufacturer, which place the device into more than one class, it will be classified in the higher class.
3. 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.
4. Determine that the device is not subject to special national rules that apply within a particular jurisdiction.

NOTE: Where special national rules are applied, resulting in a device class other than that suggested by the present rules, then a different conformity assessment procedure may be indicated. This may have an effect on the acceptability of such devices for free movement in a global context unless other, or additional, conformity assessment procedures are carried out. For example, where such special national rules result in the lower classification of a particular IVD medical device than that indicated in the rules indicated below, and as a consequence, a less vigorous conformity assessment procedure is carried out, this may be unacceptable to other jurisdictions.

9.0 Classification Rules

Rule 1: 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.

Examples: Tests to detect infection by HIV, HCV, HBV, HTLV. This Rule applies to first-line assays, confirmatory assays and supplemental assays.

Rule 2: IVD medical devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation, are classified as Class C, except when intended to determine 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), RHW1],
Kell system [Kell (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.

Examples: HLA, Duffy system (other Duffy systems except those listed in the rule as Class D are in Class C).

Rule 3: 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.
Examples: Sexually transmitted diseases, such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*.
- in detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation.
Examples: *Neisseria meningitidis* or *Cryptococcus neoformans*.
- 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.
Examples: diagnostic assay for CMV, *Chlamydia pneumoniae*, Methycillin Resistant *Staphylococcus aureus*.

- in pre-natal screening of women in order to determine their immune status towards transmissible agents.
Examples: Immune status tests for Rubella or Toxoplasmosis.
- 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.
Examples: Enteroviruses, CMV and HSV in transplant patients.
- 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
Examples: Huntington's Disease, Cystic Fibrosis
- 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.
Examples: Cardiac markers, Cyclosporin, Prothrombin time testing.
- in the management of patients suffering from a life-threatening disease or condition.
Examples: HBV monitoring marker, HCV viral load, HIV Viral Load and HIV and HCV geno- and subtyping
- in screening for congenital disorders in the foetus or embryo.
Examples: Spina Bifida or Down Syndrome
- 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 for this rule, which is as follows: devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.

Rule 4: IVD medical devices intended for self-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.

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.

Example for self-testing class C: Blood glucose monitoring.

Example for self-testing class B: Pregnancy self-test, Fertility testing.

Rule 5: 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; or
- Specimen receptacles.

NOTE: 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 IVD medical device, as defined in this document.

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.

Examples: General culture media (excluding the dehydrated powders which are considered not to be a finished IVD medical device), wash solutions, instruments and plain urine cup.

NOTE 1: In certain jurisdictions there may be differences as to whether a device classified in this rule is considered an IVD medical device.

NOTE 2: 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 test kit.

NOTE 3: The interdependence of the instrument and the test methodology prevents the instrument from being assessed separately, even though the instrument itself is still classified as Class A.

Rule 6: 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, however other information is available, such as presenting signs and symptoms or other clinical information, which may guide a physician, such that 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.

Examples: Blood gases, *H. pylori* and physiological markers such as hormones, vitamins, enzymes, metabolic markers, specific IgE assays and celiac disease markers.

Rule 7: 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.