FINAL DOCUMENT

Global Harmonization Task Force

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

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Preface

This document was produced by the Global Harmonization Task Force, a voluntary consortium of representatives from medical device Regulatory Authorities and trade associations from around the world. The document is intended to provide non-binding guidance to Regulatory Authorities for use in the regulation of medical devices and has been subject to consultation throughout its development and endorsement by the current Chair.

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1.0 Introduction

The objective of the Global Harmonization Task Force (GHTF) 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 Global Harmonization Task Force (GHTF) 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 on Principles of Conformity Assessment for IVD medical devices that recommends conformity assessment requirements appropriate to each of the four risk classes proposed herein. The link between development of documents on classification and conformity assessment is important to ensure a consistent approach across all countries/regions adopting the global regulatory model recommended by the GHTF, 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 GHTF 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.

The regulatory requirements of some countries do not, at this time, align fully with this guidance.

This guidance document has been prepared by Study Group 1 of the Global Harmonization Task Force (GHTF). Comments or questions about it should be directed to either the Chairman or Secretary of GHTF Study Group 1 whose contact details may be found on the GHTF web page.

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.*

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. An IVD medical device is defined as a device which, whether used alone or in combination, is 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: International reference materials (e.g. WHO) and materials used for external quality assessment schemes are excluded.

3.0 References

GHTF final documents

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

GHTF/SG1/N029:2005 *Information Document Concerning the Definition of the Term 'Medical Device'.*

GHTF/SG1/N041:2005 *Essential Principles of Safety and Performance of Medical Devices.*

GHTF/SG1/N043:2005 *Labelling for Medical Devices.*

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

4.0 Definitions

Accessory : an article which, is intended specifically by its manufacturer to:

- be used together with an IVD medical device to enable that device to be used in accordance with its intended use as an IVD medical device.
- or to augment or extend the capabilities of that device in fulfilment of its intended use as an IVD medical device.

and therefore should be considered an IVD medical device.

IVD medical device for Self-testing: any IVD medical device intended by the manufacturer for use by lay persons.

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.

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

Hazard: potential source of harm.

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.

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

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: In some jurisdictions, some IVD medical devices may be covered by separate regulations.

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

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

Near patient (testing): testing performed outside a laboratory environment by a healthcare professional not necessarily a laboratory professional , generally near to, or at the side of, the patient.

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

Self-testing: testing performed by lay persons.

Specimen receptacle: a device, whether vacuum-type or not, specifically intended by its manufacturer for the primary containment of specimens derived from the human body.

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

Transmission: the conveyance of disease to a person.

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.

The GHTF guidance documents *Essential Principles of Safety and Performance of Medical Devices* and *Labelling for 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 (including but not limited to specific disorder, populations, condition or risk factor for which the test is intended)
- 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

Certain jurisdictions may lower the classification of IVD medical devices for which traceability is established through the use of reference measurement procedures and/or available reference materials.

6.0 Recommendations and Factors Influencing IVD Medical Device Classification

- Regulatory Authorities should work towards the establishment of a global classification system specific to IVD medical devices.
- Such a system should be based upon common features of existing national requirements with the aim of future convergence.
- This system should consist of four risk classes. Based on experience of GHTF Founding Members, this is sufficient to accommodate all IVD medical devices and allows an efficient and defined conformity assessment system.
- The determination of classification for an IVD medical device should be based on a set of rules derived from those features that create risk.
- 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 future technological developments.
- Decisions on final classifications, which deviate from the initial rules-based classification, should be weighed against the disadvantages of disharmonized international classification
- Where more than one of the classification rules applies to the IVD medical device, the device should be allocated to the highest class indicated.
- Accessories should be classified separately using this guidance document.
- 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 should not be placed in the same class as the IVD reagent(s).
- While most software is incorporated into the IVD medical device itself, some is not. Provided such standalone software falls within the scope of the definition for an 'IVD medical device', it should be classified as follows:
  - Where it controls or influences the intended output of a separate IVD medical device, it will have the same class as the device itself.
  - Where it is not incorporated in an IVD medical device, it is classified in its own right using the rules in Section 9.0 of this document.

Note 1: Performance of software or instrument that is specifically required to perform a particular test will be assessed at the same time as the test kit.

Note 2: The interdependence of the instrument and test methodology prevents the instrument from being assessed separately, even though the instrument itself is still classified as Class A.

Study Group 1 of GHTF continues to support and encourage regulatory harmonization. It recognises that some Regulatory Authorities may have to reflect different local needs when they introduce new regulations on classification. Study Group 1 hopes any such differences will disappear in the course of time.

7.0 Proposed General Classification System for IVD Medical Devices

A four class system is proposed. The use of an alphabetical system in this document is chosen as a distinctive format for GHTF.

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.

CLASS	RISK LEVEL	EXAMPLES
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser , prepared selective culture media
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
D	High Individual	HIV Blood donor screening, HIV Blood

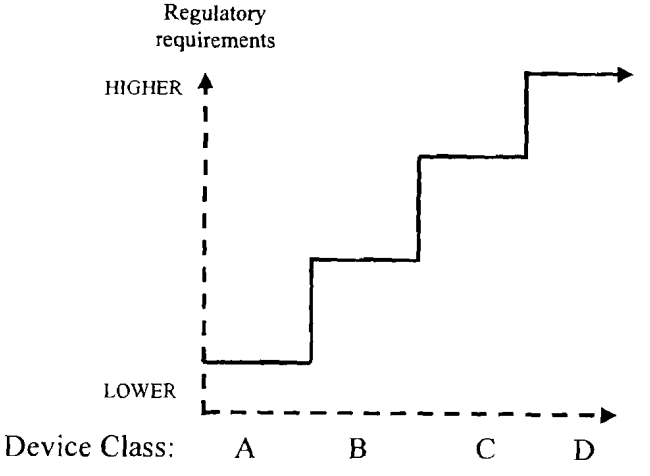
	Risk and High Public Health Risk	diagnostic

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, blood derivatives, cells, tissues or organs in order to assess their suitability for transfusion or transplantation, or
- Devices intended to be used to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening, often incurable, disease with a high 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 for ABO system [A (ABO1), B (ABO2), AB (ABO3)], rhesus system [RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e)], Kell system [Kel1 (K)], Kidd system [JK1 (Jka), JK2 (Jkb)] and Duffy system [FY1 (Fya), FY2 (Fyb)] determinations which 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 where there is a significant risk that an erroneous result would cause death or severe disability to the individual or fetus being tested. 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 for the patient. Examples: Enteroviruses, CMV and HSV in transplant patients.

- in screening for selection of patients for selective therapy and management, or for or for disease staging, or in the diagnosis of cancer. Example: personalized medicine. NOTE: those IVD medical devices where the therapy decision would usually be made only after further investigation and those used for monitoring would fall into class B under rule 6.
- 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. Examples: Cardiac markers, Cyclosporin, Prothrombin time testing.
- In the management of patients suffering from a life-threatening infectious disease. Examples: HCV viral load, HIV Viral Load and HIV and HCV geno- and subtyping.
- In screening for congenital disorders in the fetus. Examples: Spina Bifida or Down Syndrome.

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 medically critical status, or is preliminary and requires follow-up with the appropriate laboratory test in which case they are Class B.
IVD medical devices intended for blood gases and blood glucose determinations for near-patient testing would be Class C. Other IVD medical devices that are intended for near-patient should be classified in their own right using the classification rules.

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 are used by individuals with no technical expertise and thus the labelling and instructions for use are critical to the proper outcome of the test.

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

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

Rule 5: The following IVD medical devices are classified as Class A:

- Reagents or other articles which possess specific 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: Any product for general laboratory use not manufactured, sold or represented for use in specified in vitro diagnostic applications are not deemed to be IVD medical devices, as defined in this document. However, in certain jurisdictions products for general laboratory use are considered to be IVD medical devices.

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: Selective/differential microbiological media (excluding the dehydrated powders which are considered not to be a finished IVD medical device), identification kits for cultured microorganisms, 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.