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April 24, 1998

**To: Medical Devices Stakeholders**

**Subject: Guidance for the risk based classification system of *in vitro* diagnostic devices (Draft)**

The proposed *Medical Devices Regulations* set out the requirements governing the sale, importation and advertisement of medical devices. The goal of the Regulations is to ensure that medical devices distributed in Canada are safe, effective, and meet quality standards. It is the intention of the Therapeutic Products Programme to have these proposed Regulations published in Canada Gazette II in May 1998 and begin implementation on July 1, 1998.

This draft document, titled Guidance for the risk based classification system of *in vitro* diagnostic devices, sets out the Programme's guidance for Industry on the subject. It is being provided now in a draft format so that interested stakeholders can comment and participate in its development. Section numbers of the final CGII published version may differ from the Section numbers referenced in this draft document. This will be corrected in the final version of all guidance documents.

The goal of this document is to help manufacturers, importers and distributors understand the risk-based classification system for *in vitro* diagnostic devices described in Part II of Schedule I of the *Medical Devices Regulations* and to provide guidance on how to classify their devices.

To comment or to get more information on the risk based classification system for *in vitro* diagnostic devices please contact by May 15, 1998 the following:

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Thank you for providing your  
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Attachments

**Therapeutic Products Programme**

**Programme des produits thérapeutiques**

OUR MISSION: To ensure that the drugs, medical devices, and other therapeutic products available in Canada are safe, effective and of high quality.  
NOTRE MISSION: Faire en sorte que les médicaments, les matériels médicaux et les autres produits thérapeutiques disponibles au Canada soient sûrs, efficaces et de haute qualité.

# ***DRAFT***

Therapeutic Products Programme  
GUIDANCE DOCUMENT

## **Guidance For The Risk Based Classification System of *In Vitro* Diagnostic Devices**

Date Prepared / Draft Number	March 17, 1998/ Draft #2 (ivdd_rsk.wpd)
Supersedes	January 6, 1998 / Draft #1
Date Approved by Responsible Authority	
Date Transmitted for External Consultation	
Document Number	GD007/RevDR-MDB

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## **1 Introduction.**

### **1.1 Purpose.**

The purpose of this document is to provide guidance on how to classify *in vitro* diagnostic devices (IVDDs) in accordance with the risk-based classification system (RBCS) for *in vitro* diagnostic devices described in Part II of Schedule I of the *Medical Devices Regulations*.

### **1.2 Background**

As a result of the 1992 “Report of the Medical Devices Committee” (Hearn’s Report), a new regulatory framework for medical devices was developed. This framework is based on two principles, the first being that the level of scrutiny afforded a device is dependent upon the risk the device presents. Secondly, the safety and efficacy of medical devices can be best assessed through a balance of premarket scrutiny, quality systems, and post market surveillance. This new approach based on principles of risk assessment and risk management involved the need to move to a risk-based classification system of all medical devices. This document describes the RBCS that was developed for IVDDs as well as the intent of each rule. It also provides examples in each case.

### **1.3 Scope**

This document is to be used by manufacturers of IVDDs to classify their device in accordance with the RBCS for *in vitro* diagnostic devices described in Part II of Schedule I of the *Medical Devices Regulations*. It is not intended to give guidance to manufacturers on what is a licensable item. This is described in the document entitled "Guidance on how to determine the device licence type", document number GD002/RevDR-MDB.

In this document, examples of IVDDs are provided for each rule. These are not intended to be exhaustive lists. For products not specifically mentioned, the sponsor must determine their risk class based on the rules and principles, as explained in this document. The risk class will be confirmed by the TPP upon receipt of the licence application.

## 2 Definition of an *in vitro* diagnostic device.

An *In Vitro* Diagnostic Device, or IVDD means a medical device or a product subject to section 3 of the *Medical Devices Regulations*, that is to be used *in vitro* for the examination of specimens derived from the human body.

Section 3. (1) These regulations apply to an *in vitro* diagnostic product that is a drug or that contains a drug as if the product were a medical device.

(2) Subsection (1) does not apply to *in vitro* diagnostic products that are or contain drugs listed in Schedule E or F to the *Act*, in the Schedule to Part G or Part J of the *Food and Drug Regulations*, in the Schedules to the *Controlled Drugs and Substances Act*, or in the Schedule to the *Narcotic Control Regulations*.

### 2.1 *In vitro* diagnostic devices subject to the *Medical Devices Regulations*

The definition of IVDDs applies to reagents, articles, instruments, apparatus, equipment or systems, whether used alone or in combination, manufactured, sold or represented for *in vitro* diagnostic use. The term “diagnostic” refers to the examination of specimens for the purpose of providing information concerning a physiological state, state of health or disease or congenital abnormality. It encompasses all applications such as screening, diagnosis (disease status), monitoring, etc. This interpretation is similar to those of other jurisdictions such as United States' Food and Drug Administration, Australia's Therapeutic Goods Administration and the European Communities (proposed IVDD Directives).

In the context of this document, a "test" or an "assay" refers to an analysis to determine the presence, absence or quantity of a specific chemical or substance. A "test kit" means an IVDD that consists of reagents or articles or any combination of these, and that is intended to be used to conduct a specific test or assay, e.g. an HIV test kit.

The classification of IVDDs is largely dependent upon the information provided about its intended use and indications for use. These may be derived from any part of the labelling. In cases of ambiguous labelling the higher risk class will apply. IVDDs labelled "For Research Use Only" are not exempt from the *Medical Devices Regulations*, if they are also labelled or otherwise represented by manufacturers for a specific diagnostic application. This includes being labelled with specific performance characteristics or including a bibliography listing articles referring to the use of the marker for a specific application.

## **2.2 *In vitro* diagnostic products not subject to the *Medical Devices Regulations***

Reagents, instruments, apparatus, equipment or systems not manufactured, sold or represented by manufacturers for use in *in vitro* diagnostic applications are not considered to be IVDDs. This includes many products sold for general laboratory applications, even if they are used by laboratories to develop "home brewed" diagnostic assays for the laboratory's own use.

IVDDs labelled "For Research Use Only" that are not otherwise labelled or otherwise represented by manufacturers for a specific diagnostic application are exempt from the *Medical Devices Regulations*.

In accordance with subparagraph 3(2) of the *Medical Devices Regulations*, all *in vitro* diagnostic products that are or contain drugs listed in Schedule E or F to the *Food and drugs Act*, in the Schedule to Part G or Part J of the *Food and Drug Regulations*, in the Schedules to the *Controlled Drugs and Substances Act*, or in the Schedule to the *Narcotic Control Regulations*, are not subject to the *Medical Devices Regulations*. The following is a short description of these schedules.

Schedules E and F to the *Food and Drugs Act* are currently empty. Section 15 of the *Act* prohibits the sale of a drug mentioned in Schedule F. Therefore, if an *in vitro* diagnostic product was a drug or contained a drug listed on Schedule F to the *Act*, its sale would be prohibited. In the case of an *in vitro* diagnostic product that was a drug or contained a drug listed on Schedule E to the *Act*, it would be subject to the provisions of the *Food and Drug Regulations (F&D Regulations)*.

*In vitro* diagnostic products listed on the Schedule to Part G or the Schedule to Part J of the *F&D Regulations* are subject to the provisions of the *Controlled Drugs and Substances Act (CDSA)* and of the *F&D Regulations*. The Schedule to Part G lists controlled drugs, such as barbiturates and anabolic steroids. The Schedule to Part J lists restricted drugs, such as some amphetamines and lysergic acid diethylamide. All drugs listed in Schedules G and J of the *F&D Regulations* are also listed on the Schedules to the CDSA.

*In vitro* diagnostic products listed on the Schedule to the *Narcotic Controlled Regulations* are subject to the provisions of the CDSA (also listed in its schedules) and of the *Narcotic Controlled Regulations*.

In addition to the products listed on Schedules G and J of the *F&D Regulations* and on the Schedule to the *Narcotic Controlled Regulations*, there are other products listed on the schedules to the CDSA that are also not subject to the *Medical Devices Regulations*.

### 3 Overview of the risk based classification system for *in vitro* diagnostic devices (IVDDs)

The following RBCS is based on the degree of risk associated with the use of an IVDD. It classifies all IVDDs into four classes: I, II, III and IV. An IVDD with the highest risk is classified as Class IV while an IVDD with the lowest risk is classified as Class I.

Criteria used to determine the risk class of each IVDD include its intended and indication(s) for use (the specific disorder, condition, or risk factor for which the test is intended), its application (screening, patient-based testing/diagnosis, monitoring, etc.), the technical/ scientific/medical expertise of the intended user (testing laboratories vs near-patient testing), 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, and the impact of the result (true and false) to the individual and/or to the public health.

Important patient-related factors that were considered include the outcome of unnecessarily delaying or subjecting an individual to treatment (false diagnosis), the stress/anxiety resulting from the information (e.g. genetic testing, home-testing) and the nature of the possible follow-up measures (e.g. in cases of genetic testing or foetal testing).

The impact of a result to the public health addresses the issue of potential propagation of transmissible agents due to erroneous results, such as a contaminated blood donation, a misdiagnosed (false negative) carrier of human immunodeficiency virus or a carrier of a methicillin resistant strain of *Staphylococcus aureus* in a hospital setting. Criteria such as the mode of transmission, the efficacy of the transmission, the nature of the disease and available treatment were considered.

The intent of the four different classes within this classification can be described as:

Class IV IVDDs are those that, through their use, present a high public health risk to the community in general. It includes IVDDs used for donor screening or for the diagnosis of life-threatening diseases caused by transmissible pathogens such as HIV and hepatitis viruses. These are diseases that result in death or long term disability, that are often untreatable or require major therapeutic interventions and where an accurate diagnosis is vital to mitigate the public health impact of the condition.

Class III IVDDs are those that, through their use, present either a moderate public health risk or a high individual risk. They present a moderate public health risk, to the community in general or in some cases to a more confined environment such as a hospital, as they are used to detect transmissible agents that causes diseases that, although

often treatable, may result in death or long term disability if not treated in a timely manner and where an accurate diagnosis offers an opportunity to mitigate the public health impact of the condition. Examples include sexually transmitted agents and infectious agents that cause nosocomial infections. Class III IVDDs that present a high individual risk are those where an erroneous result would put the patient in an imminent life-threatening situation (e.g. IVDDs used in cases of suspected meningitis or septicaemia) or would have a major negative impact on outcome (e.g. result in death or severe disability) as they are a critical, or even the sole, determinant (cancer screening, prenatal screening). 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 (e.g. genetic testing, congenital disorders).

Class II IVDDs are those that, through their use, present either a low public health risk or a moderate individual risk. These present a low community risk because they detect infectious agents that are not easily propagated in a population or because they cause self-limiting diseases. They present a moderate individual risk as they are not the sole determinant or, if they are, it is not likely that an erroneous result will cause death or severe disability, have a major negative impact on outcome or put the individual in immediate danger.

Class I: IVDDs that, through their use, present a minimal risk such as general *in vitro* diagnostic laboratory equipment, microbiology and cell culture media and general diagnostic reagents.

The following sections (4 to 6) give specific explanations as to the intent of each of the rules. The rules are listed (*in italics*) as they appear in Part II of Schedule I of the *Medical Devices Regulations*, followed by the explanations and examples.

#### **4 Classification of IVDDs for use with respect to transmissible agents**

Rules 1 to 3 apply to IVDDs used to gain information about the disease status or immune status of individuals with respect to transmissible agents. These IVDDs are used for different purposes such as screening, diagnosis or patient management. In the context of the RBCS, the term "transmissible agents" designates conventional infectious agents such as bacteria, viruses, fungi and protozoa as well as agents such as prions and toxins. It does not include genetic traits.

#### 4.1 Rule 1: IVDDs used for donor screening

*An IVDD that is intended to be used to detect the presence of, or exposure to, a transmissible agent in blood, blood components, blood derivatives, tissues or organs to assess their suitability for transfusion or transplantation is classified as Class IV.*

This rule applies specifically to IVDDs that are intended to be used to ensure the safety of blood, blood components, blood products, tissues and organs intended for transfusion or transplantation with regard to transmissible agents. In most cases, a positive result would preclude its use for transfusion or transplantation. The IVDD may be used for the detection of structural components of the infectious agent (detect the presence of), such as p24 Ag (HIV test kits) or nucleic acids, or for the detection of surrogate markers (detect exposure to), such as antibodies to the agent.

This rule applies to all screening assays that currently must be performed in Canada on donated blood as required by the Bureau of Biologics and Radiopharmaceuticals, Therapeutic Products Programme. It also applies to all assays that must be done on donated tissues and organs as prescribed in the "Canadian General Standard on the Safety of Tissues and Organs for Transplantation".

It also applies to assays marketed for pyrogenicity testing of blood products, assays marketed for the detection of bacterial contamination of blood components, or assays marketed for plasma pool testing in the manufacturing of blood derivatives.

Examples of IVDDs that presently could be considered Class IV according to this rule are:

HBsAg	anti-HTLV I and/or II
anti-HBc	<i>T. pallidum</i> (non-treponemal and treponemal assays)
anti-HCV	anti-CMV (cytomegalovirus)
anti-HIV-1, anti-HIV-2 or anti-HIV-1/-2	anti-EBV (Epstein-Barr virus)
p24 HIV	

An IVDD for one of the above markers that is labelled clearly "Not for donor screening" is not subject to this rule. In some instances this will change the classification of the IVDD. For example, IVDDs for the detection cytomegalovirus, Epstein-Barr virus or *Treponema pallidum* intended for use as an "as an aid in the diagnosis of..." and bearing the mention "not for donor screening" are not subject to this rule but rather to rule 2 and are classified as Class III. In other cases, such as anti-HIV or HBsAg, the classification of the IVDD will not change as they are still classified as Class IV according to rule 2.

#### **4.2 Rule 2: IVDDs used to determine disease status or immune status**

*An IVDD that is intended to be used to detect the presence of, or exposure to, a transmissible agent is classified as Class II, unless*

*[a] it is intended to be used to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening disease and where there is a risk of propagation in the Canadian population, in which case it is classified as Class IV; or*

*[b] it falls into one of the following categories, in which case it is classified as Class III, namely,*

*i) it is intended to be used to detect the presence of, or exposure to, a transmissible agent that causes a serious disease and where there is a risk of propagation in the Canadian population,*

*ii) it is intended to be used to detect the presence of, or exposure to, a sexually transmitted agent,*

*iii) it is intended to be used to detect the presence of an infectious agent in cerebrospinal fluid or blood, or*

*iv) there is a risk that an erroneous result would cause death or severe disability to the individual being tested, or to the individual's offspring.*

This rule applies to IVDDs that are intended to be used to determine the disease status or the immune status of individuals with regard to transmissible agents.

In the context of this rule, the word "detect" is interpreted to include all types of assays, such as first-line assays, confirmatory assays and supplemental assays. Their principles may be based on the detection of structural components (presence of) or surrogate markers (exposure to). It includes all assays used within a proper testing algorithm to establish a firm diagnosis [enzyme immunoassays, western blots, immunofluorescence assays, nucleic acid based assays, etc.]. Many are marketed "as an aid to the diagnosis of ...".

The classification of these IVDDs is mainly based on the agents they intend to detect, their application (screening vs patient-based testing), the transmissibility of the agent, its pathogenicity, its incidence, the availability of treatment, the importance of the result as part of

the overall diagnostic work-up and the impact of an erroneous result to the individual or to the public health.

IVDDs used for patient management, such as those used to follow an individual's response to drug therapy or to follow the evolution of a disease, are not covered by this rule. In many cases, IVDDs used for patient management purposes (see rule 3) are classified in a lower risk class than those used to diagnose the disease. Since the label claims will determine the classification of all IVDDs, those with ambiguous claims will be assigned the higher classification.

This rule does not apply to microbiological and cell culture media or to serological or chemical reagents used for the confirmation of resulting cultures. These are classified as Class I.

#### 4.2.1 Class II

IVDDs classified as Class II are those that, through their use, present a low community risk because they detect infectious agents that are not known to be easily propagated in the Canadian population or, if they do, because they normally cause self-limiting diseases. As diagnostic tools, they are used in many cases with other diagnostic information and an erroneous result is not likely to result in death or severe disability or put the individual in immediate danger.

Examples of Class II IVDDs include those use to detect infection by the following agents:

Adenovirus	Parvovirus B19
<i>Bordetella pertussis</i>	Respiratory Syncytial Virus
<i>Borrelia burgdorferi</i> (Lyme disease)	Rotavirus
<i>Helicobacter pylori</i>	Rubeola (Measles) Virus
Hepatitis A virus	<i>Salmonella</i>
<i>Histoplasma capsulatum</i>	<i>Trichinella spiralis</i>
Influenza Virus A, B, C	<i>Trypanosoma cruzi</i>
Mumps Virus (Paramyxovirus)	Varicella-Zoster Virus
Parainfluenzae virus	

#### 4.2.2 Class III - subrule [b]

IVDDs classified as Class III under subrule (b)(i) are those used to detect transmissible agents that cause serious human diseases that are also of significant public health importance (moderate public health risk), that is, they are known to, or potentially could, present a risk of

transmission in the Canadian population if not detected in a carrier and where an accurate diagnosis offers an opportunity to mitigate the public health impact of the condition. Serious diseases are diseases that, although often treatable, represent an immediate danger, such as death or severe disability, if not treated in a timely manner. Examples would include IVDDs such as those for the detection of *Mycobacterium sp.* and *Legionella*.

Rule (b)(i) applies to IVDDS that are intended to be used for the detection of transmissible agents responsible for nosocomial infections, such as those caused by *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* or *Enterococcus sp.* (formerly called *Streptococcus*).

IVDDs used for the detection of sexually transmitted agents are also subject to rule (b)(i), however, for the purpose of clarity subrule (b)(ii) was included. An IVDD for the detection of infection by *Treponema pallidum* (syphilis) specifically labelled "for diagnostic purposes only" and bearing the note "not for donor screening", would be subject to this rule and not to rule 1.

Subrule [b][iii] and [b][iv] apply to IVDDs intended to be used for the detection of transmissible agents that cause diseases that may be of less significance from a public health perspective (low public health risk) but where the use of the IVDD presents a high risk to the individuals being tested, i.e. there is a risk that an erroneous result would lead to death or severe disability. Examples include IVDDs used for the detection of infection by CMV, EBV because of their special importance in the management of transplant recipients (Canadian General Standard on the Safety of Tissues and Organs). IVDDs for the detection of anti-CMV or anti-rubella are also critical in cases of neonatal infections. IVDDs used in instances of suspected infection by *Chlamydia pneumoniae* or of suspected meningitis or septicaemia are also subject to this rule, even though the latter two were included as a separate subrule, [b][iii] for the purpose of clarity.

As mentioned above, subrule [b][iii] applies to IVDDs that are used in instances of suspected meningitis (bacterial or aseptic) or septicaemia. Any IVDD intended for the direct detection of infectious agents in blood or cerebrospinal fluid, which are indicative of those conditions, will be subject to this rule. According to current technologies, this would largely be IVDDs that detect structural component of infectious agent, for example a surface antigen, as well as nucleic acid-based detection IVDDs (e.g. PCR, LCR). This rule does not cover assays based on the detection of human antibodies produced in response to the presence of an infectious agent (exposure to). However, if such an IVDD becomes available it would be classified as a Class III under subrule [b][iv]. Examples of IVDDs that would be subject to this rule are those used for the detection of *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus B*, *Cryptococcus neoformans*, or Enterovirus in CSF or blood.

Subrule [b][iv] also includes IVDDs used for targeted population screening such as prenatal women screening to determine a woman's immune status towards agents such as rubella virus or *Toxoplasma gondii* or to establish colonization by agents such as *Streptococcus B*.

Below is a list of examples of transmissible agents, including those mentioned in the above discussion, for which IVDDs intended for their detection would be subject to subrule 2[b]:

<i>Chlamydia trachomatis</i> <sup>A</sup>	<i>Staphylococcus aureus</i>
Papilloma virus <sup>A</sup>	<i>Pseudomonas aeruginosa</i>
Herpes Simplex Virus, type II <sup>A</sup>	<i>Neisseria meningitidis</i>
<i>Haemophilus ducreyi</i> <sup>A</sup>	<i>Streptococcus</i>
<i>Neisseria gonorrhoeae</i> <sup>A</sup>	<i>Haemophilus influenzae</i>
<i>Trichomonas vaginalis</i> <sup>A</sup>	<i>Cryptococcus neoformans</i>
<i>Treponema pallidum</i> <sup>A</sup>	Cytomegalovirus (CMV)
<i>Mycobacterium</i>	Epstein-Barr virus (EBV)
<i>Chlamydia pneumoniae</i>	Enterovirus
<i>Legionella</i>	<i>Toxoplasma gondii</i>
<i>Enterococcus</i>	Rubella virus
<i>Escherichia coli</i>	

<sup>A</sup> Sexually transmitted agents according to World Health Organization

#### 4.2.3 Class IV - subrule [a]

IVDDs classified as Class IV (subrule a) are those intended to detect infection by transmissible agents that cause life-threatening diseases and that are known to, or potentially could, present a risk of transmission in the Canadian population if not detected in a carrier and where an accurate diagnosis is vital to mitigate the public health impact of the condition. These are diseases that often result in death or severe chronic disability. Many of these diseases are untreatable or require major medical interventions such as a transplantation. Hepatitis, caused by Hepatitis viruses B, C and D, and the Acquired Immunodeficiency Disease Syndrome are examples of very serious human diseases caused by infectious agents. This includes near-patient-IVDDs for any of the concerned transmissible agents.

Examples of IVDDs that are currently subject to this rule include:

HBsAg, anti-HBsAg, HbC, HBe, anti-HBe EIAs and confirmatory assays  
anti HIV-1 and/or HIV-2 EIA, HIV-1 and/or HIV-2 WB, IFA and RIA  
HIV-1 DNA PCR  
anti-HTLV-1 and/or anti-HTLV-2 EIA or WB  
anti-HCV, HCV PCR

### **4.3 Rule 3: IVDDs used for patient management purposes**

*An IVDD that is intended to be used for patient management is classified as Class II, unless it falls into one of the following categories, in which case it is classified as Class III:*

*[a] it is intended to be used for the management of patients suffering from a life-threatening disease; or*

*[b] there is a risk that an erroneous result would lead to a patient management decision that results in an imminent life-threatening situation to the patient.*

This rule applies to IVDDs that are used with respect to transmissible agents for purposes other than determining disease status or immune status (rule 2), such as prognosis or monitoring (to follow the evolution of a disease or to establish the effectiveness of a specific treatment). Many of these IVDDs are quantitative or semi-quantitative assays. The classification of these IVDDs is based primarily on the nature of the disease caused by the transmissible agent, the availability of treatment and the impact of an erroneous result to the individual being tested.

#### **4.3.1 Class II**

Those are IVDDs whose results are not critical in determining an initial course of therapy or where the likelihood of an erroneous result leading to a decision resulting in immediate danger to the patient is minimal. It includes IVDDs currently used to determine drug susceptibility of microorganisms from isolated cultures or colonies such as sensitivity discs and tablets, MIC (minimum inhibitory concentration) panels, fully automated STIC (short-term incubation cycle) antimicrobial susceptibility devices and DNA probe tests (detects genes that would confer resistance).

#### **4.3.2 Class III - subrules [a] and [b]**

Subrule [a] applies to any IVDDs used for the management of patients afflicted of diseases caused by infectious agents such as HIV, HBV or HCV. Examples include p24 Ag HIV (prognosis only), HIV RNA viral load tests (monitoring only) and IVDDs for the determination of drug resistance gene of HIV isolates.

Subrule [b] classifies as Class III, IVDDs where there is a risk that an erroneous result would lead to a patient management decision resulting in an imminent life-threatening situation to the patient.

## 5 Classification of IVDDs for uses other than for transmissible agents

Rule 4 applies to IVDDs that are intended for use to establish disease status or for patient management purposes. Rule 5 applies to IVDDs that are used for blood grouping or tissue typing.

### 5.1 Rule 4: IVDDs used for disease status and for patient management

*An IVDD that is not subject to rules 1 to 3 and that is intended to be used in diagnosis or patient management is classified as Class II, unless it falls into one of the following categories, in which case it is classified as Class III:*

*[a] it is intended to be used in screening for or in the diagnosis of cancer;*

*[b] it is intended to be used for genetic testing;*

*[c] it is intended to be used in screening for congenital disorders in the fetus;*

*[d] there is a risk that an erroneous diagnostic result would cause death or severe disability to the patient being tested, or to that patient's offspring;*

*[e] it is intended to be used for disease staging; or*

*[f] it is intended to be used to monitor levels of drugs, substances or biological components where there is a risk that an erroneous result would lead to a patient management decision that results in an imminent life-threatening situation to the patient.*

The classification of these IVDDs is based primarily on their application (screening vs patient-based testing), frequency of use, the nature of the condition being determined, the importance of the information to the diagnosis and the impact of the result (true or false) to the individual. Since all near-patient IVDDs are classified as Class III (see rule 6), this rule applies to IVDDs for use in testing laboratories.

### 5.1.1 Class II - disease status and patient management

IVDDs classified as Class II include most IVDDs used to determine levels (quantitative or semi-quantitative) of therapeutic drugs, narcotic drugs, antibiotics, heavy metals, physiological markers (e.g. hormones, amino acids, vitamins, metabolic intermediates, enzymes, total proteins), etc. Most qualitative IVDDs indicative of metabolic disease or disorders, such as autoimmune disorders, would also be subject to this rule. Many of these are IVDDs that are used as minor determinants or as one of several determinants in diagnosis or patient management. An erroneous result is not likely to put the individual in immediate danger or have a significant negative impact on long-term outcome.

This rule also may apply to some IVDDs that are used as critical determinants in emergency situations (e.g. drug overdose) but where the risk of an erroneous result directly causing death or long term disability is not significant.

Examples of Class II IVDDs include those used for:

MEGX	carbamazepine
amitriptyline	estradiol
nortriptyline	CA15-3/CA125/CE/PSA/hCG
imipranine & desipramine	(monitoring)
N-acetylprocainamide	prostatic acid phosphatase
theophylline	drugs of abuse
phenobarbital	neuron specific enolase (NSE)
digoxin	progesterone
digitoxin	blood analytes (except K <sup>+</sup> )
methotrexate	glucose

IVDDs for cancer markers intended to be used for monitoring purposes or to detect the recurrence of cancer or residual disease only are classified as Class II.

### 5.1.2 Class III: IVDDs for disease status - subrules [a] to [d]

Subrules [a] to [d] apply to IVDDs where their use present a higher risk than those described in section 5.1.1 primarily because of the impact of the result (true or false) on the individuals or because of the importance of the information to the diagnosis. This includes all IVDDs used for genetic testing, for disease staging, for the diagnosis of cancer and for the screening of cancer or congenital disorders in fetus.

The classification of serum tumour markers such as prostate specific antigen (PSA),

carcinoembryonic antigen (CEA), human chorionic gonadotropin (hCG), cancer antigen (CA) 15-3, CA125, HER-2/neu, estrogen and progesterone receptors, etc., will be made in accordance with the label claims, which, as stated before, can be derived from any part of the labelling. IVDDs used for screening (for early detection of cancer) or for the diagnosis of cancer are classified as Class III, while those used for monitoring (for disease progression or response to therapy) or for the detection of recurrence of cancer or of residual disease, are classified as Class II. For example, IVDDs intended to be used to determine free PSA levels and total PSA levels that also state that the ratio of free to total PSA can be used as an aid in discriminating between prostatic hyperplasia and prostate cancer are both deemed to be Class III.

IVDDs such as automated PAP smear readers are also classified as Class III in accordance with subrule [a].

Genetic testing is defined as "the analysis of human DNA, RNA, or chromosomes, for purposes such as the prediction of disease or vertical transmission risks, monitoring, diagnosis or prognosis". This definition includes testing for genetic predisposition. Examples of genetic testing would include testing for diseases/disorders such as cystic fibrosis, sickle cell disorder, breast cancer, Huntington's disease and Alzheimer's disease. It also includes imaging systems intended to be used to detect genetic abnormalities using DNA probes.

Subrule [c] applies to IVDDs used during pregnancy on either maternal or foetal specimens in order to determine congenital disorders of a fetus. This rule does not apply to IVDDs that are routinely used to assess the general health of the fetus during pregnancy. Those are Class II IVDDs. Examples of IVDDs subject to subrule [c] include those for the quantitative determination of serum or CSF levels of alpha foetoprotein in prenatal testing of spina bifida or Down Syndrome, the latter being determined in conjunction with serum levels of hCG and oestriol, themselves classified as Class III for that indication.

Subrule [d] applies to IVDDs not captured by previous rules that are deemed critical determinants in establishing disease status and where there is a risk that an erroneous result would lead to death or severe disability. It includes:

- C IVDDs intended to be used for prenatal or neonatal testing for conditions such as lung maturity (lecithin/sphingomyelin ratio in amniotic fluid), hyperphenylalaninemia (phenylalanine assay) or primary congenital hypothyroidism (neonatal thyroid stimulating hormone). Any IVDD based on a dot blot spot (DBS) procedure for neonatal markers is considered to be intended to be used in neonatal testing;
- C IVDDs intended to be used for the screening of or diagnosis of late-onset disorders such as Huntington's disease or Alzheimer's disease;
- C IVDDs intended to be used for the detection of cardiac markers, such as CK-MB,

myoglobin and troponin, indicative of myocardial infarction or minor myocardial damage or used as predictors of cardiac events;

- C IVDDs, such as partial thromboplastin time tests and prothrombin time tests, intended to be used as general, or primary, screening procedure for the detection of coagulation abnormalities.

### 5.1.3 Class III - Patient management - subrules [e] and [f]

Subrules [e] and [f] apply to IVDDs used for patient management where their use present a higher risk than those described in section 5.1.1 primarily because of the importance of the information obtained or because of the impact of an erroneous result.

In the context of subrule [e], disease staging refers to the characterization of the nature or extent of a medical condition such as the degree of metastasis of a cancer tumour. This information is considered critical to make accurate and appropriate patient management decisions, including initial treatment planning.

Subrule [f] applies to monitoring IVDDs where the accuracy of the result is paramount to the management of the patient. It applies to:

- C IVDDs intended to be used to monitor the level of drugs with narrow therapeutic ranges such as immunosuppressive drugs (e.g. cyclosporin and tacrolimus);
- C IVDDs, such as prothrombin time test and heparin analysers, intended to be used for monitoring anticoagulant therapy;
- C IVDDs used to determine and monitor blood potassium (K<sup>+</sup>), blood gases and pH

## 5.2 Rule 5: IVDDs for immunological typing

*An IVDD that is intended to be used for blood grouping or tissue typing to ensure the immunological compatibility of blood, blood components, tissue or organs that are intended for transfusion or transplantation is classified as Class III.*

This rule applies to all IVDDs, including single reagents, kits or automated systems, used to ensure the immunological compatibility of donated blood, tissues or organs. It applies to all markers, ABO and RhD blood groupings, red cell reagents, HLA typing, Rhesus(C,c,E,e), anti-Kell, anti-Duffy and anti-Kidd as well as reagents and reagent products for determining irregular anti-erythrocytic antibodies and unusual antibodies.

## 6 Special rules

Rules 7 to 9 were developed to address specific issues related to IVDDs, such as the IVDDs used outside central laboratories.

### 6.1 Rule 6: Near-patient IVDDs

*A near-patient IVDD is classified as Class III.*

A near-patient IVDD is defined as an IVDD for use outside a laboratory environment for home testing or for point-of-care testing. Point-of-care testing is considered to be testing performed generally near to, or at the site of, the patient, such as in a health care professional's office, a clinic, a pharmacy or at the bedside. IVDDs for point-of-care testing are often labelled "For professional use only".

In the context of this document, home testing refers to IVDDs that are marketed for home use (for lay use). This includes both testing carried out by patients under the supervision of their physician and testing carried out by the lay public on their own initiative. In case of the latter, IVDDs are generally marketed over-the-counter to the general public.

IVDDs for home testing and point-of-care testing are often based on technologies that yield results in matter of minutes.

Except for NPT-IVDDs for transmissible agents such as HIV or hepatitis viruses, which are Class IV devices, and those listed in the table under rule 6 (used to detect pregnancy or for fertility testing), which are Class II IVDDs, all other NPT-IVDDs are Class III devices.

Examples of near-patient IVDD include those for the detection of *Streptococcus*, occult blood test kits, prothrombin time tests and blood glucose monitors.

### 6.2 Rule 7: IVDDs specifically intended to used together

*In cases where an IVDD, including analysers, reagents and software, is intended to be used with another IVDD, the class of both IVDDs will be that of the IVDD in the class representing the higher risk.*

According to this rule, all instruments, software, calibrators, controls and quality controls reagents, etc. associated with a specific assay are classified in the same risk class as that assay.

It follows that each individual component of a test kit (e.g. sample buffers, dilution buffers, controls, coated microplates) is classified to the same risk class as that test kit. The same may apply to automated analysers and on-board reagents (see below). However, this rule does not imply that each of these component needs to be licensed individually. In order to determine what is a licensable item in such cases, and in some of the examples given below, refer to the document entitled "Guidance on how to determine the device licence type", document number GD002/RevDR-MDB.

Rule 7 not only applies to all instruments, calibrators, control reagents, quality control reagents and software developed by a manufacturer for use with one or more of its own test kit(s) or IVDDs (closed instrumentations), but also to those developed by a manufacturer for use with test kit(s) or IVDD(s) of different manufacturer(s) (open instrumentation). For example, an EIA automated analyser developed by Company A for use specifically with Class III diagnostic assays manufactured and sold by Company B and Company C, is itself classified as a Class III. Similarly, a positive control manufactured by Company Z and marketed for use with HIV test kits from any manufacturer is a Class IV IVDD.

For automated or semi-automated analysers, such as EIA Analysers, if they are designed for the automation of specific assays where the parameters of each assay, in accordance with package insert instructions, are intrinsic to the analyser, they are classified to the same risk class as the highest classified assay it supports. In this context, intrinsic means that the design of the analyser does not allow for the user to alter the test parameters. Analysers sold without specific test parameters intrinsic to the device but with user programmable software for the user's own adaptation (open architecture design) are not subject to this rule. These are classified as Class I devices.

Analysers and other automated instruments not specifically intended for use with another IVDD but where their application necessarily results in their use with a very specific type of assays, are also classified at the same risk class as the IVDDs they are intended to be used with. For example, EIA microplate autodilutors or EIA microplate autoreaders manufactured, sold or represented for use in blood banking operations are classified as Class IV as they are specifically intended for use with IVDDs used for donor screening (rule 1). Similarly, an automated analyser for blood grouping, on which any reagent manufactured for that application can be used, is classified as Class III. This interpretation does not extend to much broader general applications such as diagnostic or monitoring.

This rule does not apply to reagents represented by manufacturers as general diagnostic reagents, that is, not labelled or intended for a specific application. These are classified as Class I.



### 6.3 Rule 8: Class I IVDDs

*If rules 1 - 7 do not apply, all other IVDDs are classified as Class I.*

It includes all microbiological growth media (selective, differential and selective-differential), and associated supplements, used to identify or infer the identity of a microorganism from a specimen derived from the human body as well as serological and chemical reagents used to infirm or confirm the identity of a cultured microorganism. The latter includes bacterial identification systems to be used on cultured microorganisms. As there was concern that some of these products would be interpreted as being subject to rules 1 and 2 under the wording "used to detect", they were included in the Table under rule 9 as IVDDs classified as Class I.

IVDDs classified as Class I also include cell culture media, and associated animal sera, salt solutions and reagents. These are used to grow cells for use in the isolation of viruses from specimens derived from the human body or to grow cells that will be used in the diagnosis of congenital chromosome abnormalities. In the latter case, they are not designed to probe for any specific defect.

This rule applies to all general laboratory products (reagents, instruments, apparatus, equipment or system) manufactured, sold or represented for use for *in vitro* diagnostic examinations. These are not labelled or intended for a specific application. It could include equipment and instruments such as automated analysers with open architecture design, microscopes, spectrophotometers, pipetters, specimen container (not the same as collection device), etc.

For general diagnostic reagents the labelling would be limited to information such as quantity, purity (including impurities), storage conditions, warnings and hazards. They are not labelled or otherwise represented with specific analytical and performance characteristics.

Any general laboratory product not manufactured, sold or represented for use in *in vitro* diagnostic applications are not deemed to be IVDDs.

#### 6.4 Rule 9: Special classification

*Despite rules 1 to 8, an IVDD set out in column 1 of an item of the table to this rule is classified as the class set out in column 2 of that item*

Column 1	Column 2
near-patient IVDD for the detection of pregnancy or for fertility testing	Class II
near-patient IVDD for determining cholesterol level	Class II
microbiological media used to identify or infer the identity of a microorganism	Class I
IVDDs used to identify or infer the identity of a cultured microorganism	Class I

This rule lists IVDDs for which the classification according to the rules were judged inappropriate and sets out the classification at which they will be regulated.

## 7. Application of the rules - Flow Diagram







