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# In Vitro Diagnostic Medical Devices
## Decision rules for IVD-classification

Marianne L. Hollestelle, Adrie C.P. de Bruijn

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The possibilities for a rule-based classification system for in vitro diagnostic medical devices (IVDs) were explored as an alternative for lists of devices given in Annex II of the European IVD Directive 98/79/EC. The proposed rule-based system can classify IVDs into four risk classes, is compatible with the current legislation, but offers more flexibility for the introduction of new IVDs.

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Contact:
A.C.P. de Bruijn
Centre for Biological Medicines and Medical Technology
National Institute for Public Health and the Environment
Adrie.de.Bruijn@rivm.nl

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RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: + 31 30 274 91 11; telefax: + 31 30 274 29 71, website: www.rivm.nl

## Abbreviations

| | |
|---|---|
| ARTG | Australian Register of Therapeutic Goods |
| CFR | Code of Federal Regulations (US) |
| CLIA | Clinical Laboratory Improvement Amendments (US) |
| CTS | Common Technical Specifications (EU) |
| FDA | Food and Drug Administration (US) |
| GHTF | Global Harmonization Task Force |
| IVD | In Vitro Diagnostic medical device |
| NPT | Near-patient test |
| PBS | Pharmaceutical Benefits Scheme (Australia) |
| RIVM | National Institute for Public Health and the Environment (Netherlands) |
| TGA | Therapeutic Goods Administration (Australia) |
| TPD | Therapeutic Products Directorate (Canada) |

# Summary

The possibilities for a rule-based classification system for in vitro diagnostic medical devices (IVDs) were explored in this report as an alternative to the system in Annex II of the European IVD Directive 98/79/EC. In a rule-based system decision-rules can classify IVDs into four risk classes (A-D) where, from a public health perspective, Class A represents IVDs with a low risk and Class D IVDs with a high risk. Derived from the Canadian model, seventeen rules have been formulated with respect to IVDs intended to detect transmissible agents and IVDs for uses other than transmissible agents. Besides this, special rules could be applied to devices for self-testing. The proposed model, which is able to classify the large majority of existing and future IVDs, offers greater flexibility than the lists in Annex II. It also fits in with the current Annex II classification, since each Annex II IVD will still be classified as ‘high risk’ (class D) or ‘moderate to high risk’ (class C). Moreover, other IVDs which present a more than moderate risk will be classified accordingly.

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# 1 Introduction

## 1.1 Purpose

The Dutch Health Care Inspectorate has requested the National Institute for Public Health and the Environment (RIVM) to investigate possibilities for drafting a decision tree that might be used for classification of in vitro diagnostic medical devices (IVDs). This would function as an alternative to Annex II of the European IVD Directive 98/79/EC, hereafter referred to as the Directive [The European Parliament and the Council of the European Union, 2003].

The purpose of this document is to:

- list classification criteria for IVD medical devices classification;
- draw a decision tree for IVD medical devices classification.

## 1.2 Scope

This document describes classification systems for IVDs that either are, or will be, applied in the EU, Canada, Australia and the United States. Based on these systems a decision tree has been developed to categorise IVDs according to their potential risk. This is a proposal on how IVD classification could be carried out in the future. An attempt has been made to have it conform to the lists in Annex II of the Directive [The European Parliament and the Council of the European Union, 2003].
Noteworthy is that any rule system has limitations and may not accommodate all IVDs. Additional rules might be needed in situations where the rules would result in an inappropriate risk class.

## 1.3 Background

Regulatory controls applicable to medical devices are intended to safeguard the health of patients, of users and of other persons by ensuring that manufacturers of medical devices follow specified procedures during design, manufacture and marketing of the product [GHTF, 2006].
From an economic point of view it is not feasible to subject all medical devices to the most rigorous conformity assessment procedures available. A graduated system of control in which the level of control corresponds to the level of potential risk inherent to the type of device concerned is more appropriate [European Commission, 2001]. The risk presented by a medical device depends substantially on its intended purpose and the effectiveness of risk management techniques applied during design, manufacture and use. It also depends on its intended user(s), its mode of operation and materials or components used [ISO 2000; GHTF, 2006].

It has been decided to set up a similar system for medical devices on the European market. Classification rules have been formulated within the Medical Device Directive to channel devices into the proper conformity assessment route, so that manufacturers can classify their own devices [Council of the European Communities, 2003].

A set of classification rules based on technical features of existing and future medical devices seems impossible because of the vast number and changing nature of variables involved. Therefore the European legislator has established a set of classification rules based on the *human body*. These rules, based on terms related to duration of contact with the patient, degree of invasiveness and the part of the body affected by the use of the device, can be combined in various ways. In total eighteen rules have been formulated to determine the risk class of a medical device [Medical Device Directive, Annex IX]. The manufacturer must take into consideration all the rules as well as all the device characteristics in order to establish the proper classification for his device. The characteristics or combination of characteristics - in accordance with the intended purpose of the device – which lead to the highest risk class determine the class for the device as a whole [European Commission, 2001a].
Guidance for the classification can be found in '*Guidelines for the classification of medical devices*', Part 1 & 2 [European Commission, 2001a and 2001b].

For IVDs there is still no system within the EU in which classification rules are applied. Instead, prescriptive lists of '*high risk*' (list A) and '*moderate risk*' (list B) IVDs have been formulated in Annex II of the IVD Directive [The European Parliament and the Council of the European Union, 2003]. Besides these IVDs, there are devices for self-testing[1].
IVDs indicated as 'high risk' are those intended for the determination of certain human blood group systems (i.e. ABO system and the five main rhesus antigens) and some infectious diseases with a high impact on the population or the individual (HIV, human T-cell leukaemia virus type 1 and 2 and some of the hepatitis viruses). List B, for example, includes IVDs for the determination of the blood group systems, anti-Duffy and anti-Kidd, human infections (Chlamydia and Cytomegalovirus), the tumoral marker PSA and IVDs for evaluating the risk of Down-syndrome (see Appendix I).
All IVDs covered by lists A and B are subject to third-party conformity assessment procedures. For devices for self-testing a Notified Body shall carry out an examination of the design (Annex III of the Directive, Section 6). However, for manufacturers of self-testing devices, it is also possible to follow the procedure in Annex IV (Full Quality Assurance System) or V (EC type-examination). All 'ordinary' IVD products can be CE-marked using the 'self-certification' route (i.e. EC Declaration of conformity, Annex III of the Directive) [The European Parliament and the Council of the European Union, 2003].

[1] Devices for self-testing are those IVDs 'intended by the manufacturer to be able to be used by lay persons in a home environment' [The European Parliament and the Council of the European Union, 2003].

## 2 Methods

Surveyed were classification criteria, decision rules and risk classes of IVD regulatory systems in other countries. Information published on governmental websites was used for this purpose. Additionally, key stakeholders (government, notified body, industry) were consulted on this topic. Their suggestions have been incorporated in the model and/or discussion.

# 3 Results

## 3.1 Definition of an in vitro diagnostic device

An *in vitro* diagnostic medical device is defined as [The European Parliament and the Council of the European Union, 2003]:

"*any medical device which is a reagent, reagent product, calibrator, control material kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:*
*-concerning a physiological or pathological state, or*
*-concerning a congenital abnormality, or*
*-to determine the safety and compatibility with potential recipients, or*
*-to monitor therapeutic measures'.*

Under the Directive specimen receptacles (e.g. sample tubes) are considered to be IVDs. Products for general laboratory use are not IVDs unless such products are specifically intended by their manufacturer to be used for in vitro diagnostic examination. Laboratory products that are not usually considered to fall within the scope of the Directive include sterilisers, general purpose automatic pipettes, multi purpose tubes etc. where such systems have no specifically intended in vitro diagnostic use.
'Products for research use only' without medical purpose fall outside the scope of the Directive. The Directive does not apply to devices manufactured and used only within the same health institution [European Commission, 2001; The European Parliament and the Council of the European Union, 2003].

The definition of an IVD in other regulations is highly comparable. Regulations differ somehow in scope as it comes to 'in-house tests'[2] and products 'for research use only'.

## 3.2 IVD risk classes

The purpose of IVD classification is to determine the level of regulatory oversight that is required before putting an IVD on the market. As with medical devices the IVD classification systems classify those products according to their risk. It must be noted that when it comes to IVDs there is a unique link between safety and effectiveness since safety of these devices is not generally related to contact between the device and the patient. For IVD devices the safety of the device is rather related to the impact of incorrect or delayed results on a patient's health or on public health.

[2] Tests developed and used in a laboratory and not supplied commercially.

To determine the risk class of an IVD there are two distinct systems: (a) *prescriptive systems*, such as the current system in the EU, and (b) *rule-based systems*.
In cases where classification systems are extremely prescriptive, a regulatory amendment is required in order to add new devices to the lists, or to move a product category from one class to the other.
In rule-based systems manufacturers classify their products using a set of decision rules. Rule-based systems are recognised as a more flexible approach to determine the extent of regulatory oversight needed in the pre-market process. Such systems possess the immediate ability to deal with emerging diseases, new parameters and new technologies, while prescriptive lists become outdated quickly [TGA, 2003; TGA/Medsafe 2006]. A rule-based system is currently applied in Canada (Appendix II). Based on this, Australia has recently developed a new regulatory framework for IVDs.
Moreover, the Global Harmonization Task Force (GHTF) has set out principles of *medical devices* classification [GHTF, 2006]. An IVD-specific sub-group of GHTF Study Group 1 is currently exploring the issues of classification of IVDs. To date, no final guideline on IVD classification has been published.

An overview of risk-based classification systems is presented in *Table 1*. Of these systems only the EU sets out a separate class for devices for self-testing. In other legislation, devices for self-testing are not classified in a separate class. Further details of each system are presented in Appendix II.
Based on this overview three to four risk classes seem sufficient to group IVDs. Further refinement will make the classification process and conformity assessment unnecessarily complex, while fewer classes may lead to either insufficient or exaggerated regulatory oversight for some categories of IVDs.

***Table 1 International risk-based classification systems for IVDs.***

| | **Prescriptive risk classification** | | | **Rule-based risk classification** | | |
|---|---|---|---|---|---|---|
| **Risk class** | *EU (IVD Directive 98/79/EEC, 2003)* | *United States (Federal Food, Drug, and Cosmetic Act, 2004)* | *Australia (Therapeutic Goods Regulations, 1990)* | *Australia (new framework)*[3] | *Canada (Medical Device Regulations, 1999)* | *United States (CLIA, 1988)* |
| Increasing degree of regulatory oversight ↑ | Annex II List A (high risk) | Class III (general controls + premarket approval) | 'Registrable' (high risk):<br>-Kits used in screening blood supply and for diagnosis of HIV and Hepatitis C | Class IV<br>-high public health risk | Class IV<br>-high public health risk to the community in general | Tests of high complexity |
| | Annex II List B (moderate risk) | Class II (general + special controls) | 'Listable' (medium risk):<br>-IVDs for home use<br>-IVDs covered by the Pharmaceutical Benefits Scheme[4]<br>-Kits containing materials of human origin (incl. controls or sera) | Class III<br>-moderate public health risk<br>-high personal risk | Class III<br>-moderate public health risk<br>-high individual risk | Tests of moderate complexity |
| | | | | Class II<br>-low public health risk<br>-moderate personal risk | Class II<br>-low public health risk<br>-moderate individual risk | |
| | -Devices for self-testing<br>-Other IVDs: IVDs not in list A or B and not for self-testing | Class I (general controls)<br>-minimal potential for harm and are simpler in design | 'Exempt' (low risk):<br>-all other IVDs | Class I<br>-no public health risk<br>-low personal risk | Class I<br>-minimal risk | 'Waived tests'<br>-simple laboratory examinations, likelihood of erroneous results negligible<br>-pose no reasonable risk or harm to patient if performed incorrectly |

[3] The draft version of the new framework is expected to be available for consultation no later than March 2007 [Clinica – World Medical Technology News, issue 1227, October 13, 2006].
[4] Pharmaceutical Benefits Scheme (PBS): the Commonwealth Government system of subsidizing the cost of most prescription medicines and a limited number of IVD products.

## 3.3 IVD classification rules

In order to make sure that classification rules are, and will be, applied in a consistent manner, these rules should be clear and written in a language that is easy to interpret. They should be able to classify future IVDs (e.g. new technologies, new markers), be clinically logical and should accommodate, where possible, the end use of the IVD [NCCTG IVD Working Group, 2003; GHTF, 2006]. Classification criteria precede the definition of rules. Possible classification criteria as well as classification rules are described in this paragraph.

*Classification criteria*

In rule-based systems, several criteria have been taken into consideration to set up decision rules. Considerations that have been used in these systems are presented in *Textbox 1*.

***Textbox 1 Classification criteria used in other regulatory systems.***

| | | |
|---|---|---|
| *Canada/Australia* | | |
| - Intended purpose and indication(s) for use | → | disorder, risk factor, condition for which the test is intended |
| - Function of the IVD | → | screening, patient-based testing/diagnoses, monitoring of substances/drugs etc. |
| - The intended user | → | professional vs. lay person or laboratory vs. near-patient testing |
| - The importance of the information to the diagnosis | → | sole determinant or one of several |
| - Impact of the test result to the individual | → | treatment, anxiety, follow-up measures etc. |
| - Impact of the test result to public health[5] | → | potential propagation due to false results, available treatment etc. |
| *US [CLIA, 1988]* | | |
| - Technical complexity of test | → | required knowledge, training/experience, reagents and materials preparation, operational steps, materials, troubleshooting and equipment maintenance, interpretation and judgement |

Both Canada and Australia (new framework) use highly comparable criteria to assign an IVD into one of four classes. These classification criteria are related to the intended purpose of the test and the impact of the test result on the individual or on public health.

[5]Criteria that may be considered to determine the impact of a disease on public health are lists of notifiable diseases[a] (such as infectious diseases listed in the Dutch law on Infectious diseases[b]) or harmfulness of microorganisms to determine the gravity of illnesses and following from this the risk class of the IVD. Microorganisms are classified according to the level of risk of infection (e.g. pathogenicity of the agent, mode of transmission, host range of the agent, availability of effective preventive measures and availability of effective treatment). For instance, risk classification of microorganisms is described in the Directive 2000/54/EC [European Parliament and the Council, 2000] and the Laboratory Biosafety Manual [WHO, 2004].
(a) Diseases which must, by law, be reported to governmental authorities by medical practitioners.
(b) Dutch Law on Infectious diseases [Stb. 1998, 394].

Furthermore, in the US criteria related to the technical complexity of the test are weighed up under the Clinical Laboratory Improvement Amendments [CLIA, 1988]. These include required knowledge and experience of the user, stability of materials used, and operational steps. The higher the complexity of a given test, the more regulatory oversight is needed. Because there is less resemblance between this system and the current EU system, the US classification has been left out of consideration.

*Applied decision rules*

An overview of decision rules which are listed in the classification systems of Canada and Australia (new framework) is given in Appendix II of this report. In general, these rules refer to broader categories of diseases (such as infectious diseases, sexually transmitted diseases, cancer, and genetic diseases) and/or intended purposes (e.g. screening, monitoring, or diagnosis), while Annex II of the European Directive lists only a limited number of IVDs out of these categories. For example, in Annex II only IVDs for determining the tumoral marker PSA are mentioned as it comes to cancer.

The described rules in Canada and Australia (new framework) relate roughly to the following subjects:
-*IVDs for detection of transmissible agents* (including IVDs to assess suitability of blood, cells, organs and tissues for transfusion or transplantation, IVDs for sexually transmitted diseases, IVDs used for infectious diseases in cerebrospinal fluid or blood).
-*IVDs for uses other than transmissible agents* (including IVDs used in patient management, detection of cancer, genetic testing, screening for congenital disorders in the foetus, drug monitoring IVDs and IVDs for immunological or tissue typing to ensure immunological compatibility of blood/tissue/organs intended for donation);
-*special categories of IVDs* (including near-patient and home testing devices, IVDs intended to be used together, IVDs that cannot be categorised by means of decision-rules or IVDs where classification according to the rules will result in a risk class that is too high or low).
In both the Canadian and the proposed Australian system, IVDs intended to detect the presence of transmissible agents are generally categorised as a greater hazard than IVDs for 'other uses' because of their impact on public health (i.e. transmission) in case of erroneous results. In addition, IVDs are considered to present a higher risk when they are related to life-threatening diseases with a risk of propagation in the population than when they are related to life-threatening diseases without a risk of propagation. In such a manner, emphasis is laid on the impact of the test outcome on public health.
Tests used for universal screening and confirmatory testing of the blood supply and organ and tissue donations for pathogens are considered to be high-risk IVDs (Class IV).
Moreover, IVDs intended to *diagnose* a given disease are grouped in higher risk classes than those used in *patient monitoring* or those intended to follow the evolution of a disease[6]. IVDs intended for patient monitoring only are captured by separate rules in both the Canadian and the new Australian framework, making them either Class II or III devices, depending on the impact that an erroneous result would have

[6] IVDs for purposes such as monitoring or prognosis (to establish the effectiveness of a given treatment). Many of these IVDs are quantitative or semi-quantitative assays [TPD, 1998].

on the patient's health. For instance, a Hepatitis C test could be considered a Class III IVD if intended only for monitoring response to therapy, while it could be put into Class IV when intended for diagnosis [TGA/Medsafe, 2006]. Another example may be newborn screening for phenylketonuria (PKU) and dietary monitoring of patients with PKU. In the EU, no difference is made between tests for screening or diagnosis and monitoring tests.

## 3.4 Proposal for a decision tree

Based on the Canadian and the new Australian system a decision tree has been drafted. The proposed tree (p. 18-20) is mainly derived from the Canadian decision model, but differs as it comes to classification of IVDs for blood-grouping/tissue typing, IVDs used to identify sexually transmitted diseases, and special rules (e.g. self-testing devices). Analogous to the Canadian framework, rules are divided into three subcategories and IVDs are assigned to one of four risk classes (*Textbox 2*).

***Textbox 2 Proposed subcategories of IVDs and risk classes.***

**Subcategories of IVDs**

*1. IVDs with respect to transmissible agents (Rule 1 - Rule 7)*

*2. IVDs with respect to uses other than transmissible agents (Rule 8 – Rule 15)*

*3. Special rules (Rule 16 - Rule 17)*

*Ad. 1.* 'IVDs with respect to transmissible agents' refer to IVDs that detect infectious agents such as bacteria, viruses, fungi and protozoa as well as agents such as prions [TPD, 1998].

*Ad. 2.* 'IVDs for other uses' could comprise IVDs for patient management purposes, such as prognosis or monitoring (to follow the evolution of a disease or to establish effectiveness of a given treatment) and IVDs for immunological typing or tissue typing used to ensure immunological compatibility of donated blood, tissue and organs (e.g. ABO system, Rhesus blood groupings, HLA typing, anti-Duffy).

*Ad. 3.* There will be some IVDs that may need to be classified according to factors other than those covered by general rules. Therefore, additional rules could be applied.

**Risk Classes**[7]

*A. Low risk: no public health risk/low individual risk*

*B. Low - moderate risk: low public health risk/moderate individual risk*

*C. Moderate - high risk: moderate public health risk/high individual risk*

*D. High risk: high public health risk*

*Application of the rules*

In advance of applying the decision rules, it needs to be determined whether the device concerned is an IVD. Subsequently, to classify an IVD all rules need to be applied. In cases where more than one rule applies, the rule that rates the highest class determines the eventual classification. Besides, an IVD with different intended purposes (e.g. screening/diagnosis and monitoring) should be classified according to the intended purpose that leads to the highest risk class to prevent that those IVDs will be undervalued. IVDs 'specifically intended to be used together' may be classified separately or in its entirety under rule 17. Therefore, rule 17 may be seen as an optional rule.

[7] In the proposed model risk classes (A-D) are named after the GHTF classification system of Medical Devices [GHTF, 2006].

The following rules are suggested:

**1. IVDs with respect to transmissible agents**

*Rule 1. IVDs intended to detect the presence of, or exposure to, a transmissible agent should be classified as Class B, unless one of the rules 2 to 7 applies.*

This refers to IVDs that present a low public health risk because they detect transmissible agents that are not easily propagated and a false result is not likely to put an individual in immediate danger.

Examples: detection of Rotavirus, Salmonella, Varicella-Zoster Virus, Influenza virus A, B, C.

*Rule 2. IVDs intended for donor screening should be classified as Class D.*

This rule refers to IVDs intended 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.

Examples: markers of anti-HTLV I and/or II, anti-HBc, anti-HIV-1, and assays marketed for the detection of bacterial contamination of blood components.

*Rule 3. IVDs intended to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a risk of propagation in the population should be classified as Class D.*

This relates to IVDs intended to detect infections by transmissible agents where accurate diagnosis is important to mitigate the public health impact of the disease/condition.

Examples: IVDs to detect Hepatitis viruses B, C, D, HIV, including self-testing devices for the concerned transmissible agents.

*Rule 4. IVDs intended to detect the presence of, or exposure to, a transmissible agent that causes a serious disease with a risk of propagation in the population, including serious sexually transmitted diseases, should be classified as Class C.*

This refers to IVDs that detect transmissible agents with a significant public health importance and immediate danger for an individual, such as death or severe disability if not treated in a timely manner.

Examples: IVDs for the detection of nosocomial infections (e.g. MRSA), Syphilis.

*Rule 5. If there is a risk that an erroneous result would lead to death or severe disability to the patient, foetus or offspring, IVDs should be classified as Class C, including IVDs intended to detect transmissible agents in cerebrospinal fluid or blood, IVDs applied for prenatal screening and neonatal testing.*

This includes IVDs intended to detect diseases that may be of less significance from a public health perspective, but with a high risk for the individual being tested.

Examples: test for the detection of meningitis, CMV, Epstein-Barr virus, prenatal screening to determine a woman's immune status towards agents such as rubella virus or toxoplasma gondii.

*Rule 6. IVDs intended for patient management of patients suffering from a life-threatening disease and IVDs presenting a risk that an erroneous result could lead to a patient management decision that results in a potentially life-threatening situation to the patient should be classified as Class C.*

With this rule it is suggested to classify patient monitoring IVDs in a lower risk class than those to diagnose diseases.

Examples: p24 Ag HIV for prognosis only, HIV RNA viral load test for monitoring only.

*Rule 7. Despite the rules above microbiological media used to identify or infer (cultured) micro organisms from a specimen derived from the human body should be classified as Class A, unless rule 2 applies.*

To prevent that these IVDs will be classified too high, these IVDs may be expressly included in this rule.

Examples: Bacterial identification systems.

**2. IVDs with respect to uses other than transmissible agents**

*Rule 8. All IVDs for uses other than transmissible agents (and not intended for diagnosis or patient management, blood grouping, or tissue typing) should be classified as Class A, unless one of the rules 9 to 15 applies.*

This rule refers to general laboratory products, intended specifically for in vitro diagnostic examinations but not labelled or intended for a specific application.

Examples: automated analyzers with open architecture design.

*Nb. Products for general laboratory use are not IVDs under the Directive unless the manufacturer specifically intends such products to be used for in vitro diagnostic purposes because of its specific characteristics [European Commission, 2004a].*

*Rule 9. IVDs intended to be used in screening for or in the diagnosis of cancer should be classified as Class C.*

This rule relates to tests used for early detection (screening) or diagnosis, while those tests used for monitoring response to therapy could be classified as Class B (see rule 14).

Examples: testing for cancer antigens, PSA.

*Rule 10. IVDs intended for predictive genetic testing should be classified as Class C.*

This concerns the analysis of human DNA, RNA, or chromosomes for purposes such as the prediction of disease or vertical transmission of risks, monitoring, diagnosis or prognosis.

Examples: testing for Cystic Fibrosis, genetic testing for breast cancer (prognosis), Alzheimer, testing for genetic predisposition.

*Rule 11. IVDs intended for screening for congenital disorders in the foetus should be classified as Class C.*

This concerns IVDs used during pregnancy on maternal or foetal specimens in order to determine congenital disorders of a foetus.

Examples: prenatal testing on spina bifida or Down syndrome.

*Rule 12. If there is a risk that an erroneous result would cause death or severe disability to the patient or his/her offspring these IVDs should be classified as Class C.*

This rule comprises IVDs that are critical in establishing disease status. If diagnosed incorrectly there is a risk that this results in death or severe disability.

Examples: prenatal or neonatal testing (lung maturity, congenital hypothyroidism), screening or diagnosis of late-onset disorders (Huntington's disease, Alzheimer), cardiac markers.

*Rule 13. IVDs intended for disease staging should be classified as Class C.*

This rule relates for example to tests where treatment planning is based on the test outcome.

Examples: testing for the degree of metastasis of a cancer tumour.

*Rule 14. IVDs intended for diagnosis or IVDs for monitoring substances, medicinal products and biological components should be classified as Class B, unless there is a risk that an erroneous result leads to a patient management decision that results in a potentially life-threatening situation to the patient. Those IVDs should be classified as Class C.*

Monitoring tests where accuracy is of importance should be classified as Class C. If an erroneous result is not likely to put an individual in immediate danger or have a significant negative impact on long-term outcome an IVD should be classified as Class B.

Examples of Class C: monitoring tests for drugs with narrow therapeutic ranges, IVDs intended to be used for monitoring anticoagulant therapy.

Examples of Class B: IVDs indicative of metabolic diseases.

*Rule 15. IVDs for blood grouping or tissue typing to ensure the immunological compatibility of blood, blood components, tissues or organs that are intended for transfusion or transplantation should be classified as Class C, unless an erroneous result could lead to a potentially life-threatening situation to the patient, in which case they should be classified as Class D.*

In the decision tree it is suggested that IVDs for immunological typing or tissue typing may be divided in 'high risk' and 'moderate to high' risk analogous to the division made in the list A and B of the Directive.

Examples of 'high-risk' tests: determination of blood groups A, B, O, Rhesus and anti-Kell.

Examples of 'moderate to high-risk' tests: anti-Duffy, anti-Kidd, products for determining irregular anti-erythrocytic antibodies and unusual antibodies.

**3. Special rules**

*Rule 16. IVDs intended for self-testing should be classified as Class B, unless other rules apply.*

Through this rule, it can be ensured that IVDs for self-testing are sufficiently regulated.

IVDs intended to detect transmissible agents that cause life-threatening diseases are placed in Class D according to rule 3. IVDs for self-testing may also be classified in Class B or C depending on the adverse effects of an erroneous result on public health or the individual.

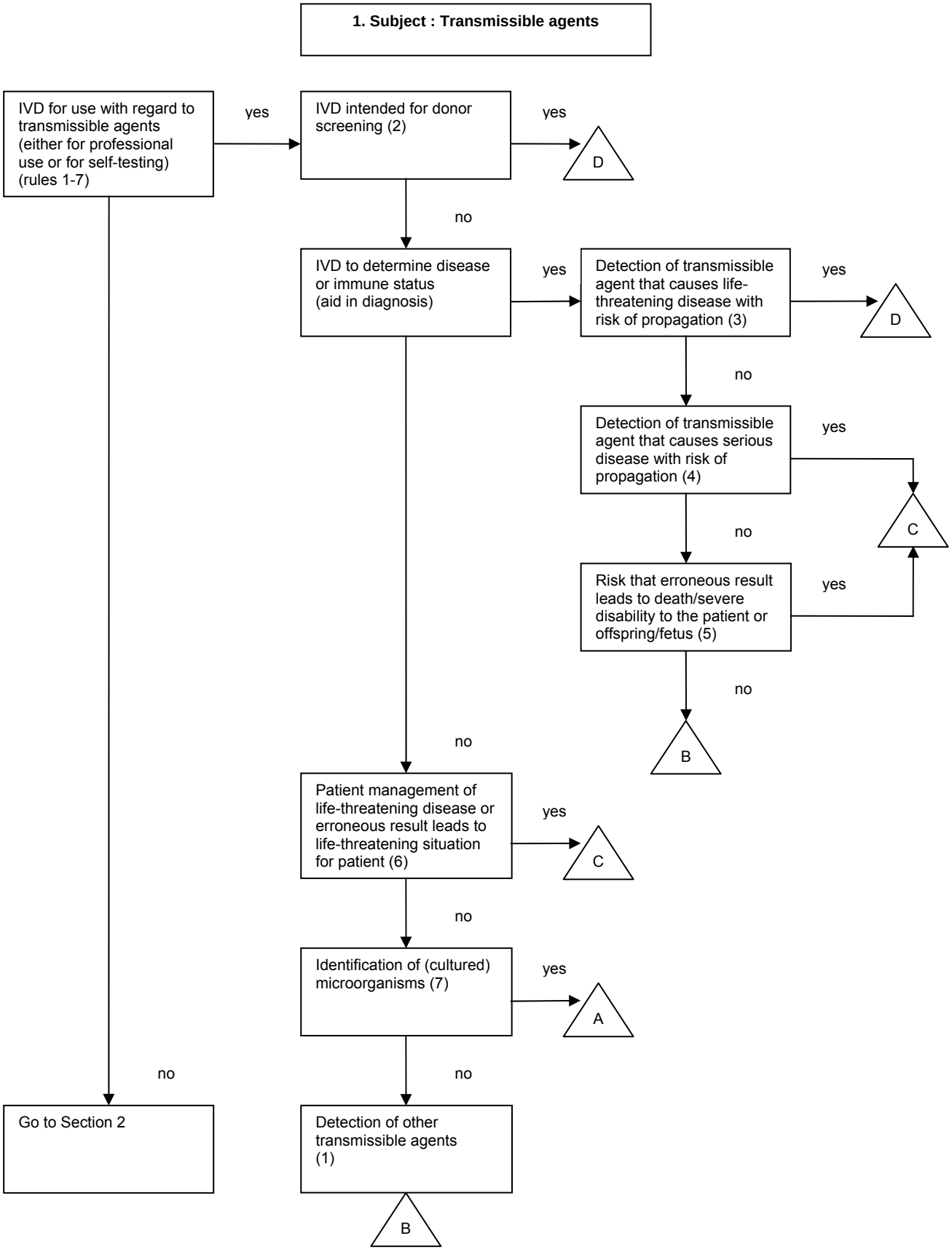
Examples of Class D IVDs: self-testing devices for HIV or Hepatitis C.

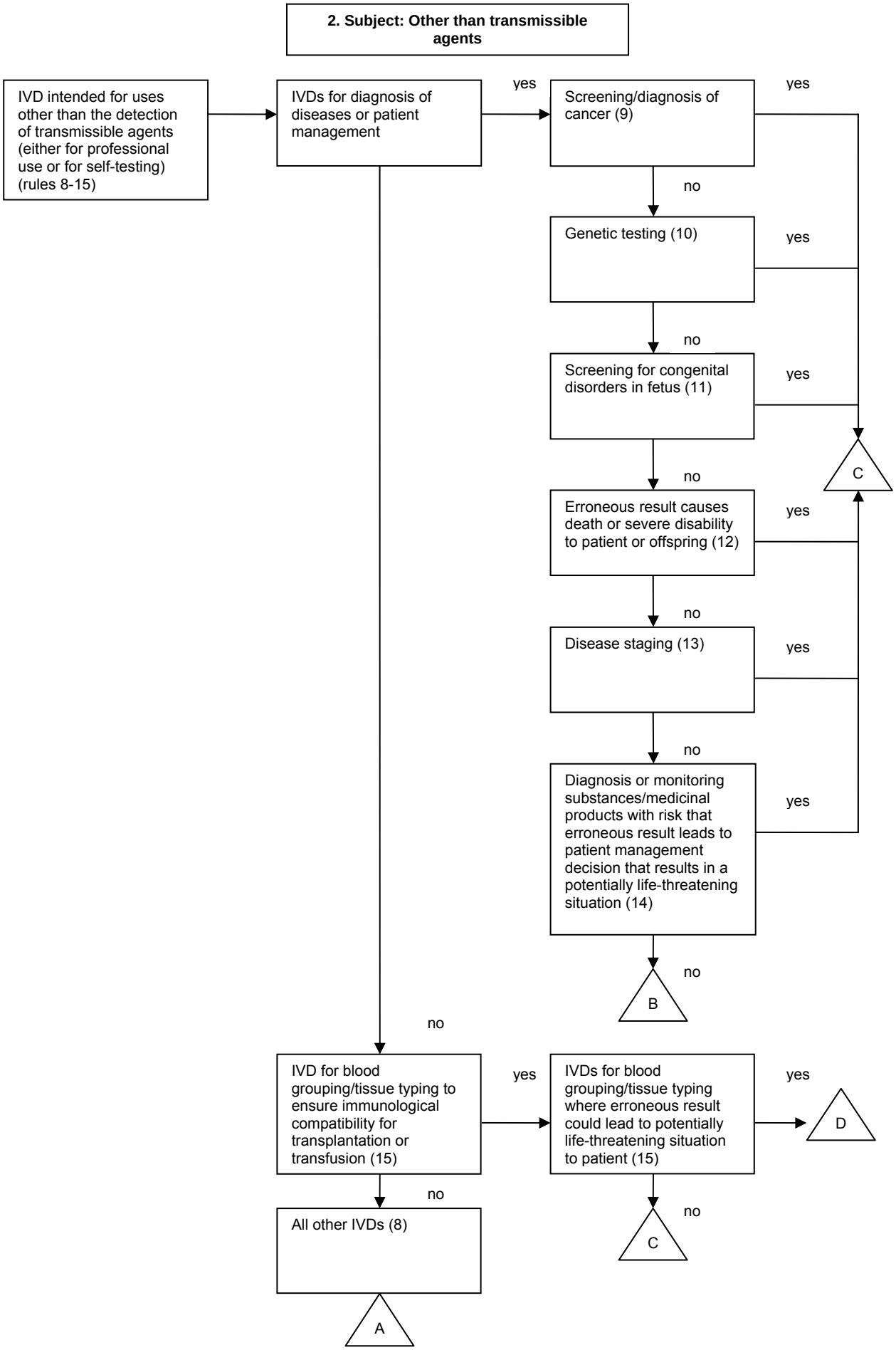
Examples of Class C IVDs: testing for cardiac markers (troponin), home glucose monitoring devices.

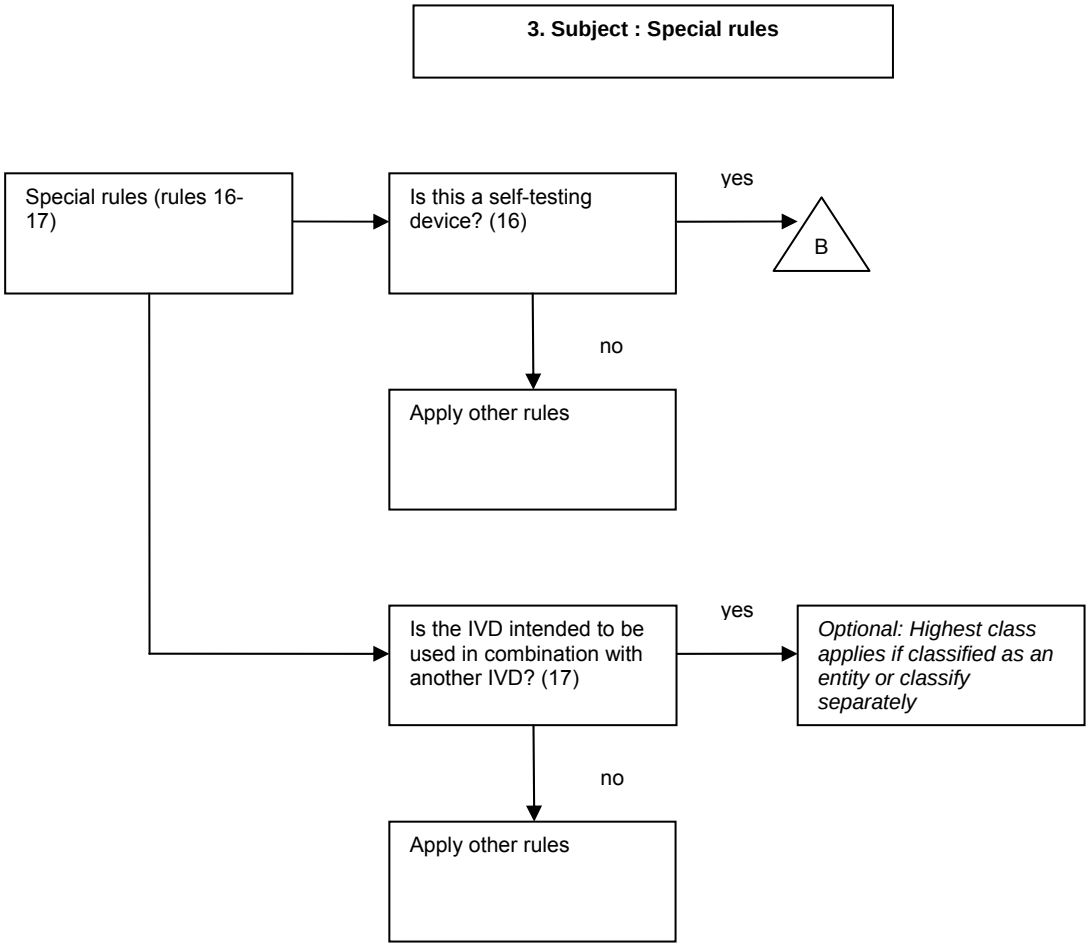
Examples of Class B IVDs: cholesterol tests, pregnancy testing.

*Rule 17. In cases where an IVD is intended to be used in combination with another IVD the highest risk class may apply or they may be classified separately.*

IVDs 'specifically intended to be used together' may be (a) classified separately or (b) in its entirety under this rule. In the latter case instruments, software, calibrators, controls and quality controls reagents, etc. associated with a specific assay are classified in the same risk class as that assay.


1. Subject : Transmissible agents
IVD for use with regard to transmissible agents (either for professional use or for self-testing) (rules 1-7)
yes
IVD intended for donor screening (2)
yes
D
no
IVD to determine disease or immune status (aid in diagnosis)
yes
Detection of transmissible agent that causes life-threatening disease with risk of propagation (3)
yes
D
no
Detection of transmissible agent that causes serious disease with risk of propagation (4)
yes
C
no
Risk that erroneous result leads to death/severe disability to the patient or offspring/fetus (5)
yes
C
no
B
no
Patient management of life-threatening disease or erroneous result leads to life-threatening situation for patient (6)
yes
C
no
Identification of (cultured) microorganisms (7)
yes
A
no
Detection of other transmissible agents (1)
B
no
Go to Section 2


2. Subject: Other than transmissible agents
IVD intended for uses other than the detection of transmissible agents (either for professional use or for self-testing) (rules 8-15)
IVDs for diagnosis of diseases or patient management
yes
Screening/diagnosis of cancer (9)
yes
no
Genetic testing (10)
yes
no
Screening for congenital disorders in fetus (11)
yes
no
C
Erroneous result causes death or severe disability to patient or offspring (12)
yes
no
Disease staging (13)
yes
no
Diagnosis or monitoring substances/medicinal products with risk that erroneous result leads to patient management decision that results in a potentially life-threatening situation (14)
yes
no
B
no
IVD for blood grouping/tissue typing to ensure immunological compatibility for transplantation or transfusion (15)
yes
IVDs for blood grouping/tissue typing where erroneous result could lead to potentially life-threatening situation to patient (15)
yes
D
no
All other IVDs (8)
no
C
A


3. Subject : Special rules
Special rules (rules 16-17)
Is this a self-testing device? (16)
yes
B
no
Apply other rules
Is the IVD intended to be used in combination with another IVD? (17)
yes
Optional: Highest class applies if classified as an entity or classify separately
no
Apply other rules

# 4 Discussion and conclusions

The classification of IVDs in the EU is laid down in Annex II of the IVD Directive. Due to the prescriptive character of this Annex, several IVDs are lacking on this list of 'high' and 'moderate' risk IVDs. IVDs intended for genetic testing, screening and diagnosis of cancer, detection of serious transmissible diseases (e.g. SARS), serious sexually transmitted diseases (e.g. syphilis), and moderate to high-risk IVDs used for home monitoring (e.g. oral anticoagulation monitoring systems for home use) are examples of IVDs currently not included in Annex II. However, these do pose considerable risks. It is also questionable whether vulnerable groups (pregnant women, newborns) are sufficiently protected. In addition, new analytical techniques or markers are obviously not on the list and the process to amend the Directive is time consuming.

Given the incompleteness of Annex II, the use of decision rules to classify the large majority of existing and future IVDs may be considered here. Rule-based systems are generally recognised as being a more flexible and more rational approach to determining the extent of regulatory oversight needed in the pre-market process of IVD development, as compared to prescriptive lists, such as Annex II. In a rule-based system, the *end use* (intended purpose and function) of the IVD and the *impact of erroneous results* on the individual or the community might be weighed up to determine the risk class.

The Canadian model provides a useful point of departure for a European decision model, since the Canadian risk classes fit in with the current classification in Annex II without major modifications. Analogous to this model, we have divided classification rules into sections: (1.) *use in transmissible agents*, (2.) *other uses* and (3.) *special rules*. Subsequently, the Canadian rules were adapted in several ways. For example, in the proposed model, IVDs for blood grouping/ tissue typing (rule 15) are classified as 'high' or 'moderate to high' risk, which is in conformity with their current status in List A and B, while in Canada these IVDs are classified as one category.

The consequences of the decision model as proposed are:

- According to the proposed model, all Annex II IVDs will still be classified as 'high' (Class D) or 'moderate to high' (Class C) risk (see Appendix III). It should be noted however, that some Annex II IVDs are further differentiated if classified using decision rules: IVDs that detect HIV, HTLV or Hepatitis (List A Annex II) may be in Class C or D, depending on the intended purpose (i.e. diagnoses (Class D) or screening (Class C)). The same applies to IVDs that detect CMV and Chlamydia (moderate risk IVDs, list B Annex II): these are Class D if intended for donor screening, Class C if not. As pointed out previously, in cases where a single IVD has different intended purposes, i.e. screening/diagnosis and monitoring, the IVD concerned should be classified according to the intended purpose leading to the highest risk class.
- Compared to list A and B, the proposed rules relate to larger groups of IVDs. For example, not only IVDs that determine the tumoral marker of PSA will be classified as 'moderate to high' risk (List B of the Directive: '*determining the following tumoral marker: PSA*'), but all IVDs intended for screening or diagnosis of cancer as well. Similar effects will occur with IVDs for congenital infections and serious sexually transmitted diseases etc. Consequently, when re-classifying IVDs, more IVDs will be classified as 'high' (Class D) or 'moderate to high' (Class C) risk.

-Some groups of IVDs, which are currently *not* in Annex II, may be classified as Class C or Class D IVDs. Examples are IVDs intended to detect transmissible agents in cerebrospinal fluid or blood (see proposed decision model: rule 5); these will be put into Class C when applying the proposed rules.
- With respect to the interpretation of classification rules for IVDs, guidance documents will be needed. In addition, some definitions used in the Directive may need adaptation. '*Devices for self-testing*' for example are now defined as 'those IVDs intended by the manufacturer to be able to be used by lay persons in a home environment' [The European Parliament and the Council of the European Union, 2003]. In the Canadian system, and the new Australian framework as well, not only are self-testing devices subject to special rules, but so are point-of care testing[8] devices. Together these devices form the 'near-patient IVDs'. For the purpose of a European classification system consideration could be given to broadening the scope of self-testing devices to: 'all tests not conducted in a laboratory or by laboratory workers'. The characteristics of non-laboratory tests, and the performance of these tests, may differ substantially from laboratory tests. Another consideration is the entry of the term '*professional use*' into the Directive, referring to the use of IVDs within a laboratory.
- A rule-based classification system has implications for the Common Technical Specifications (CTS) for IVDs [The commission of the European Communities, 2002]. Class D IVDs which are not yet classified as 'high risk' in the current system (List A, Directive) will not be covered by the present CTS. Moreover, if a rule-based system is implemented, the categories of IVDs to be classified as 'high risk' (Class D) will have to be determined before setting up the Specifications. Consequently, future technologies (i.e. IVDs to detect new markers, and new diseases) will not be covered by the CTS.
- The proposed model may fit in with the current European conformity assessment procedures. When classified into one of four classes, IVDs may follow the existing conformity assessment routes. In re-evaluating conformity assessment routes, the current lack of possibilities by the Notified Bodies to assess the performance of an IVD should be considered, particularly when it comes to devices for self-testing.

In conclusion, this model represents an example of how risk classification of IVDs could take place within the EU in the future. It is able to classify the large majority of existing and future IVDs, and shows greater flexibility than the lists in Annex II. Finally, it is advisable to verify the practical applicability of a decision model by consulting such key stakeholders such as industry and the Notified Bodies.

[8] Point-of-care testing is considered to be testing performed generally near to, or at the site of, the patient, e.g. a health care professional's office, a clinic, a pharmacy or at bedside [TPP, 1998].

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## Appendix I – Annex II IVD Directive [98/79/EC]

**List A**
*Reagents and reagent products, including related calibrators and control materials for:*

-Determining the blood groups of the ABO system and Rhesus (C, c D, E, e) anti-Kell
-Detection, confirmation and quantification of human specimens of markers of HIV infection (1 and 2), HTLV I and II, and Hepatitis B, C, D

**List B**

*Reagents and reagent products, including related calibrators and control materials for:*

-Determining the blood groups: Anti-duffy and Anti-Kidd
-Determining irregular anti-erythrocytic antibodies
-Detection and quantification of congenital infections: Rubella and Toxoplasmosis
-Diagnosing the hereditary disease: Phenylketonuria
-Determining the human infections: Cytomegalovirus and Chlamydia
-Determining of HLA tissue groups: DR, A, B
-Determining of Tumoral marker: PSA
-Evaluating the risk of Trisomy 21 (including software)
-Devices for self-diagnosis and measurement of blood sugar (glucose)

# Appendix II - Overview of risk-based classification system for IVDs (other than EU)

**Canada**

In Canada medical devices, including IVD's, are subject to the '*Medical Device Regulations*' (SOR/98-282) under the '*Food and Drugs Act*' (R.S., 1985, c. F-27).

The interpretation of an IVD under the Medical Devices Regulations is similar to that in the EU. IVDs labelled 'For research use only' are exempt from the Medical Devices Regulations, unless they are presented by a manufacturer for a specific diagnostic application. There are no provisions or requirements for 'in-house tests'.

Under the Medical Device Regulations, a risk based classification system has been implemented to categorise medical devices as to their potential risk. Part 2 of the Medical Device Regulations describes the risk classification of IVDs. The actual classification of an IVD is largely dependent upon the information provided about its intended use and its indications for use. These may be derived from any part of the labelling. In cases of ambiguous labelling the higher risk class will apply.

The system is based on four classes (I, II, III, and IV) representing increasing degrees of risk. In common with other regulatory systems, the level of scrutiny of the certification procedures is dependent upon the risk the device presents. Manufacturers of Class II, III and IV devices must obtain a license for their devices from the Therapeutic Product Directorate (TPD), prior to selling them. The topics that must be addressed in a medical device license submission for each of the Class II, III and IV devices are described in a guidance document on the application for a new medical device [TPD, 1999].

Several criteria are used to determine the risk class of an IVD [TPD, 1998]:

- intended purpose and indication(s) for use (disorder, condition or risk factor for which the test is intended)
- scope of application of the IVD (screening, patient-based testing/diagnoses, monitoring etc.)
- 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)
- impact of the test result (true and false) to the individual, including:
    - unnecessarily delaying or subjecting an individual to treatment in case of false diagnosis;
    - stress/anxiety resulting from the information (e.g. genetic testing, home-testing);
    - nature of possible follow-up measures (e.g. genetic testing, foetal testing);
- impact of the test result (true and false) to public health. This concerns the issue of potential propagation of transmissible agents due to erroneous results. Factors that were considered are:
    - mode of transmission;
    - efficacy of transmission;
    - nature of disease;
    - available treatment.

These criteria have been the starting-point for the formulation of nine decision rules [Medical Devices Regulations, 1999, Part 2] that classify all IVDs into one of four classes (*Figure 1*).

***Figure 1 Overview of the Canadian risk based classification system for IVDs – rules and exceptions (risk class).***

**A. Classification of IVDs for use with respect to transmissible agents**

- rule 1: IVDs used for donor screening (IV)
- rule 2: IVDs used to determine disease status or immune status (II)

  *exceptions:*

  *-detection of transmissible agents that cause a life-threatening disease and where there is a risk of propagation (IV)*

  *-detection of transmissible agents that cause a serious disease and where there is a risk of propagation (III)*

  *-detection of sexually transmitted agents (III)*

  *-detection of infectious agents in cerebrospinal fluid/blood (III)*

  *-risk that an erroneous result causes death/severe disability to individual being tested or to the individual's offspring (III)*

- rule 3: IVDs used for patient management purposes (II)

  *exceptions:*

  *-IVDs intended for management of patients suffering from a life-threatening disease (III)*

  *-risk that erroneous result leads to patient management decision that results in an imminent life-threatening situation to the patient (III)*

**B. Classification of IVDs for uses other than for transmissible agents**

- rule 4: IVDs used for disease status and for patient management (II)

  *exceptions:*

  *-screening for or diagnosis of cancer (III)*

  *-genetic testing (III)*

  *-screening for congenital disorders in the foetus (III)*

  *-risk that erroneous diagnostic result causes death/severe disability to the tested patient or to the patient's offspring (III)*

  *-disease staging (III)*

  *-monitoring levels of drugs/substances/biological components where there is risk that an erroneous result would lead to a patient management decision that results in an imminent life-threatening situation to the patient (III)*

- rule 5: IVDs for immunological typing (III)

**C. Special rules**

- rule 6: near-patient IVDs (III)
- rule 7: IVDs specifically intended to be used together (highest risk class applies)
- rule 8: Other IVDs (I)
- rule 9: Special classification

The decision rules are illustrated in a guidance document of the Therapeutic Products Directorate [TPD, 1998]. It provides many examples of IVDs in each risk class and explains the rationale behind the rules. This document also contains a flow diagram.

Assigned into the highest risk classes are IVDs with respect to *transmissible agents*[9] (rule 1-3) - in particular IVDs intended for donor screening (Class IV) and IVDs intended for detection of 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 (Class IV) -. IVDs with respect to transmissible agents used for patient management purposes are classified lower than those to determine disease or immune status: monitoring IVDs intended to follow the evolution of a disease or to establish the effectiveness of a specific treatment are generally classified as Class II, unless they are intended for the management of patients suffering from a life-threatening disease (e.g. HIV RNA viral load test for monitoring only) or erroneous results lead to a patient management decision that results in an imminent life-threatening situation to a patient. In those cases the IVD is classified higher (Class III).

Several rules have been formulated to classify IVDs for uses *other than for transmissible agents*.
IVDs used for *patient management* are initially classified as Class II (rule 4). Exceptions are those IVDs intended to be used in screening for or in the diagnosis of cancer, for genetic testing, in screening for congenital disorders in the foetus, and for disease staging. Such devices will be classified as Class III. In addition, if there is (1) a risk that an erroneous result would cause death or severe disability to the patient or the patient's offspring or (2) if 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 IVD will also be placed into Class III.
Rule 4 applies to IVDs for use in testing laboratories, since initially all near-patient IVDs are classified as Class III according to rule 6. Examples are IVDs used to determine levels of therapeutic drugs, antibiotics, hormones, and qualitative IVDs indicative of metabolic diseases.
An IVD 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 (rule 5). This rule 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. In the EU IVDs used to determine the main blood groups systems are spread among list A and B of Annex II [European Parliament and the Council of the European Union, 2003].

*Near-patient tests (NPT)* form a special group. A near-patient IVD is defined as "*an IVD intended 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

[9] The term '*transmissible agents'* refers to infectious agents such as bacteria, viruses, fungi and protozoa as well as agents such as prions (for example Creutzfeldt-Jacob) and toxins. It does not include genetic traits [TPD, 1998]

professional's office, a clinic, or at the bedside. IVDs for point-of-care testing are often labelled 'for professional use only', while home tests are for 'lay use'. Except for NPT intended to detect transmissible agents such as HIV or hepatitis viruses (Class IV, according to rule 2), and pregnancy, fertility, or cholesterol tests (Class II according to rule 9), all other NPT are Class III devices. Since IVDs for professional use can also be labelled as NPT, these IVDs comprise a larger group of devices than solely self-testing devices as defined in the IVD Directive [The European Parliament and the Council of the European Union, 2003].

The Canadian approach of classifying is 'bottom-up'. If rules 1-7 do not apply, the IVD is automatically classified as 'low risk' according to rule 8. This category includes for example all microbiological growth media used to identify a micro-organism from a specimen derived from the human body, serological and chemical reagents used to identify or confirm the identity of a cultured micro-organism (for example bacterial identification systems), and cell culture media. This rule also applies to all general laboratory products 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 microscopes, pipetters, spectrophotometers and specimen containers etc. Any general laboratory product not manufactured, sold or presented for use in in vitro diagnostic applications is not considered to be an IVDs.
In the EU products for general laboratory use are not considered to be IVDs either, unless the manufacturer specifically intends such products to be used for in vitro diagnostic purposes on the basis of its specific characteristics [European Commission, 2004a].

The last rule (rule 9) comprises IVDs for which the classification according to the rules was judged inappropriate and sets out the classification at which these devices will be regulated. Special classification applies to NPT IVDs for the detection of pregnancy/fertility and determining cholesterol levels (both classified as Class II).
It also stresses that microbiological media that are used to identify or infer the identity of a micro-organism or a cultured micro-organism are classified as Class I as there was some concern that some of these products would be classified according to rule 1 or 2.

**Australia**

*Regulatory requirements for IVDs under the Therapeutic Goods Act*

IVDs are regulated in Australia under the provisions of the Therapeutic Goods Act 1989 (the Act) and the Therapeutic Goods Regulations 1990 (the Regulations). For the purposes of the Act, and as defined in the Regulations, IVDs are classified into high risk (*registrable*), medium risk (*listable*) and low risk (*exempt*) products[10]. This categorisation of goods determines the degree of pre-market assessment by

[10] IVDs used in screening the blood supply and for the diagnosis of HIV and Hepatitis C are '*registrable*'. IVDs that are for home use, covered by the Pharmaceutical Benefits Scheme (PBS) or that incorporate material of human origin (including controls or sera) are '*listable*'. All other IVD's are '*exempt'.* Exempt means not required to be entered

the Therapeutic Goods Administration (TGA) prior to inclusion of the IVD in the Australian Register of Therapeutic Goods (ARTG). Under the Act, the process of risk classification is carried out by the TGA.

The objective of the Act was providing a national framework for the regulation of therapeutic goods supplied in or exported from Australia. However, since the Act came into force in 1991, the nature of IVD technology has advanced to such an extent, that they are now not subject to appropriate regulatory control [TGA, 2003].

Problems with this regulatory framework include [TGA, 2003; TGA, 2006]:

-*inadequate pre-market assessment of new technologies* (e.g. it cannot ensure the protection of the population through high quality IVDs to detect emerging threats such as Bird Flu, SARS and West Nile Virus);

-*the level of protection afforded to consumers is not commensurate with the level of risk*, particularly for a number of IVDs used for mass screening of blood and tissue donations for transmissible agents;

-*lack of regulatory oversight* for a large number of 'exempt' IVDs;

-*the current classification system is extremely prescriptive* which makes it rigid. A regulatory amendment is required in order to add new categories of products to the 'listable' or 'registrable' classes, or to move a product category from one class to the other.

-*the system is out of step with international best practice*. This results in an increased regulatory burden for industry, raises the possibility of importing inferior quality IVDs in Australia and involves significant numbers of recalls, mainly due to performance or quality control issues. In addition, for IVDs there are often problems with the manufacture's timeframes for implementing corrective action.

Together these factors have led to the development of a new IVD regulatory framework [TGA, 2003].

*New regulatory framework*

In January 2002, the TGA started the development of a new regulatory framework for IVDs. This framework will complement the new regulatory system for medical devices. To date, the new IVD framework is finalised[11]. The framework is aligned with the principles of the GHTF-model, but also takes into account the special nature of IVDs with a separate classification system and classification rules [TGA/Medsafe, 2006].

In the new framework, the process of classification will be the manufacturer's responsibility: manufacturers shall use classification rules to classify their products and follow the appropriate conformity assessment process prior to supplying their product in Australia. The new framework will also cover 'in-house' IVDs, which are those developed within a laboratory or laboratory network and not supplied commercially. Commercial IVDs being used for a purpose other than originally intended by the manufacturer are also classed as 'in-house' IVDs [TGA/Medsafe, 2006].

on the Australian Register of Therapeutic Goods (ARTG) but must meet labeling and advertising provisions of the Act.

PBS = the Commonwealth Government system of subsidizing the cost of most prescription medicines and a limited number of IVD products.

[11] The draft version is expected to be available for consultation no later than March 2007 (06-10-20) [Clinica – World Medical Technology News, issue 1227, October 13, 2006].

In the new system IVDs will be classified into four classes instead of three, based on risk, with levels of regulatory oversight commensurate with the risk posed [TGA/Medsafe, 2006]. Those classes correspond to the classes of the Canadian framework.

Earlier, the TGA released a discussion paper detailing the proposal for the new framework [NCCTG, IVD Working Group, 2003]. This paper discusses possible classification rules for IVDs and international regulatory frameworks are compared. Several criteria are mentioned that may determine the risk class IVDs. Those are:

- the impact of the test result on public health
- the importance of the information resulting from the IVD's use to the overall diagnosis (sole determinant vs. an array of diagnostic tools)
- intended user of the test
- the function of the test (e.g. screening or monitoring)
- the technology used in the test

These considerations are in line with the criteria that have been applied in Canada.

In the discussion paper, 11 rules are proposed. It must be noted, that rules may be adapted in the final version of the regulatory system.

Highly comparable to the Canadian system, those rules are divided into the sections: *use with transmissible agents*, *use in patient management*, *other uses*, and *special rules* (*Figure 2*). Whereas Canada distributes patient management IVDs among the categories 'IVDs with respect to transmissible agents' and 'IVDs for uses other than transmissible agents', in the proposed system IVDs for 'patient management'[12] form a separate section.

According to the draft rules high-risk IVDs will be those products with respect to testing of blood, organs and tissue for pathogens prior to donation or transfusion. It is suggested to group tests which are intended to detect transmissible agents that cause serious diseases (such as Hepatitis B, HIV) with a risk of propagation into Class IV under rule 1 (Option A), or these products may be subject to rule 2 (Option B). In the latter case, those IVDs will be classified as Class III.

Another outstanding feature is the division of IVDs for blood groups into two subsets depending on the nature of the blood group antigen the IVD is designed to detect [TGA, 2003]. The rationale for this has been the impact of erroneous results: transfusion of a unit of blood that is mismatched for A, B, or O antigens could result in an imminent life-threatening situation for the patient, whereas transfusion of blood mismatched for anti-Duffy antibodies would not be expected to have a similar effect.

Again, a special rule is formulated for near-patient tests, including those intended for home use. Compared to the Canadian system near-patient IVDs are initially classified lower (Class II). Exceptions are IVDs where an erroneous result poses the patient to an imminent life-threatening situation (Class III).

[12] This comprises IVDs either for establishing disease status or used in patient management.

***Figure 2 Overview of <u>proposed</u> decision rules for IVDs - main rules (risk class) as described in a Discussion paper of the NCCTG IVD Working Group (2003).***

**A. IVDs with respect to transmissible agents**

- rule 1: transmissible agents in blood, blood components, blood products, cells, tissues or organs to assess suitability for transfusion or transplantation (IV)
- rule 2: transmissible agents (II)

  exceptions:

  -detection of transmissible agent that causes a serious disease with a risk of propagation (Class III or subject to Class IV under rule 1)

  -detection of serious sexually transmitted agent (III)

  -detection of infectious agent in cerebrospinal fluid or blood which constitutes a significant public health risk (III)

  -detection of infectious agent where there is a risk that an erroneous result would cause death or severe disability to the individual or foetus being tested (III)

  -screening of prenatal women in order to determine immune status towards transmissible agents (III)

**B. Rules IVDs used in patient management (*establishing disease status or patient management*)**

- rule 3: determination of infective disease status or immune status (II)

  exception:

  -erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient (III)

- rule 4: screening or diagnosis of cancer, including cancer staging (II)

  exception:

  -initial therapeutic decisions will be made based on the outcome of the test results (III)

- rule 5: monitoring levels of medicines, substances or biological components (II)

  exception:

  -erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient (III)

- rule 6: genetic diagnosis, screening or management of genetic conditions (II)

  exception:

  -predictive, pre-natal, pre-implantation or neonatal genetic screening, when the outcome of the test would ordinarily result in a substantial impact on the life of the individual (III)

**C. Other uses**

- rule 7a: detection of commonly occurring irregular red blood cell antibodies, or determination of blood groups anti-Duffy or anti-Kidd (II)
- rule 7b: tissue typing or determination of blood groups A, B, O, Rhesus (C, c, D, E, or e) or anti-Kell (III)
- rule 8: detection of agent presenting low public health risk or moderate personal risk (II)

**D. Special rules**

- rule 9: IVDs for home use or point-of-care testing (II)
  exception:
  -IVDs for home use or point of care testing and where there is an immediate therapeutic management decision to be made based on the results, or where the results of testing will have a moderate public health impact (III).

- rule 10: IVDs presenting low individual risk and no public health risk (I)
- rule 11: pregnancy or fertility testing (II)

The content of each risk class (*Table 2*) is illustrated in a collective report on the joint regulatory scheme for the regulations of therapeutic products, including IVDs, in Australia and New Zealand [TGA/Medsafe, 2006]. A single, bi-national authority, the Australia New Zealand Therapeutic Good Administration, will administer this joint regulatory scheme. The latest information on the forthcoming regulatory framework can be found at the TGA website: http://www.tga.gov.au/devices/devices.htm#ivd.
It is expected that the draft IVD rule will be available for consultation no later than 2007[13].

[13] Clinica – World Medical Technology News, issue 1227, October 13, 2006.

***Table 2 Content of IVD risk classes in the new framework [TGA/Medsafe, 2006].***

| Class | Description | Groups of IVDs included | Examples of IVDs |
|---|---|---|---|
| **Class I** | IVD presents no public health risk, or low personal risk | -laboratory equipment intended for in-vitro diagnostic testing | -HPLC instrument<br>-automated differential cell counter |
| **Class II** | IVD presents a low public health risk and moderate personal risk | -detection of transmissible agents that are not easily propagated or that cause self-limiting diseases<br>-IVDs not intended as sole determinant in a diagnostic situation<br>-IVDs where an erroneous result rarely puts individual into immediate danger | -pregnancy/ovulation test<br>-tests for sodium<br>-ALT (enzyme present in liver cells)<br>-lactic dehydrogenase<br>-ferritin or folate<br>-computerised cervical cytology<br>-Epstein Barr virus<br>-autoimmune test |
| **Class III** | IVD presents a moderate public health risk or high individual risk | -diagnoses of serious infectious diseases with risk of propagation in community | -Australian Notifiable Diseases List[14] (e.g. Rabies) except where they are classified as IV |
| | | -detection of serious sexually transmitted agents | -Chlamydia trachomatis<br>-Neisseria gonorrhea |
| | | -detection of presence in cerebrospinal fluid or blood of an infectious agent with significant public health risk | -Neisseria meningitidis |
| | | -detection of presence of an infectious agent with significant risk that erroneous result would cause death/severe disability to the individual or foetus | -Toxoplasma<br>-Varicella Zoster Virus |
| | | -screening pre-natal women to determine immune status towards transmissible agents | -Rubella |
| | | -determining infective disease status or immune status and risk that erroneous result will lead to patient management decision resulting in an imminent life-threatening patient | -Influenza<br>-Haemophilus influenzae B |
| | | -screening or diagnosis of cancer, incl. cancer staging, where initial therapeutic decisions will be made on base of test result<br>NB. If diagnosis is made after follow-up the IVD could be placed in Class II (e.g. faecal occult blood test) [TGA, 2003] | -Immunological assay for myeloperoxidase staining of bone marrow aspirate to determine the lineage of haemopoietic blast cells |
| | | -predictive genetic screening | -Guthrie test for phenylketonuria<br>-Huntington's disease<br>-Cystic Fibrosis |
| **Class IV** | IVD presents a high public health risk | -universal screening and confirmatory testing of the blood, organ and tissue donations for pathogens | -tests for HIV, HBV, HCV, syphilis, HTLV |
| | | -screening of blood and tissue in selected populations | -CMV<br>-IgG<br>-Dengue fever<br>-malaria<br>-West Nile Virus<br>-Parvovirus B 19 NAT |
| | | -diagnosing diseases with a high public health impact | -IVDs to diagnose HIV, HCV |
| | | -detection agents used in bio warfare activities | -Anthrax |
| | | -high risk blood grouping tests | -ABO, Rhesus and anti-Kell |

[14] Australian Notifiable Diseases List: http://www.health.gov.au/internet/wcms/publishing.nsf/content/cda_nndss_dislist.htm; for example HIV, Hepatitis, Creutzfeldt-Jacob disease, diphtheria.

**USA**

The Food and Drug Administration (FDA) classifies IVDs (or other medical devices) products into Class I, II or III according to the level of regulatory control that is necessary to assure safety and effectiveness. The classification determines the premarket process [Federal Food, Drug, and Cosmetic Act, 2004].
Class I IVDs are subject to the least regulatory control ("general controls"). They present minimal potential for harm to the user and are often simpler in design than Class II or III. Most Class I devices are exempt from premarket notification and/or good manufacturing practices regulations. Examples are over the counter cholesterol tests, Chlamydia serological reagents, Epstein Barr virus serological agents, and Total spinal fluid immunological test systems.
Class II IVDs are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II IVDs are subject to special controls, for example special labelling requirements, mandatory performance standards and post marketing surveillance. A few Class II devices are exempt from premarket notification. Examples of Class II devices are over the counter blood glucose test systems, and serological reagents for Rubella virus, Toxoplasma gondii, and West Nile virus.
Class III IVDs are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Most Class III devices are subject to Premarket approval. This is the required process of scientific review to ensure the safety and effectiveness of Class III devices.
The Code of Federal Regulations (CFR) lists the classification of existing IVDs which makes classification prescriptive (21CFR 862: *Clinical Chemistry and Toxicology devices*, 21 CFR 864*: Hematology and pathology devices*, 21 CFR 866: *Immunology and microbiology devices*).
Novelty and the amount of available information on safety and effectiveness play a role in the process of risk classification.

In addition, IVDs are also subject to the Clinical Laboratory Improvement Amendments [CLIA, 1988]. This regulation establishes quality standards for laboratory testing and an accreditation program for clinical laboratories. The requirements vary according to the *technical complexity* in the testing process and risk of harm in case of erroneous results. The regulations established three categories of testing: '*waived tests*', '*tests of moderate complexity*', and tests of '*high complexity*'.
Waived test are simple laboratory examinations and procedures that have been approved by the FDA for home use[15], or that are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that employ methodologies that are so simple and accurate where the likelihood of erroneous results by user is negligible or tests that pose no unreasonable risk of harm to the patient if performed incorrectly [CDRH, 2005]. Tests that are listed as waiver include ovulations tests, faecal occult blood tests, urinalysis (none automated) of glucose, ketone, bilirubin [www.fda.gov.cdrh/clia/].

[15] Tests approved by the FDA for home use automatically qualify for CLIA waiver. Professional use versions of home used tests are not automatically waived.

Laboratories performing ‘moderate’- or ‘high complexity’ testing or both must meet requirements for proficiency testing, patient test management, quality control, quality assurance, and personnel. These requirements do not apply to tests in the ‘waived’ category. The categorisation of commercially marketed tests under CLIA is the responsibility of the FDA.

To determine the level of complexity of a test the following criteria are weighed up [FDA, 2001; CDRH, 2005]:

- *required knowledge*: minimal scientific and technical knowledge is required to perform the test vs. specialised scientific and technical knowledge is required in all phases of the testing (preanalytic, analytic, post analytic);
- *required training and experience*: minimal vs. specialised training;
- *reagents and materials preparation*: reagents and material are generally stable and reliable vs. reagents and materials may be labile and require special handling to assure reliability;
- *characteristics of operational steps*: operational steps such as pipetting, temperature monitoring, or timing steps) are either automatically executed or are easily controlled vs. operational steps in the testing process require close monitoring or control and may require for example special specimen preparation or timing of procedural steps or extensive calculations;
- *stability of calibration, quality control, and proficiency testing materials*: calibration materials, quality control materials and external proficiency testing are all stable and readily available vs. materials may be liable.
- *test system troubleshooting and equipment maintenance*: test system troubleshooting is automatic or self correcting or clearly described or requires minimal judgment and maintenance is provided by the manufacturer, is seldom needed or can easily be performed vs. troubleshooting is not automatic and requires decision-making and direct interventions to resolve problem, maintenance requires special skills, knowledge and abilities;
- *interpretation and judgment*: minimal interpretation and judgment are required to perform the phases of the testing process and resolution of problems requires limited independent interpretation and judgment vs. extensive independent interpretation and judgment are required and resolution of problems requires extensive interpretation and judgment.

From this it can be concluded that characteristics of the test performance are stressed when making the classification, rather than intended purpose.

## Appendix III – Risk Classes of Annex II IVDs and self-testing devices according to the model

| IVDs Annex II | Risk Class | Rationale |
|---|---|---|
| **List A IVDs** | | |
| *Reagents and reagent products, including related calibrators and control materials for:* | | |
| -Determining the Blood groups of the ABO system and Rhesus (C, c D, E, e) anti-Kell | D | Rule 15: Immunological typing: 'high risk' blood group |
| -Detection, confirmation and quantification of Human specimens of markers of HIV infection (1 and 2), HTLV I and II, and Hepatitis B, C, D | D/C | Depending on purpose:<br>Rule 2: Donor screening or diagnosis (Class D) or<br>Rule 6: Monitoring therapy (Class C) |
| **List B IVDs** | | |
| *Reagents and reagent products, including related calibrators and control materials for:* | | |
| -Determining the blood groups Anti-duffy and Anti-Kidd | C | Rule 15 Immunological typing, 'moderate risk' |
| -Determining irregular anti-erythrocytic antibodies | C | Rule 15 Immunological typing, 'moderate risk' |
| -Detection and quantification of Rubella and Toxoplasmosis | C | Depending on purpose:<br>Rule 4: Detection of transmissible agent that causes a serious disease with risk of propagation or<br>Rule 5: Detection of transmissible agent with risk that erroneous result leads to death/severe disability |
| -Diagnosing Phenylketonuria | C | Depending on purpose:<br>Rule 10: Genetic testing or<br>Rule 12: Risk that erroneous result causes death or severe disability |
| -Determining the infectious Cytomegalovirus and Chlamydia | C/D | Depending on purpose:<br>Rule 2: IVD intended for donor screening or<br>Rule 4: Detection of transmissible agent that causes a serious disease with risk of propagation |
| -Determining of HLA tissue groups DR, A, B | C | Rule 15: Immunological typing, 'moderate risk' |
| -Determining of Tumoral marker PSA | C | Rule 9: Screening or diagnosis of cancer |
| -Evaluating the risk of Trisomy 21 (including software) | C | Rule 11: Screening for congenital disorders in the foetus |
| -Devices for self-diagnosis and measurement of blood sugar (glucose) | C | Rule 14: Monitoring substances, medicines, biological components |
| **Self-testing devices** | B/C/D | Class B under rule 16, unless other rules apply |