



A RISK BASED APPROACH FOR THE ASSESSMENT OF IN VITRO DIAGNOSTICS (IVDs)

Prequalification of Diagnostics

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1. Introduction

In vitro diagnostic medical devices (IVDs) play a critical role in both individual health and public health. Individual patient management depends upon the availability of reliable and accurate IVDs for clinical decisions on diagnosis and treatment, as does screening of blood/blood products for transfusion and human organs/tissues for transplantation. Likewise, good quality IVDs for the detection of infectious agents, for example, are crucial to controlling their transmission and to the appropriate allocation of valuable and often limited resources (i.e. medicines, laboratory testing, clinical expertise). Therefore, incorrect test results carry with them the potential to have serious health consequences. For this reason, a growing number of authorities assess IVDs for quality, safety, and performance prior to acceptance for procurement (generally known as pre-market assessment) and following their placing on the market (generally referred to as post-market surveillance).

Whereas the clinical setting demands that IVD quality be high, it is not feasible that all IVDs be assessed in the pre-market phase in the same manner, given both the number of products available for a very broad range of analytes and the resources available to conduct assessments. This has led to the use of a risk-based approach to assessment, in which IVDs are classified according to the risk they pose to public and individual health, and taking into account the potential outcomes and impact if the test does not perform properly or is not available. The risk class then determines the level of scrutiny applied for the regulatory assessment, ensuring that resources are focused on those IVDs associated with the greatest potential risk.

2. Intended Audience and Scope

This document provides information to WHO Member States, manufacturers submitting to the WHO Prequalification of Diagnostics Programme, regulators and other stakeholders on an internationally recognized risk-based approach to the regulatory assessment of IVDs to determine the level of scrutiny of the assessment of an IVD and to assure their quality, safety and performance in clinical use.

This approach describes a mechanism that can be adapted or applied by other bodies undertaking the assessment of the quality, safety and performance of an IVD.

3. Definitions

Intended use (1)

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.

Note: Aspects that are considered in the intended use include

- what is detected
- its function (e.g. screening, monitoring, diagnosis or aid to diagnosis);
- the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;

- whether it is automated or not;
- whether it is qualitative or quantitative;
- the type of specimen(s) required (e.g. serum, plasma, whole blood, tissue biopsy, urine);
- testing population ;
- the intended user (e.g. lay person, highly trained laboratory professional, minimally trained health care worker, self-testing);
- the intended setting of use (e.g. point of care, reference or diagnostic laboratory setting, primary health care setting)

In vitro diagnostic medical device (2)

“A medical 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. IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.”

Risk (3)

“Combination of the probability of occurrence of harm and the severity of that harm.”

Risk assessment (3)

“Overall process comprising a risk analysis and a risk evaluation.”

Conformity Assessment (4)

The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles of Safety and Performance of Medical Devices.

Conformity Assessment Body (4)

A body engaged in the performance of procedures for determining whether the relevant requirements in technical regulations or standards are fulfilled. A Conformity Assessment Body (CAB) is authorized to undertake specified conformity assessment activities by a Regulatory Authority (RA) that will ensure performance of the CAB is monitored and, if necessary, withdraw designation.

4. Abbreviations

CAB	Conformity Assessment Body
EP	Essential Principles of Safety and Performance for Medical Devices
GHTF	Global Harmonization Task Force
IMDRF	International Medical Device Regulators Forum
IVD	In vitro diagnostic medical device
QMS	Quality Management System

5. Risk Classification

The risk posed by the use of an IVD can be categorized or classified according to a set of classification rules. (5) These rules were created by the Global Harmonization Task Force (GHTF), a voluntary group of representatives from regulatory authorities (United States, Canada, European Union, Japan, and Australia), as well as representatives from the medical device industry. In 2012 GHTF was replaced by a regulators-only group, the International Medical Device Regulators Forum (IMDRF), which has adopted the GHTF classification rules and other GHTF regulatory guidelines. IMDRF continues to maintain GHTF guidelines and develop more guidance that will encourage international regulatory convergence and support innovation and timely access to safe and effective medical devices globally. GHTF and IMDRF documents have been created and approved by working parties comprised of both regulatory authorities and major industry groups, ensuring that the recommendations are acceptable and implementable at a global level. Internationally, the outputs of IMDRF and GHTF are being adopted by several countries introducing regulation of IVDs and other medical devices. Additionally, established regulatory agencies are also converging practices in line with the recommendations of GHTF and IMDRF, in recognition of the fact that these represent regulatory best practice for a global market.

GHTF created the risk classification rules to determine the level of pre-market regulatory assessment that is required for an IVD, with the purpose that these controls are considered to be sufficient for each risk class to safeguard the health and safety of patients, users and other persons. The outcome of the rules is to group IVDs into one of four classes representing increasing individual and public health risk (Classes A to D), shown in Table 1.

Table 1: GHTF Risk Classes and Risk Level

Classification	Individual Health Risk		Public Health Risk
Class A IVD	Low	and	Low
Class B IVD	Moderate	and	Low
Class C IVD	High	and/or	Moderate
Class D IVD	High	and	High

This risk classification system is based on two regulatory principles. First, the level of scrutiny afforded a device is dependent upon the risk the device presents. Second, the safety and performance of medical devices can be best assessed through a balance of pre-market scrutiny, adequate manufacturer quality management systems, and the implementation of effective post-market surveillance mechanisms.

It is the responsibility of the manufacturer to apply the risk classification rules and determine the risk class, based on the intended use of the IVD. The manufacturer should document the

justification for placing the IVD into a particular risk class. However it is the responsibility of the regulatory authority or conformity assessment body to confirm that the risk class determined by the manufacturer is consistent with applicable classification rules and appropriate for the intended setting.

When applying the rules, risk considerations will vary depending upon the setting in which a product is intended to be used. For example, several critical aspects are particular to risk considerations for IVDs used in resource-limited settings compared to high-income countries. These include differences in endemicity and prevalence of various diseases, the way the test result is used for clinical-decision making, the level of treatment and care available for a patient with the disease, the availability of follow-up or reference testing, and significant variations in the level of training of professional and non-professional staff utilizing the IVD. This means that the risk classification of an IVD in a low- or middle-income country can be considerably different (usually posing higher risk) to that when evaluated for use of the IVD in a high-income country.

It is important to note that the risk classification does not determine the level of effort to be undertaken by the manufacturer to create sufficient evidence of safety and performance of the IVD. All IVDs, no matter the risk class, should be designed and manufactured under conditions that will result in a quality product with an expected level of performance. Rather, risk classification is intended to provide the appropriate amount of oversight by a regulatory authority or conformity assessment body. For instance, the classification does not determine the size and complexity of the clinical performance studies to be undertaken. These are determined by other factors, guided by an appropriate risk analysis conducted by the manufacturer that addresses factors such as the design of the IVD, as well as all performance claims related to intended use such as the intended users and testing population. However, the risk classification may influence the type of information required for assessment. For example, only summary data are usually required for lower risk products, whereas complete data sets are assessed for higher risk products, and information supporting the design and development of a IVD are needed to assess higher risk or novel IVDs.

The following criteria are used to apply the GHTF rules for classification of IVDs:

- the intended use and indications for use as specified by the manufacturer (including aspects such as the specific disorder, condition or risk factor for which the test is intended, the intended setting/environment for use)
- the technical/scientific/medical expertise of the intended user (lay person or professional)
- the importance of the test result 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.

The risk classification rules for IVDs as described by GHTF are found in **Annex 1**. In some cases, more than one classification rule may be applicable to an IVD; in this case the higher risk classification is applied.

6. Assessing IVDs – Critical Elements

GHTF identifies elements that should be considered in the regulatory assessment of an IVD (4):

- Quality management system
- Post-market surveillance
- Technical documentation
- Declaration of conformity to the Essential Principles of Safety and Performance
- Registration of manufacturers and their devices

The following sections outline what GHTF identifies as the manufacturer's responsibility for each of these elements and what level of assessment of each element by either the regulatory authority or the conformity assessment body (CAB) is most appropriate for each risk class of IVD. IVDs that present the greatest risk (Classes C and D) typically require objective evidence of the safety, quality, performance, benefits and risks of the IVD. Such evidence is usually documented in a technical file available at the site of manufacture. An inspection of the manufacturer's quality management system would typically include the review of particular records from the technical file. In addition, a product dossier that includes selected records from the technical documentation is assessed as part of the pre-market assessment. The GHTF document, "*Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*" (this documentation is referred to as the STED), provides recommendations for dossier content for Class C and D IVDs. (6) In some jurisdictions, an independent performance evaluation to verify the claims (performance and operational characteristics) made by the manufacturer in the product dossier and associated quality documentation may be performed.

6.1. Assessment Element: Quality Management Systems

The responsibilities associated with this element are in **Table 2** below.

Manufacturer's Responsibility: An appropriate quality management system should be in place for all classes of IVDs. Quality management systems, when implemented effectively, will ensure the manufacturer has in place mechanisms that not only ensure quality production (and an uninterrupted supply), but also should ensure the IVD will be safe and effective. Such mechanisms include the use of risk management procedures, with risks identified, monitored and addressed, throughout the product life cycle.

The scope and complexity of the quality management system that a manufacturer needs to establish is influenced by varying needs, objectives, the products provided, processes employed, the size and structure of the organization, and specific regulatory requirements.

Examples of quality management standards for IVDs that have been acceptable to regulatory authorities include ISO 13485:2003 (*Medical devices -- Quality management systems -- Requirements for regulatory purposes*) and the United States Food and Drug Administration Quality System Regulations (Code of Federal Regulations Title 21, Part 820).

Regulatory Authority (RA)/Conformity Assessment Body (CAB) Responsibility: Assessment of the effectiveness of a manufacturer’s quality management system is primarily influenced by the class of the IVD. For Class C and Class D IVDs, the assessment process will ensure that not only is there an effective control of manufacturing and other processes, that there is also control of the design and development of the IVD that forms the basis for the manufacturing of the IVD. As shown in **Table 2**, assessment for classes B to D can range from review of relevant certification to comprehensive on-site inspection and auditing of the manufacturer’s quality management system. Factors other than risk class that can influence the form and depth of the assessment include the regulatory authority or conformity assessment body’s knowledge of the manufacturer (assessed at prior inspections for other products), external reports of quality issues associated with the product or the manufacturer, and the findings of other inspection reports generated as part of a comprehensive regulatory review process.

Table 2: Assessment of Quality Management Systems According to Risk Classification

Class	Manufacturer Responsibility	RA/CAB Responsibility
A	Establish and maintain a full QMS or a QMS without design and development controls.	Premarket regulatory audit not required.
B	Establish and maintain a full QMS or a QMS without design and development controls.	Be satisfied that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.
C	Establish and maintain a full QMS.	Be satisfied that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.
D	Establish and maintain a full QMS.	Be satisfied that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.

6.2. Assessment Element: Technical Documentation

The responsibilities associated with this element are in **Table 3** below.

Manufacturer’s Responsibility: Sufficient technical documentation should exist to prove that the GHTF “*Essential Principles of Safety and Performance of Medical Devices*” (identified as simply the Essential Principles [EP]) have been met. (7) Manufacturers of all classes of IVDs are expected to demonstrate conformity of the IVD to the EP through the preparation and holding of technical

documentation that shows how each IVD was developed, designed and manufactured, together with the descriptions and explanations necessary to understand the manufacturer’s determination with respect to such conformity. This technical documentation is updated as necessary to reflect the current status, specification, configuration and post-market experience of the IVD.

Regulatory Authority (RA)/Conformity Assessment Body (CAB) Responsibility: An assessment body assessing conformity to the EP (e.g. a regulatory authority) will review the STED at greater depth as the risk class increases.

The GHTF document notes that the documentation for a Class C IVD medical device will contain less elaborate information than the STED for a Class D device. The main difference for a Class D STED would be in the level of details in the clinical/performance data and details of the manufacturer’s QC release program. Although a regulatory authority/conformance assessment body should not normally require more elaborate information for a Class C device, this does not preclude the regulatory authority/conformity assessment body from requesting such information in specific cases.

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Table 3: Assessment of Technical Documentation According to Risk Classification

Class	Manufacturer Responsibility	RA/CAB Responsibility
A	Upon request prepare STED.	Premarket submission of STED not required. May be requested to investigate specific safety or regulatory concerns.
B	Upon request prepare STED.	Premarket submission normally not required but if requested, receive and conduct a review of the STED to determine conformity to Essential Principles.
C	Prepare and submit STED for review.	Receive and conduct a premarket review of the STED to determine conformity to Essential Principles.
D	Prepare and submit STED for review. A STED for this class should contain more extended information such as full performance evaluation reports.	Receive and conduct a premarket review of the STED to determine conformity to Essential Principles.

6.3. Assessment Element: Post-Market Surveillance

The responsibilities associated with this element are in **Table 4** below.

Manufacturer’s Responsibility: A system for post-market surveillance of the product should be in place to monitor manufactured product quality, safety and performance. Prior to placing the product on the market, the manufacturer will put in place, as part of its quality management

system, a process to assess the continued safety and performance of the throughout the life cycle of the IVD. This process will include having procedures for, at a minimum, complaint handling, vigilance reporting, procedures for recalls, and corrective and preventive action.

Regulatory Authority (RA)/Conformity Assessment Body (CAB) Responsibility: An assessment body can review the effectiveness of post-market surveillance mechanisms through inspection on site and/or through the availability of relevant documentation (including existence of appropriate standard operating procedures). The level of review should again be strongly influenced by the risk class of the IVD as well as the additional factors identified above for assessment of the quality management system.

It is important to note that an adverse event reporting procedure is a necessity for each regulatory authority to maintain.

Table 4: Assessment of Post-Market Surveillance According to Risk Classification

Class	Manufacturer Responsibility	RA/CAB Responsibility
A	Establish and maintain an adverse event reporting procedure according to GHTF SG2 guidance.	May audit post-market to investigate specific safety or regulatory concerns.
B	Establish and maintain an adverse event reporting procedure according to GHTF SG2 guidance.	Be satisfied that a current and appropriate adverse event reporting procedure is in place as part of the QMS.
C	Establish and maintain an adverse event reporting procedure according to GHTF SG2 guidance.	Be satisfied that a current and appropriate adverse event reporting procedure is in place as part of the QMS.
D	Establish and maintain an adverse event reporting procedure according to GHTF SG2 guidance.	Be satisfied that a current and appropriate adverse event reporting procedure is in place as part of the QMS.

6.4 Assessment Element: Declaration of Conformity

The responsibilities associated with this element are in **Table 5** below.

Manufacturer's Responsibility: A declaration of conformity to the EPs is likewise a requirement, providing assurance that the manufacturer is meeting appropriate standards for quality in the design and manufacture of its IVD.

Regulatory Authority (RA)/Conformity Assessment Body (CAB) Responsibility: Review for compliance with the EPs is a necessity for three of the four risk classes.

Table 5: Assessment of Declaration of Conformity According to Risk Classification

Class	Manufacturer Responsibility	RA/CAB Responsibility
A	Prepare, sign and maintain.	On file with the manufacturer; available upon request.
B	Prepare, sign and maintain.	Review and verify compliance with requirements.
C	Prepare, sign and maintain.	Review and verify compliance with requirements.
D	Prepare, sign and maintain.	Review and verify compliance with requirements.

6.5 Assessment Element: Registration of Manufacturers and their Devices

The responsibilities associated with this element are in **Table 6** below.

Registration of manufacturers and their devices is viewed as a basic regulatory requirement for any IVD and therefore it is necessary that the manufacturer registers as appropriate for the regulatory system and that the regulatory authority/conformity assessment body maintains the registry and verifies registration as appropriate.

Table 6: Assessment of Registration of Manufacturers and their Devices According to Risk Classification

Class	Manufacturer Responsibility	RA/CAB Responsibility
A	Perform according to regulatory requirements.	Maintain and verify as appropriate.
B	Perform according to regulatory requirements.	Maintain and verify as appropriate.
C	Perform according to regulatory requirements.	Maintain and verify as appropriate.
D	Perform according to regulatory requirements.	Maintain and verify as appropriate.

7. Performance Evaluations and Lot Release Testing

GHTF also acknowledges that performance testing is another element to be considered as part of conformity assessment. (5).

Manufacturer's Responsibility: IVDs should have performance characteristics (such as sensitivity, specificity, linearity, etc) appropriate for the intended setting when used by intended users. Special considerations for the variable conditions encountered in diverse settings should be considered in the design and development of the IVD to ensure that these performance characteristics can be achieved. Such considerations may include use of the IVD in areas with extremes of temperature and humidity, and with operators of various skill levels. The manufacturer should have considered these aspects in a thorough risk assessment and hold evidence through performance testing and other means that the benefits of using the IVD in the intended use setting by intended users will outweigh any residual risk.

Additionally, the manufacturer should have in place effective lot release procedures to ensure performance characteristics are maintained for each lot of product manufactured. Lot release testing should thus ensure that where appropriate, the sensitivity and specificity, or other critical performance characteristics remain unchanged for each lot by the testing of sufficient numbers of relevant specimens. Maintenance of lot release panels is therefore a critical procedure within the quality management system to ensure ongoing consistency.

Regulatory Authority (RA)/Conformity Assessment Body (CAB): In many cases, regulatory/evaluating bodies rely solely on information from studies conducted by, or on behalf of, the manufacturer to evaluate the IVD's performance. Others conduct their own independent evaluation through performance studies to supplement or verify those performed by the manufacturer.

The need to undertake independent evaluation should follow the risk based principles identified in GHTF guidance "*Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*" (8), taking into account considerations such as the risk class of the IVD, the novelty of the technology, the manufacturer's experience level with the type of IVD and if the type of IVD raises specific public health concerns. The evaluation can take the form of a performance study verifying the manufacturer's performance claims, and/or through lot testing to ensure each lot meets set criteria. Performance studies for regulatory are different in their purpose than those for health technology assessment (HTA) purposes. The goal for regulation usually encompasses verification of clinical validity, whereas for HTA, clinical utility is being reviewed. HTA studies investigate implementation aspects such as cost benefit ratios, taking into account aspects such as training, educational and facility requirements.

Lot testing can be performed by the RA or the CAB to ensure the quality of the assays before distribution in view of the potential effect of transportation on product performance when it is shipped into country. Depending on the risk class of the product and its use in a particular jurisdiction, an alternative to lot testing by the regulatory authority is review of the manufacturer's lot release data for each of the lots accepted into that jurisdiction.

8. Conclusion

By using an internationally recognized risk classification scheme for IVDs to determine routine regulatory oversight, regulatory authorities and conformity assessment bodies ensure that the level of assessment is proportionate to the degree of risk, taking into account the benefits offered by the IVD.

Such an approach to IVD assessment takes into account the number and diversity of IVDs available, as well as the limited resources available to undertake assessment. Another proven advantage is that the classification scheme is rules based and not prescriptive. This means it can accommodate new and innovative IVDs. WHO recommends the adoption of this approach for WHO Member States regulating IVDs and those considering doing so.

Because of its international acceptance, WHO has adopted this risk based assessment approach for the purposes of WHO prequalification of IVDs. WHO undertakes PQ assessment activities according to the risk class as determined by applying the GHTF classification rules. For more information regarding this WHO activity , refer WHO PQDx_0172 "*Risk Based Classification of Diagnostics for WHO Prequalification*".

Any inquiries regarding this risk based assessment approach should be addressed to:
diagnostics@who.int

9. References

1. GHTF/SG1/N070:2011 *Labels and Instructions for Use of Medical Devices*
2. GHTF/SG1/N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device*
3. ISO/IEC Guide 51:1999 *Safety aspects -- Guidelines for their Inclusion in Standards*
4. GHTF/SG1/N046:2008 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*
5. GHTF/SG1/N045:2008 *Principles of In Vitro Diagnostic (IVD) Medical Devices Classification*
6. GHTF/SG1/N063:2011 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*
7. GHTF/SG1/N68:2012 *Essential Principles of Safety and Performance of Medical Devices*

Annex 1. GHTF Classification Rules (refer to GHTF/SG1/N045:2008 “Principles of In Vitro Diagnostic (IVD) Medical Devices Classification”)

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 [Ke1 (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.