RISK BASED CLASSIFICATION OF DIAGNOSTICS FOR WHO PREQUALIFICATION

Prequalification of Diagnostics

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1. Introduction

The WHO Prequalification of Diagnostics Programme determines the depth of its prequalification assessment of IVDs for priority diseases according to the risk posed by the product to the health of the public and/or an individual in WHO Member States, and to the risk of an incorrect result arising from the use of the IVD in that setting. Therefore the level of assessment aims to provide reasonable assurance of the safety, quality and performance of IVDs. This rational, risk-based assessment approach ensures the goal of timely access to safe and effective IVDs and the judicious use of WHO resources.

This document describes how WHO utilizes an internationally accepted regulatory mechanism to determine the stringency of assessment of products submitted to the WHO Prequalification of Diagnostics Programme. The risk based assessment approach utilizes a set of classification rules that will place IVDs into 4 risk classes. The higher the risk class, the greater the stringency of assessment that is applied to a product. This approach is also used by regulatory authorities to determine the level of pre-market control to apply to IVDs.

2. Intended Audience and Scope

This document is intended for use by WHO staff to determine the risk classification of IVDs accepted for WHO prequalification to guide the depth of assessment. It provides information that can be used by regulatory authorities intending to regulate IVDs on how the WHO applies the classification rules, and it informs manufacturers and other stakeholders of the risk-based approach undertaken by the WHO Prequalification of Diagnostics Programme to determine the stringency required for the WHO prequalification assessment of a IVD product.

3. Definitions

In vitro diagnostic medical device (IVD) (1)

> 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 (1)

> Combination of the probability of occurrence of harm and the severity of that harm.

4. WHO Prequalification of Diagnostics Requirements

WHO requires manufacturers of IVDs undertaking WHO Prequalification to have objective evidence of the safety, quality, performance, benefits and risks, and operational utility of the IVD. This evidence is the subject of the assessment, which determines if the IVD conforms to the

Essential Principles of safety and performance when used in WHO Member States (refer GHTF document "*Essential Principles of Safety and Performance of Medical Devices"*. (2)

Evidence of safety, quality and performance can be grouped into 4 assessable elements:

4.1. Technical Documentation

Manufacturers of all classes of IVDs are expected to demonstrate conformity of the IVD to the Essential Principles of safety and performance of IVDs (2) 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 and configuration of the IVD. Subsets of this documentation should be available for assessment in the format of a product dossier. WHO recognizes the Global Harmonization Task Force (GHTF) recommendations for dossier content for IVDs. (3)

4.2. Performance and operational utility

WHO expects that an IVD performs as it is intended to (e.g. sensitivity and specificity, precision, trueness of measurement, etc.) when used by operators in WHO Member States. Special considerations for the variable conditions encountered in such diverse settings must be considered in the design and development of the IVD. 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 process and hold evidence through testing and other means that the benefits of using the IVD in a WHO Member State will outweigh any residual risk.

4.3. Quality Management Systems

An appropriate quality management system must be in place that, for high risk IVDs, includes in its scope control of the design and development and manufacture of the IVD. WHO refers to 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 Part 820) as acceptable standards for the quality management standards of IVDs. These quality management systems are recognized internationally as best practice.

4.4. Post Market Surveillance

The manufacturer must have a system for post-market surveillance. 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 throughout the lifecycle 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.

5. The WHO Prequalification Risk-Based Assessment Approach

The risk posed by the use of an IVD can be categorized or classified according to an internationally accepted classification system that was created by the GHTF and continues to be maintained by the International Medical Device Regulators Forum (IMDRF). (4) For additional information on using this risk-based approach for the evaluation of IVDs, see PQDx_152 "*A Risk Based Assessment Approach".*

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

Table 1: The Risk Classes

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

WHO has adopted the GHTF classification system to guide the level of stringency and scope of the assessment required for an IVD product undergoing WHO prequalification. WHO applies this classification system by considering the risks posed when the IVD is used in WHO Member States, with particular emphasis on resource-limited settings. Several critical aspects are specific to resource limited settings compared to risk classification when applied in many high income countries. These include differences in endemicity and prevalence of various diseases, the availability of follow-up or reference testing, and significant differences in the level of training of professional staff utilizing the IVD. This means that the risk classification of an IVD in resource limited settings can be considerably different (usually posing higher risk) from that when evaluated for use in a high income setting.

Table 2 below identifies the review procedures that WHO uses to assess each of the GHTF risk classes, to illustrate how the assessment activities would differ if products in these risk classes would be assessed for prequalification. This is consistent with GHTF recommendations that the depth and timing of the review of the dossier is influenced by the class of the IVD, its complexity, and the extent to which it incorporates new technology. (5)

Table 2: Summary of WHO Prequalification Assessment Activities by IVD Risk Class

WHO PQ Requirement	Assessment Element	Manufacturer Responsibility	WHO PQ Assessment			
			Class A*	Class B*	Class C	Class D
Assessment of Quality	Quality Management System	Establish and maintain a full QMS	*Inspection normally not required*	*Have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS inspection.*	Confirm that a current and appropriate QMS is in place or otherwise conduct a QMS inspection.	Confirm that a current and appropriate QMS is in place or otherwise conduct a QMS inspection.
	Post-market Surveillance	Establish and maintain a complaint reporting procedure	*May inspect to investigate specific safety or performance concerns.*	*Confirm that a current and appropriate complaint reporting procedure is in place as part of the QMS.*	Confirm that a current and appropriate complaint reporting procedure is in place as part of the QMS.	Confirm that a current and appropriate complaint reporting procedure is in place as part of the QMS.
Assessment of IVD manufacturer 's claims of safety & performance	Technical Documentation	Establish and keep up to date, technical documentation, and prepare and submit a dossier for review	*Only subsets of information to be reviewed to determine conformity to Essential Principles.*	*Only subsets of information to be reviewed to determine conformity to Essential Principles.*	Undertake a review of the product dossier sufficient to determine the product is safe and should perform as intended, including assessment of conformity to Essential Principles. Also ensure that the benefit of using the IVD in a WHO Member State outweighs the risks involved.	Undertake an **in-depth** review of the product dossier to determine the product is safe and should perform as intended, including assessment of conformity to Essential Principles. Also ensure that the benefit of using the IVD in a WHO Member State outweighs the risks involved.
Assessment of performance – Laboratory Evaluation	Laboratory Evaluation	Undertake performance studies should support the safe use and performance of the assay.	*No laboratory evaluation undertaken.*	*Laboratory evaluation undertaken in only exceptional cases identified by Member State needs)*	Laboratory evaluation undertaken **in the majority of cases** to independently evaluate performance and operational characteristics.	Laboratory evaluation undertaken to independently evaluate performance and operational characteristics.

*At time of print, *IVDs undergoing WHO Prequalification do not fall into Classes A and B.*

The GHTF Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices document on which **Table 2** is based, recommends that the documentation submitted in a product dossier for a Class C IVD will contain less detailed information than the documentation for a Class D device. (5) For WHO purposes, the main difference for a Class D dossier would be in the level of details submitted in the clinical/performance data. However, the document also notes that although a regulatory authority/conformity assessment body should not normally require more elaborate information for a Class C IVD, this does not preclude the regulatory authority/conformity assessment body from requesting such information in specific cases. WHO exercises this option for diagnostics that present additional risk as a result of their role in clinical decision-making and the areas of use (see discussion of specific tests below).

6. Determining the Risk Classification for WHO Prequalification

GHTF has generated a set of risk classification rules that are used to assign a particular IVD to a particular risk class. (4) When applying these rules to determine the risk class, WHO will also take into consideration not only the rule specific to a given IVD, but also how the IVD is generally used in clinical and laboratory (or non-laboratory testing settings) practice in its Member States. This use, along with other factors particular to Member States such as the variable technical level and/or training of the operator of the IVD, may result in a WHO risk classification higher than that recommended in existing GHTF risk classification rule examples.

The following subsections describe how IVDs are classified by WHO with reference to the relevant GHTF Classification Rules (see **Annex 1**), and describes the reasoning for the risk classification ultimately assigned by WHO for each type of IVD. Whereas this document identifies specific examples of existing technologies, as new technologies arise WHO will consider the risk that they pose, which will in turn dictate the extent of the documentation to be submitted and the scope of WHO review .

6.1. How WHO classifies an HIV serology test (including rapid diagnostic test, enzyme immunoassays and other formats)

a. *Applicable classification rule and classification:*

Rule 1 – **Class D** (specifically identifies HIV IVDs for diagnosis and those for screening of blood and blood products for transfusion as Class D)

b. *Intended use:*

For detection of antibodies to HIV-1/2 as an aid in the diagnosis of HIV infection. For screening of blood and blood products.

c. *Where the test is likely to be used in Member States:*

For laboratory-based testing: In level II (district), level III (provincial or regional), and level IV (national) laboratories.

For point-of-care testing: In level I (primary) laboratories and level 0 community-based settings, including outside of a traditional laboratory setting (minimal infrastructure, without temperature control).

d. *Expertise of likely user in WHO Member States:*

For laboratory-based testing: Trained laboratory professionals.

For point-of-care testing: Variable but likely to be minimal, if any, technical background. Minimal training, if at all.

e. *Clinical importance of test result:*

Test results are used to decide on whether to enter individuals into treatment and care using valuable resources (medicines, laboratory monitoring, clinical expertise, etc.) that may be in very limited supply.

Test results are used to determine if blood or blood products are safe to be transfused.

f. *Impact of test result in WHO Member States:*

i. *Public health impact of incorrect result*: High

False negative result: High potential for onward transmission of HIV infection on a large scale, when such a result occurs in screening for transfusion.

False positive result: Unnecessary use of limited resources

ii. *Individual health impact of incorrect result:* High

False negative result: Delay in entry into treatment and care associated with poorer health outcomes

False positive result: Misdiagnosis of HIV infection, risks associated with side effects of treatment, psychological impact on the patient and the family.

6.2. How WHO classifies a malaria rapid diagnostic test

a. *Applicable classification rule and classification:*

Rule 3 – **Class C**

b. *Intended use:*

For detection of antigen produced by the *Plasmodium* species parasite as an aid in the diagnosis of malaria.

c. *Where the test is likely to be used in WHO Member States:*

For point-of-care testing: In level I (primary) laboratories and level (0) community-based settings, including outside of a traditional laboratory setting (minimal infrastructure, without temperature control).

d. *Expertise of likely user in WHO Member States:*

Minimal, if any, technical background. Minimal training, if at all.

e. *Clinical importance of test result:*

Test results are used to decide on whether to enter individuals into care using valuable resources that may be in very limited supply.

f. *Impact of test result in WHO Member States:*

i. *Public health impact of incorrect result*: Moderate

False positive result: Unnecessary use of limited resources (medicines), possible contribution to drug resistance due to over-treatment

False negative result: Possible transmission of the disease, economic impact.

ii. *Individual health impact of incorrect result:* High

False negative result: Not initiating treatment for an infected individual can have profound implications for individual health, possibly leading to death

False positive result: Risks associated with side effects of treatment

Additional note: The epidemiology of malaria and the resultant public health response to this infection are very different in a number of WHO Member States than in most countries with established regulatory authorities (with concomitantly well developed health systems). In high income countries, malaria is not endemic and rarely affects more than a select few who typically acquired the disease from travel to or residing in an endemic region. Individuals in these countries generally undergo extensive laboratory investigations including other tests (e.g. molecular techniques) for malaria before a definitive diagnosis is made. As such, in many jurisdictions with established regulatory systems, malaria rapid diagnostic tests typically are assigned a lower risk classification due to the difference in hazards associated with the use of the test.

6.3. How WHO classifies a HIV qualitative nucleic acid technology (including laboratory-based, point-of-care and near to point-of-care testing)

a. *Applicable classification rule and classification:*

Rule 1 – **Class D**

b. *Intended use:*

As an aid in the diagnosis of HIV infection, including in infants.

c. *Where the test is likely to be used in Member States:*

For laboratory-based or near to point-of-care testing: In a level III (provincial or regional) or level IV (national) laboratories. In addition, in level II (district) laboratories for near to point-of-care.

For point-of-care testing: In level I (primary) laboratories and level (0) community-based settings, including outside of a traditional laboratory setting (minimal infrastructure, without temperature control).

d. *Expertise of likely user in WHO Member States:*

For laboratory-based and/or near to point-of-care testing: Trained laboratory professionals.

For point-of-care testing: Variable but likely to be minimal, if any, technical background.

e. *Clinical importance of test result:*

Test results are used as a possible sole basis for determining whether infants are infected with HIV and therefore entering into care and beginning antiretroviral therapy.

f. *Impact of test result in WHO Member States:*

i. *Public health impact of incorrect result*: High

False positive result: Unnecessary use of limited resources (medicines, laboratory monitoring, clinical expertise, etc.).

ii. *Individual health impact of incorrect result:* High

False negative result: Not treating an infected infant can have profound implications for individual health, possibly leading to death.

False positive result: Risks associated with side effects of treatment, especially in infants. Incorrect de facto diagnosis of infant's mother who may or may not be aware of her HIV status.

Additional note: An assay for EID is considered to be Class D because it is an HIV assay that is used as an aid in the diagnosis of HIV infection, consistent with Rule 1, even though the expected public health impact of misdiagnosing an HIV-infected infant is actually expected to be low. WHO considers this to be an exception to the strict interpretation of the GHTF risk classification.

6.4. How WHO classifies a HIV quantitative nucleic acid technology (including laboratory-based, point-of-care and near to point-of-care testing)

a. *Applicable classification rule and classification:*

Rule 3 – **Class C**

b. *Intended use:*

As an aid for patient management of individuals diagnosed as infected with HIV through quantitative detection of HIV total nucleic acid.

c. *Where the test is likely to be used in Member States:*

For laboratory-based and/or near to point-of-care testing: In a level III (provincial or regional) or level IV (national) laboratories. In addition, in level II (district) laboratories for near to point-of-care.

For point-of-care testing: In level I (primary) laboratories and level (0) community-based settings, including outside of a traditional laboratory setting (minimal infrastructure, without temperature control).

d. *Expertise of likely user in WHO Member States:*

For laboratory-based and/or near to point-of-care testing: Trained laboratory professionals.

For point-of-care testing: Variable but likely to be minimal, if any, technical background.

e. *Clinical importance of test result:*

Test results are used as a basis for deciding whether to initiate and monitor antiretroviral therapy.

f. *Impact of test result in WHO Member States:*

iii. *Public health impact of incorrect result*: Moderate

Downwards misclassification (result incorrectly low): Possible contribution to drug resistance due to prolonged use of ineffective regimen, may lead to onward transmission, including of resistant HIV strains to other individuals.

Upwards misclassification (result incorrectly high): Leads to unnecessary switching to more expensive regimens (2^{nd} and 3^{rd} line) and therefore unnecessary use of limited resources.

iv. *Individual health impact of incorrect result:* High

Downwards misclassification: Compromised ability to identify lack of adherence to antiretroviral therapy. Treatment failure not identified which can have profound implications for individual health, possibly leading to death.

Upwards misclassification: N/A

6.5. How WHO classifies a CD4 enumeration technology (including laboratory-based, point-of-care and near to point-of-care testing)

a. *Applicable classification rule and classification:*

Rule 3 – **Class C**

b. *Intended use:*

As an aid for patient management of individuals diagnosed as infected with HIV through enumeration of CD4+ lymphocytes.

c. *Where the test is likely to be used in WHO Member States:*

For laboratory-based and/or near to point-of-care testing: In a level III (provincial or regional) or level IV (national) laboratories. Level II (district) laboratories for near to point-of-care.

For point-of-care testing: In level I (primary) laboratories and level (0) community-based settings, including outside of a traditional laboratory setting (minimal infrastructure, without temperature control).

d. *Expertise of likely user in WHO Member States:*

For laboratory-based and/or near to point-of-care testing: Trained laboratory professionals.

For point-of-care testing: Variable but likely to be minimal, if any, technical background.

e. *Clinical Importance of test result:*

Test results are used as a basis for deciding whether to start (initiate) antiretroviral therapy, substitute for toxicity, or switch after suspected treatment failure.

f. *Impact of test result in WHO Member States:*

i. *Public health impact of incorrect result*: Moderate

Downward misclassification of patients (result incorrectly low): Unnecessary use of limited resources (medicines, laboratory monitoring, clinical expertise, etc.)

ii. *Individual health impact of incorrect result:* High

Upward misclassification of patients (result incorrectly high): : Not initiating antiretroviral therapy or switching therapy (in the case of treatment failure) can have profound implications for individual health, possibly leading to death.

Downward misclassification of patients: Risks associated with side effects of treatment.

Additional note: CD4 is often the only marker available for decision-making associated with initiation of antiretroviral therapy in low and middle income countries. This means that the hazards to the individual are high if an incorrect result is obtained. CD4 tests are regulated as the equivalent of Class B in many high income settings because of the low impact of an erroneous result these countries. This is due to a relatively low prevalence of HIV infection and policies of immediate initiation of treatment upon serodiagnosis, irrespective of the CD4 count (i.e. test and treat). In settings where HIV viral load (quantitative NAT) is available , CD4 generally not used as the primary determinant in monitoring of response to antiretroviral therapy. However, where there are inadequate health resources, and where CD4 provides the sole determinant for the initiation of treatment and/or monitoring response to antiretroviral therapy, the impact of incorrect classification of disease status would have a more significant potential impact on individual health.

7. Using Risk Class to Determine Level of WHO Prequalification of Diagnostics Assessment

Similar to systems implemented by stringent regulatory authorities, the WHO prequalification assessment is designed to safeguard the health and safety of patients and users of IVDs. The level of confidence that the WHO Member States will have in a IVD for a priority disease will be based on the safety and performance of these products throughout their life cycle.

It is the manufacturer's responsibility to ensure that the IVD meets WHO requirements. However, it is the role of WHO to ensure, by review and assessment, compliance with these requirements. Dossier assessment, manufacturing site inspection, the independent WHO laboratory evaluation, as well as post-market surveillance of IVDs for priority diseases, are complementary review and

assessment activities of WHO prequalification. In general, the extent of review for WHO prequalification is proportional to the risk class associated with that IVD.

By aligning with the GHTF risk based classification and assessment recommendations, WHO review and assessment processes are aligned with international best practice. (4,5)

8. Conclusion

By using an internationally acknowledged classification scheme for IVDs, and taking into account the specific attributes associated with the use of these IVDs in many WHO Member States, WHO Prequalification of Diagnostics processes ensure that the level of assessment is proportionate to the degree of risk, taking into account the benefits offered by use of the IVD.

Any inquiries regarding the risk classification of IVDs should be addressed to: *diagnostics@who.int*

9. References

1. GHTF/SC/N4:2011 *Glossary and Definitions of Terms Used in GHTF Documents*
2. GHTF/SG1/N68:2012 *Essential Principles of Safety and Performance of Medical Devices*
3. GHTF/SG1/N063:2011 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*
4. GHTF/SG1/N045:2008 *Principles of In Vitro Diagnostic (IVD) Medical Devices Classification*
5. GHTF/SG1/N046:2008 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) 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 [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.