Health Canada Santé Canada

April 1, 2016

# Notice

Our file number: 16-101754-737

**Re: Draft Guidance Document - Guidance for the Risk-based Classification System for *In Vitro* Diagnostic Devices (IVDDs)**

Health Canada is pleased to announce draft revisions to the *Guidance Document: Guidance for the Risk-based Classification System for In Vitro Diagnostic Devices (IVDDs),* for a 60-day comment period.

This guidance document clarifies the application of the risk classification rules for IVDDs set out in Part II of Schedule I of the *Medical Devices Regulations*. It was recently rewritten to: conform to Good Guidance Practices; include language for greater clarity; and update the examples.

Comments on the draft revisions should be submitted to the address below no later than May 31, 2016:

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Canada

**Stakeholder Feedback on**
**Draft Guidance Document: Guidance for the Risk-based Classification System for *In Vitro* Diagnostic Devices (IVDDs)**

Comments submitted by: <full name>, <company/association name (if applicable)>
Telephone number: <telephone number>
Address: <full mailing address>
Email: <email address>
Date: <date of comment submission>

| Comment | Section/Line #* | Comment Rationale | Proposed revised text |
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| 1. | | | |
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| 3. | | | |
| etc. | | | |

* Please refer to the Adobe Portable Document Format (PDF) version of the document to ensure accuracy in line numbers.

Health Canada Santé Canada

# DRAFT GUIDANCE DOCUMENT

## Guidance for the Risk-based Classification System for *In Vitro* Diagnostic Devices (IVDDs)

**This guidance document is being distributed for comment purposes only.**

Published by authority of the
Minister of Health

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| Draft Date | 2016/04/01 |

**Health Products and Food Branch**

Canada

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| Our mission is to help the people of Canada maintain and improve their health.<br>*Health Canada* | HPFB's Mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:<br>· minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,<br>· promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.<br>*Health Products and Food Branch* |



***Également disponible en français sous le titre : Ébauche de la ligne directrice : Orientation pour le système de classification fondé sur le risque des instruments diagnostiques in vitro (IDIV)***

# FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

66

| **Document Change Log** | | | |
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| **Document Number** | | **Replaces** | GD007/RevDR-MDB |
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67

| **Change** | **Location (section, paragraph)** | **Nature of and/or Reason for Change** |
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| 1 | Full document | Rewritten to add clarity; conform to Good Guidance Practices; and update examples. |

68

## Table of Contents

## 1.0 INTRODUCTION

The *Medical Devices Regulations* (Regulations) utilize a risk-based approach to regulating products within its scope. The safety and effectiveness evidence required to support a medical device licence application for an *in vitro* diagnostic device (IVDD) is proportional to the risk of the device, which is determined by applying the Classification Rules detailed in Part II of Schedule 1 of the Regulations. As per section 6 of the Regulations, IVDDs are classified into one of four classes, where Class I represents the lowest risk and Class IV the highest.

### 1.1 Policy Objectives

This guidance document is intended to clarify the application of the risk classification rules for IVDDs set out in Part II of Schedule I of the Regulations.

### 1.2 Policy Statements

The classification of an IVDD is primarily based on the following criteria:

- the device's intended use, indications and application (screening, diagnosis, monitoring, prognosis, predisposition) as determined by the manufacturer. These would be reflected in the specifications, instructions and information provided by the manufacturer;
- 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;
- criteria such as the mode of transmission, the efficacy of the transmission, the nature of the disease and available treatment are considered;
- the impact of the diagnostic test result to the individual, his/her offspring, and/or to public health. This includes the 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 of a methicillin resistant strain of *Staphylococcus aureus* in a hospital setting.
- Important patient-related factors that are also considered include: the outcome of unnecessarily delaying or subjecting an individual to treatment in the event of a false diagnosis, the stress/anxiety resulting from the information, and the nature of the possible follow-up measures such as in the case of genetic or fetal testing.

IVDDs are grouped into the following four risk classes based on the degree of risk associated with the use of an IVDD. An IVDD with the highest risk is classified as Class IV while an IVDD

associated with the lowest risk is classified as Class I. Each risk class can be generally described as follows:

**Class IV IVDDs**: are those devices whose use has 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 devices whose use has 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 cause 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 (for example [e.g.] IVDDs used in cases of suspected meningitis or septicaemia) or would have a major negative impact (e.g. result in death or severe disability) as they are a critical, or even the sole, determinant of a diagnosis or treatment decision (e.g., cancer or prenatal screening). Their use 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.

**Class II IVDDs**: are those devices whose use has 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 that cause self-limiting diseases. They present a moderate individual risk as they are generally not the sole determinant of a diagnosis or treatment decision and where they are, it is not likely that an erroneous result will cause death, severe disability, or other major negative health impact.

**Class I IVDDs**: are those devices whose use has minimal public or individual health risks, such as general *in vitro* diagnostic laboratory equipment and general diagnostic reagents.

## 1.3 Scope and Application

This document is to be used by manufacturers to classify their IVDDs in accordance with the rules 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 for the Interpretation of Sections 28 to 31: Licence Application Type*".

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 their own diagnostic assays for the laboratory's own use ("Laboratory Developed Tests" [LDTs]).

IVDDs which are labelled "For Research Use Only" (and are not otherwise labelled or otherwise represented by a manufacturer for a specific diagnostic application, or labelled with specific performance characteristics, or a bibliography listing articles referring to the use of the marker for a specific application) are exempt from the *Medical Devices Regulations.*

In accordance with subparagraph 3(2) of the Regulations, all *in vitro* diagnostic products that are a drug or contain a drug 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 in vitro diagnostic products 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.*

*In vitro* diagnostic products listed on the Schedule to Part G or the Schedule to Part J of the *Food and Drug Regulations* are subject to the provisions of the *Controlled Drugs and Substances Act* (CDSA) and the *Food and Drug 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 addition to the products listed on Schedules G and J of the *Food and Drug 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*.

*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.*

## 1.4 Definitions

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.*

The definition of IVDDs applies to reagents, articles, instruments, apparatus, equipment or systems, including calibrators, control materials, software, 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, prognosis, predisposition, prediction, etc. This interpretation is similar to those of other jurisdictions such as the United States Food and Drug Administration (US FDA), Australia's Therapeutic Goods Administration (TGA) and the European Communities (CE).

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.

# 2.0 GUIDANCE FOR IMPLEMENTATION

## 2.1 Explanation of the Rules

The sections that follow begin with a reproduction of the rules (in italics) as presented in Part II of Schedule I of the Regulations, and are followed by explanation and examples. The examples are not intended to be exhaustive. 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 Medical Devices Bureau upon review of the medical device licence application.

A graphical depiction of the rules is included in the Appendices.

## 2.2 Classification of IVDDs for use with respect to transmissible agents ("Use with Respect to Transmissible Agents")

Rules 1 to 3 apply to IVDDs used to obtain 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 Risk Based Classification System, the term "transmissible agents" designates conventional infectious agents such as bacteria, viruses, fungi and protozoa as well as prions and toxins. It does not include genetic traits.

**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, cells, tissues and organs intended for transfusion or transplantation with regard to transmissible agents. In most cases, a positive result would preclude their use for transfusion or transplantation. The IVDD may be used to detect the presence of structural components of the infectious agent, such as p24 Ag (HIV test kits) or nucleic acids, or to detect exposure to surrogate markers such as antibodies to the agent.

This rule applies to all screening assays that must be performed on donated blood in Canada as required by the Blood Regulations. It also applies to all assays that must be done on donated cells, tissues and organs as prescribed in the Safety of Human Cells, Tissues and Organs for Transplantation Regulations

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

Examples of IVDDs that are subject to this rule include those intended to detect:

Hepatitis B Virus (HBV)
Hepatitis C Virus (HCV)
Human Immunodeficiency Virus (HIV)
West Nile Virus (WNV)
Human T-Lymphotropic Virus (HTLV)
Cytomegalovirus (CMV)
Epstein-Barr Virus (EBV)
*T. pallidum*

An IVDD for any of the above agents that is labelled clearly "Not for donor screening" is not subject to this rule. In some instances this would change the classification of the IVDD. For example, IVDDs for the detection of cytomegalovirus, Epstein-Barr virus, *Treponema pallidum*, or West Nile virus intended for use "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 such cases as anti-HIV or HBsAg, however, the classification of the IVDD would not change as they would still be classified as Class IV according to rule 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 if 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:*

*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.). Most 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 diagnostics), 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, his/her offspring, or to 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 media which is used to identify or infer the identity of a microorganism and cell culture media or to serological or chemical reagents used for the confirmation of resulting cultures. These are classified as Class I. However it does apply to primary plating media that can be inoculated directly with clinical specimens for the direct detection of a microorganism. This includes media subject to enrichment and media for which a screening claim is made. It would also apply to the term "presumptive" (presumptive positive, presumptive identification).

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 are normally self-limiting. 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 used to detect infection by the following agents:

- Adenovirus
- Bocavirus
- *Bordetella pertussis*
- *Borrelia burgdorferi* (Lyme disease)
- Coronaviruses (except SARS*)
- *Helicobacter pylori*
- Hepatitis A virus
- *Histoplasma capsulatum*
- HHV-6
- HSV-1
- Influenza A Virus *(unless designated by the WHO as the causing agent for pandemic flu in which case it would be Class 3, by Rule 2(b)(i))*
- Influenza B, C
- Malaria
- Metapneumonia
- Mumps Virus (Paramyxovirus)
- Parainfluenzae virus
- Parvovirus B19
- Respiratory Syncytial Virus
- Rotavirus
- Rubeola (Measles) Virus
- *Salmonella*
- *Trichinella spiralis*
- Varicella-Zoster Virus

*NOTE: Any virus that is linked to a global outbreak, with rapid spread and high morbidity and/or mortality rates will be subject to Rule 2(b)(i).

Reagents such as antibodies (monoclonal or polyclonal), proteins, primers and probes which are used as critical components in laboratory developed tests are usually classified as Class II devices. These devices are sold without specific analytical and performance claims. In some jurisdictions they are known as Analyte Specific Reagents (ASRs).

**Rule 2: subrule [a]**

IVDDs classified as Class IV are those intended to detect transmissible agents that cause life-threatening diseases and that are known to, or potentially could, present a risk of transmission in the Canadian population 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 transplantation. Hepatitis, caused by Hepatitis viruses B, C and D, and the Acquired Immunodeficiency Disease Syndrome are examples of serious human diseases caused by infectious agents. This includes near-patient-IVDDs for any of the concerned transmissible agents.

Examples of IVDDs that are subject to rule 2[a] include those intended to detect:

HBV,
HIV,
HTLV, types I and II,
HCV

This rule does not apply to those tests intended to monitor infection (e.g. viral load assays). These would be Class III devices by Rule 3.

**Rule 2: subrules [b][i] and [ii]**

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

IVDDs which are used to diagnose serious infections caused by agents (e.g. influenza) designated as pandemic by the World Health Organization (WHO) will also fall under Rule 2 subrule 2(b)(i).

Rule (b) 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*, *Enterococcus sp.* (formerly called *Streptococcus*) and *Clostridium difficile*. It also applies to IVDDs used for the detection of sexually transmitted agents.

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 rather than rule 1.

**Rule 2: subrules [b][iii] and [iv]**

Subrules 2(b)(iii) and 2(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 health risk to the individuals being tested, that is (i.e.), there is a risk that an erroneous result would lead to death or severe disability.

**Subrule 2 [b][iii]** applies to IVDDs that are used in instances of suspected meningitis (bacterial or aseptic) or septicaemia. Any IVDD intended for the detection of infectious agents in blood or cerebrospinal fluids (CSF), which are indicative of those conditions, will be subject to this rule. Examples of IVDDs that would be subject to this rule are those used for the detection of *Neisseria meningitidis, Haemophilus influenza, Streptococcus pneumoniae, Streptococcus B, Cryptococcus neoformans* or Enterovirus in CSF or blood.

**Subrule 2[b][iv]** includes IVDDs used for the detection of infection by CMV and EBV because of their special importance in the management of transplant recipients (Safety of Human Cells, Tissues and Organs for Transplantation Regulations). IVDDs for the detection of anti-CMV or anti-rubella are also critical in cases of neonatal infections and would be subject to this subrule. Other examples include IVDDs used for targeted population screening such as prenatal screening of women to determine their immune status towards agents such as rubella virus or *Toxoplasma gondii* or to establish colonization by agents such as *Streptococcus* B.

IVDDs that would be subject to subrule 2[b] also include those intended to detect the following:

| | |
|---|---|
| *Clostridium difficile* | *Haemophilus influenza* |
| *Chlamydia trachomatis*[A] | Human Papilloma virus[A] |
| *Chlamydophila pneumoniae* | *Legionella* |
| *Cryptococcus neoformans* | *Mycobacterium* |
| Cytomegalovirus (CMV) | *Neisseria meningitidis* |
| Dengue virus | *Neisseria gonorrhoeae*[A] |
| Ebola virus | *Pseudomonas aeruginosa* |
| *Enterococcus* | Rubella virus |
| Enterovirus | *Staphylococcus aureus* |
| Epstein-Barr virus (EBV) | *Streptococcus* |
| *Escherichia coli* | *Toxoplasma gondii* |
| *Haemophilus ducreyi*[A] | *Trichomonas vaginalis*[A] |

Herpes Simplex Virus, type II[A] *Treponema pallidum*[A]

[A] *S*exually transmitted agents according to the World Health Organization

**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.

IVDDs classified as Class II under Rule 3 are those 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 harm 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).

**Rule 3: subrule [a]**

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

**Rule 3: subrule [b]**

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.

## 2.3 Classification of IVDDs for uses other than for transmissible agents ("Other uses")

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.

**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 diagnostics), frequency of use, the nature of the condition being determined, and the importance of the information to the diagnosis and the impact of the result 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.

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), among others. 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 one of several determinants in diagnosis or patient management. An erroneous result is not likely to put the individual in immediate harm or have a significant negative impact on long-term health 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:

| | |
|---|---|
| Amitriptyline | methotrexate |
| blood analytes | neuron specific enolase (NSE) |
| carbamazepine | nortryptiline |
| digoxin | N-acetylprocainamide |
| digitoxin | Phenobarbital |
| drugs of abuse | progesterone |
| estradiol | prostatic acid phosphatase |
| imipranine & desipramine | theophylline |
| MEGX | |

**Rule 4: subrules [a] to [c]** apply to IVDDs where their use presents a higher risk than those described above primarily because of the impact of the result on the individuals or because of the importance of the information to the diagnosis. This includes all IVDDs used for the screening, diagnosis and monitoring of cancer, for genetic testing and for the screening of congenital disorders in the fetus.

IVDDs used in the monitoring of cancer (prognostic or recurrence) are Class III devices because of the impact of an incorrect result (failure to treat or inappropriate treatment decisions). In many cases, the same tests used to detect a specific cancer marker are also used to monitor the patient during and after treatment.

IVDDs such as automated PAP smear readers are also classified as Class III in accordance with Rule 4, 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.

Genetic testing includes those tests used as companion diagnostic tests (i.e tests that are required for the safe and effective use of a specific therapeutic drug). These tests are used to identify individuals who may or may not respond to a particular therapy and are used in cancer treatment although they are not limited to this area of medicine.

**Rule 4: 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:

- 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;
- IVDDs intended to be used for the screening or diagnosis of late-onset disorders such as Huntington's disease or Alzheimer's disease;
- 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;
- IVDDs, such as partial thromboplastin and prothrombin time tests, intended to be used as general, or primary, screening procedures for the detection of coagulation abnormalities.

**Rule 4: subrule [e],** applies to IVDDs used for disease staging which refers to the characterization of the nature or extent of a medical condition such as the degree of metastasis of a cancer tumor. This information is considered critical for accurate and appropriate patient management decisions, including initial treatment planning.

**Rule 4: subrule [f]** applies to monitoring IVDDs where the accuracy of the result is paramount to the management of the patient. It applies to:

- IVDDs intended to be used to monitor the level of drugs with narrow therapeutic ranges such as immunosuppressive drugs (e.g. cyclosporine and tacrolimus);
- IVDDs, such as prothrombin time test and heparin analysers, intended to be used for monitoring anticoagulant therapy.

**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, cells, tissues or organs. It applies to all reagents and reagent products used in blood grouping systems (e.g. ABO, Kell, Duffy and Kidd), as well as for blood typing (Rh) and tissue typing (HLA, HNA). It also includes reagents/reagent products for determining irregular and anti-erythrocyte antibodies and unusual antibodies (antibody screening and identification tests).

## 2.4 Special rules

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

**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 the latter case, 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 a matter of minutes.

Except for near-patient (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 including menopause testing), which are Class II IVDDs; all other NPT-IVDDs are Class III devices.

Examples of near-patient IVDDs include those for the detection of *Streptococcus B,* fecal occult blood test kits, Prothrombin time tests, blood glucose monitors, and blood gas analyzers for point-of-care use.

**Rule 7: IVDDs specifically intended to be 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 components needs to be licensed individually. In order to determine what a licensable item in such cases is, and in some of the examples given below, refer to the document entitled, "*Guidance for the Interpretation of Sections 28 to 31: Licence Application Typ*e".

Rule 7 not only applies to all instruments, calibrators, control reagents, quality control reagents (e.g. assayed or unassayed controls) and software developed by a manufacturer for use with one or more of its own test kit(s) or IVDDs (closed instrumentation), but also to those developed by a manufacturer for use with test kit(s) or IVDD(s) of different manufacturers(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, automated instruments, software, controls, quality controls and calibrators not specifically intended for use with another IVDD but where their application necessarily results in their use with a very specific type of assay, are also classified in the same risk class as the IVDDs with which they are intended to be used. 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, which is, not labelled or intended for a specific application. These are classified as Class I.

**Rule 8: Class I IVDDs**

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

Class I IVDDs include microbiological growth media (selective, differential and selective-differential) and associated supplements used to identify or infer the identity of a

microorganism from a human specimen as well as serological and chemical reagents used to infer or confirm the identity of a cultured microorganism. The latter includes bacterial identification systems to be used on cultured microorganisms. To clarify that some of these products would not be 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. However, primary plating media plated directly from an original swab that is intended to produce colonies of a specific colour/morphology for a specific organism falls under rule 2 and would be either Class II (e.g. Candida, Salmonella) or Class III (e.g. MRSA, VRE, C. difficile). The intended use for these media is often for screening and/or direct identification and or direct detection.

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. This rule 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.

**Rule 9: Special classification**

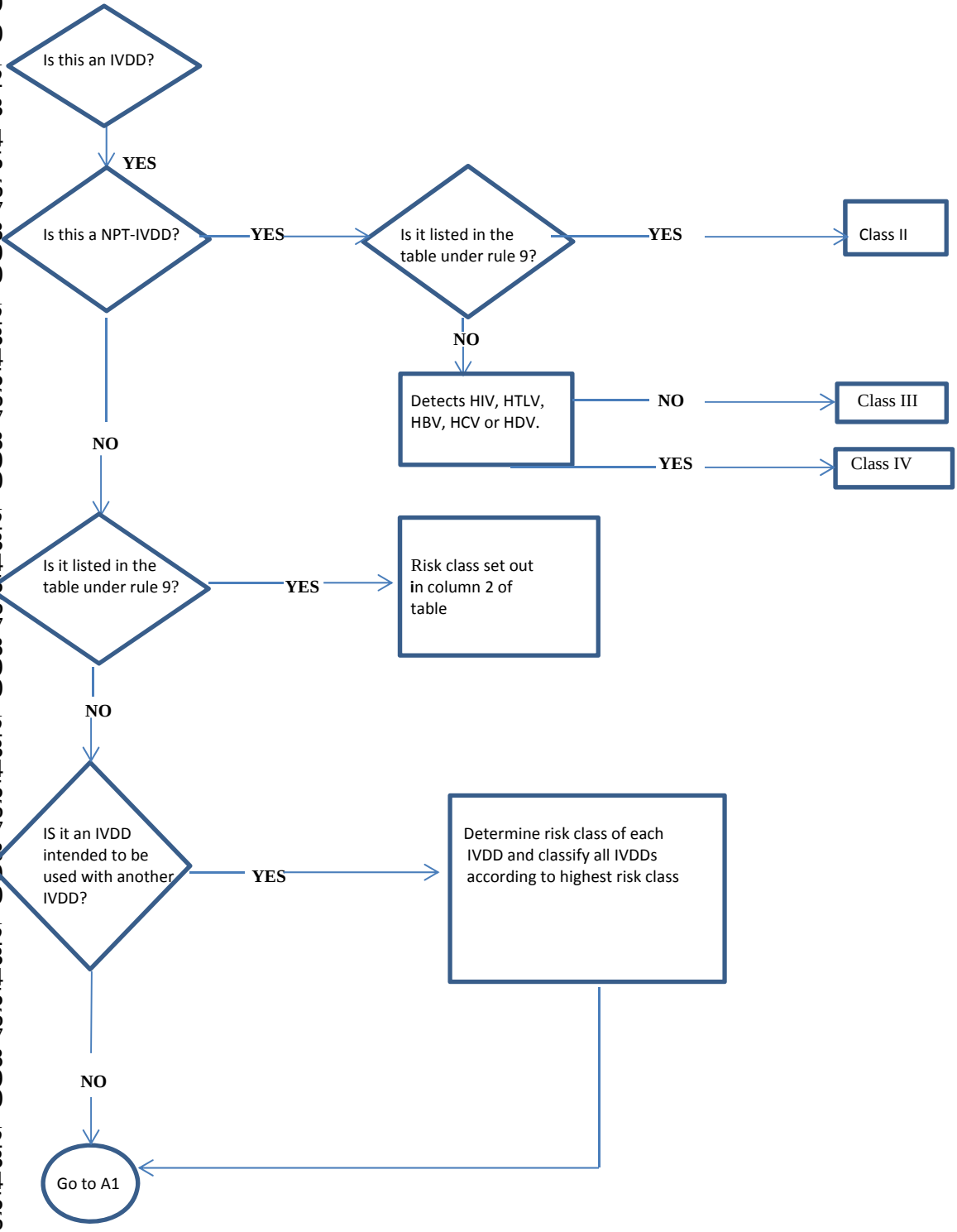
*Despite rules 1 to 8, an IVDD set out in column 1 of an item of the table to this rule is classified as the class set out in column 2 of that item*

| **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 |

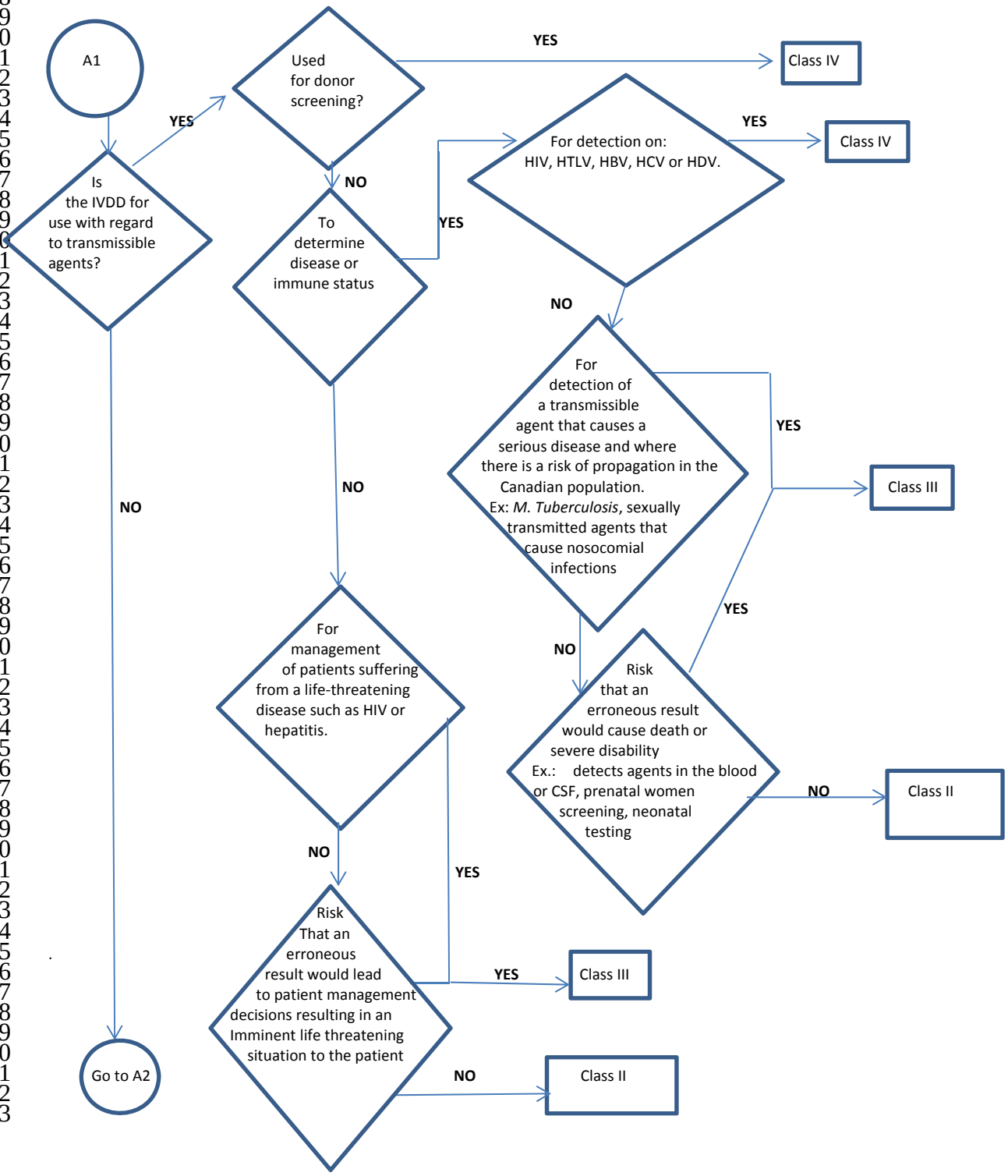
This rule sets out the classification of certain IVDDs in spite of rules 1-8. As per pregnancy and fertility testing kits, near patient menopause kits are considered Class II IVDDs.

## 3.0 APPENDICES

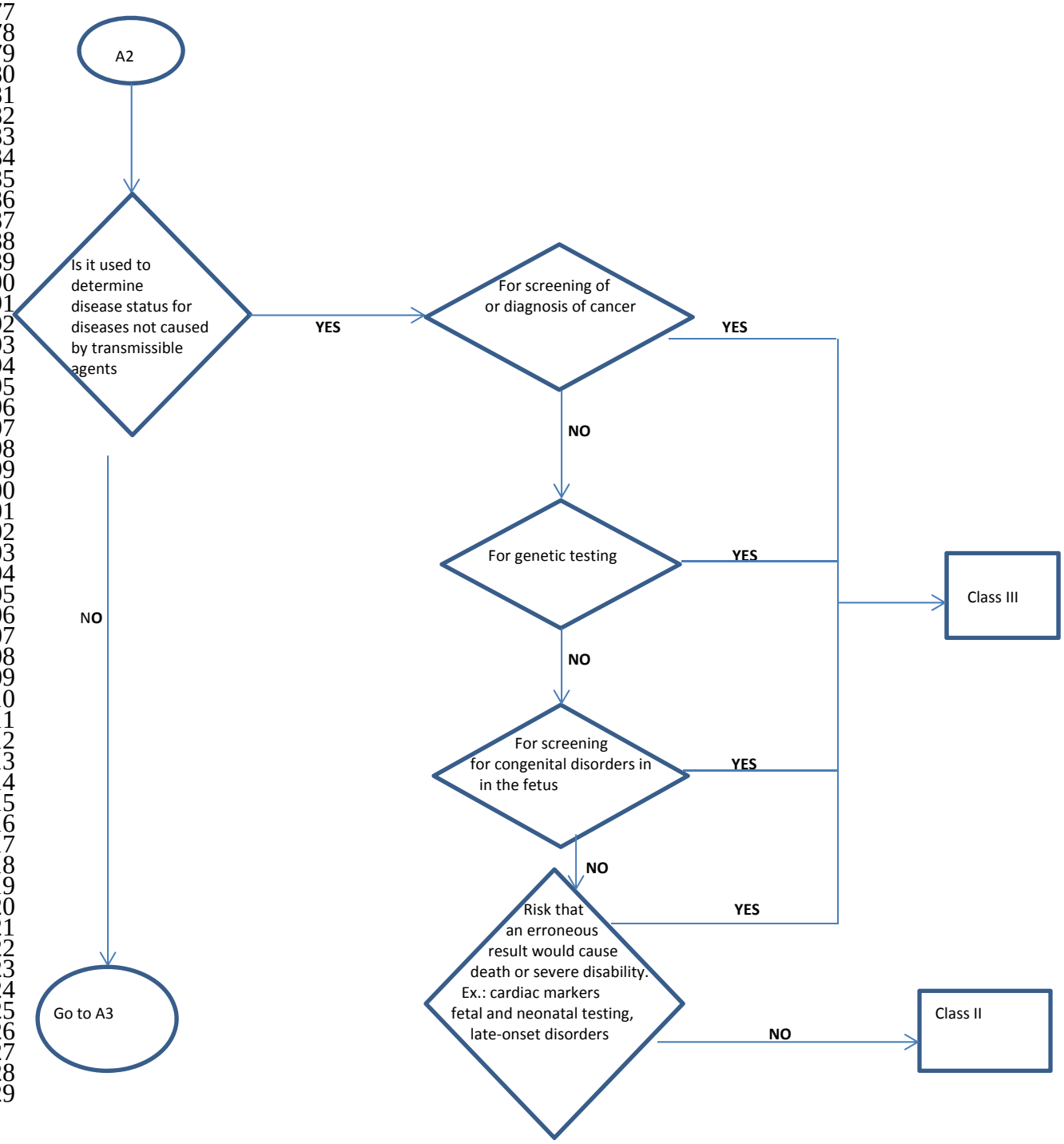
## Application of the Rules - Flow Diagram - Part 1



## Application of the Rules - Flow Diagram - Part 2



## Application of the Rules - Flow Diagram - Part 3



## Application of the Rules - Flow Diagram - Part 4