National Institute for Public Health
and the Environment
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a study on the IVDs registered in the Netherlands

RIVM Letter report 2018-0082
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Synopsis

The impact of the new European IVD-classification rules on the notified body involvement;
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In vitro diagnostics (IVDs) are medical devices for carrying out a test using human specimens such as urine or blood. Examples of these products are pregnancy tests, tests for determining the level of glucose or cholesterol in the blood, and tests that determine the blood group.

To ensure that these products are safe and effective in use, the manufacturers must go through a procedure before the IVDs may be sold. The current legislation contains two lists on which IVDs are subdivided into a medium-risk and a high-risk category. IVDs that are not on these lists are automatically classified as low risk. An example of an IVD with high risk is an HIV test, whereas a blood collection tube or a pregnancy test has a low risk. A more stringent market authorisation procedure applies for IVDs with a high risk level and additional approval by an external party, a so-called notified body, is required. For low-risk IVDs, manufacturers may carry out the licensing procedure themselves.

This system with lists is no longer sufficient. It has therefore been changed in the new European legislation for IVDs, which comes into effect in 2022. The risk of IVDs is then determined according to rules and subdivided into a cascade of four categories. Examples of factors that determine the risk are severity of the disorder tested for and possible consequences of an incorrect test result. Research carried out by the National Institute for Public Health and the Environment (RIVM) has shown that this means that many more IVDs will end up in a higher risk category (84 instead of 7 percent). This means that the number of IVDs for which the manufacturer requires approval of a notified body in order to obtain market authorization will be much greater.

This study was carried out by the order of the Dutch Health and Youth Care Inspectorate (IGJ).

Keywords: IVD, *In Vitro* Diagnostic Medical Devices, *In vitro* Diagnostic Medical Devices Directive, *In vitro* Diagnostic Medical Devices Regulation, legislation, classification, notified body

Publiekssamenvatting

De impact van de nieuwe Europese IVD-classificatieregels op de betrokkenheid van notified bodies;
Een studie over de in Nederland geregistreerde IVD's

In-vitro diagnostica (IVDs) zijn medische hulpmiddelen om lichaamsmateriaal zoals urine of bloed te testen. Voorbeelden van deze producten zijn zwangerschapstesten, testen om het gehalte van glucose of cholesterol in het bloed te meten en testen die de bloedgroep bepalen.

Om te waarborgen dat deze producten veilig en effectief in het gebruik zijn, moeten fabrikanten een procedure doorlopen voordat de IVD's mogen worden verkocht. De huidige wetgeving bevat twee lijsten waarop IVD's zijn onderverdeeld in een 'midden' en een 'hoog' risico. IVD's die niet op deze lijst staan worden automatisch ingeschaald als 'laag' risico. Een voorbeeld van een IVD met een hoog risico is een hiv-test, terwijl een bloedbuisje of zwangerschapstest een laag risico heeft. Voor IVD's met een hoog risico geldt een zwaardere toelatingsprocedure en is een extra goedkeuring door een externe partij, een zogenaamde notified body, nodig. Voor laag risico IVD's mogen fabrikanten zelf de toelatingsprocedure uitvoeren.

Dit systeem met lijsten voldoet niet meer. Daarom is het in de nieuwe Europese wetgeving voor IVD's, die in 2022 in werking treedt, veranderd. Het risico van IVD's wordt dan volgens nieuw opgestelde regels bepaald en trapsgewijs in vier klassen onderverdeeld. Factoren die van invloed zijn op het risico zijn bijvoorbeeld de ernst van de aandoening waarop wordt getest en mogelijke gevolgen van een onjuiste testuitslag. Uit onderzoek van het RIVM blijkt dat hierdoor veel meer IVD's in een hogere risicoklasse zullen vallen (84 in plaats van 7 procent). Dat betekent dat het aantal IVD's waarvoor de fabrikant goedkeuring van een notified body nodig heeft om het product op de markt te mogen brengen, veel groter zal zijn.

Dit onderzoek is uitgevoerd in opdracht van de Inspectie Gezondheidszorg en Jeugd (IGJ).

Kernwoorden: IVD, *in-vitro* diagnostische medische hulpmiddelen, Besluit *in-vitro* diagnostica, verordening *in-vitro* diagnostica, wetgeving, classificatie, notified body

Contents

Summary

In short, *in vitro* diagnostic medical devices (IVDs) are medical devices to be used for the *in vitro* examination of specimens (e.g. blood, urine) derived from the human body. IVDs cover a large variety of devices, ranging from a blood collection tube or a pregnancy test, to a multipurpose analyzer intended for hospital laboratories. Other examples of IVDs are tests to determine the level of glucose or cholesterol in blood and tests to determine the blood group. Currently, market access of IVDs in Europe is governed by the *In vitro* Diagnostic Medical Devices Directive (IVDD, 98/79/EC). In 2017, a new regulation for medical devices for *in vitro* diagnostics (*In vitro* Medical Device Regulation; IVDR) was adopted, introducing more tightened safety requirements for market authorization. After a transition period of five years, the date of application of the IVDR will be May 26th, 2022.

Currently – under the IVDD – the process of market access of IVDs is governed by the risk associated with the IVDs. Limitative lists of 'high risk' and 'moderate risk' IVDs have been included in the IVDD. All other IVDs, except devices for self-testing are by default 'low risk'. For the low risk devices, the manufacturer can use self-certification, whereas for the other devices, a third party, a so called notified body has to be involved in the market authorisation procedure.
The IVDR introduces a rule based classification system with four risk classes (A-D), A being the lowest risk class and D the highest. The classification rules take into consideration factors such as purpose of the test (e.g. assessment of suitability of blood for transfusion or monitoring the stage of a disease), the risk of propagation, the nature of the disease or agent (e.g. cancer or sexually transmitted agent), and the type of specimen (i.e. blood or urine) to establish the risk class. Devices classified in class A can be self-certified by the manufacturer. For IVDs in Class B, C or D, assessment by a notified body is required for market authorisation.

The new classification system of the IVDR is expected to result in an increase of IVDs that require assessment by a notified body in order to achieve market access. This study aimed to assess the distribution of IVDs registered in the Netherlands over the different risk classes of the IVDR, and the shift from the categories of the IVDD to the IVDR classes. To do so, a representative sample of all IVDs registered in the registration database of the Dutch Central Information Unit on Health Care Professions (CIBG) was classified according to the classification rules of the IVDR.

The classification and analysis of 946 database entries (approximately 20% of the total number of database entries) provided a statistically representative overview of the occurrence of the four IVDR risk classes in the database. Based on the Dutch situation under the IVDD, currently 7% of the registered IVDs require involvement of a notified body. When the entries were classified according to the rules in the IVDR, 1.5% of all devices are Class D, 31,0% Class C, 51,7% are Class B and 15.9% Class A. This indicates that the percentage of IVDs requiring a notified body in

order to obtain market authorisation increases from 7% to 84% (Class B-D in IVDR classification).

The classification of IVD risk classes in this study was hampered by multiple possible interpretations of some of the classification rules and by limited information for part of the IVDs in the database. For these reasons, the results provide an overall picture of the distribution of IVDs over risk classes. For the application of the classification rules in the IVDR, a guidance document is needed to facilitate consistent application of the classification rules.

1 Introduction

1.1 General

1.1.1 *In vitro diagnostic medical devices and regulation*
In short, *in vitro* diagnostic medical devices (IVDs) are medical devices to be used *in vitro* for the examination of specimens derived from the human body (full definition is addressed in Textbox 1). IVDs cover a large variety of devices, ranging from a blood collection tube or a pregnancy test, to a multipurpose analyzer intended for hospital laboratories. Other examples of IVDs are tests to determine the level of glucose or cholesterol in blood and tests to determine the blood group.

Currently, market access of IVDs in Europe is governed by the *In vitro* Diagnostic Medical Devices Directive (IVDD, 98/79/EC) [1]. This European Directive describes the procedures for market access and provided general requirements, which have to be fulfilled by all IVDs. The IVDD was transposed into Dutch legislation by the publication of the Dutch Decree on *In vitro* Diagnostics (Besluit *in-vitro* diagnostica) on June 22nd, 2001 [2]. In 2017, a new regulation for medical devices for *in vitro* diagnostics (*In vitro* Medical Device Regulation; IVDR [3]) was adopted, introducing more stringent requirements for market authorization. After a transition period of five years, the date of application of the IVDR will be May 26th, 2022.

Textbox 1: definition *in vitro* diagnostic medical device [2]

IVDR definition *In vitro* diagnostic medical device
'*in vitro* diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software 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 on one or more of the following:
   (a) concerning a physiological or pathological process or state;
   (b) concerning congenital physical or mental impairments;
   (c) concerning the predisposition to a medical condition or a disease;
   (d) to determine the safety and compatibility with potential recipients;
   (e) to predict treatment response or reactions;
   (f) to define or monitoring therapeutic measures. Specimen receptacles shall also be deemed to be *in vitro* diagnostic medical devices;

1.1.2 *Risk categories and classes*
Currently – under the IVDD – the process for market access of IVDs is governed by the proposed risk of the IVDs. In the IVDD, the risk of IVDs is laid down in two limitative lists that are addressed in Annex II of the IVDD: List A and List B (Annex I in this report). IVDs mentioned in List A are the highest risk devices and require the most extensive examination (scrutiny) of a notified body. Examples of IVDs that are on

List A are products for the determination of blood groups AB0, Human Immunodeficiency Virus (HIV), Human T-cell leukemia virus (HTLV) or hepatitis. Examples of IVDs on List B are blood glucose meters and products for the detection of chlamydia, rubella and trisomy 21. For devices mentioned on list A, the assessment by the notified body includes a full assessment of the design and testing of manufactured devices, which are not mandatory elements for a device on list B. Besides List A and B in Annex II of the IVDD, also for devices for self-testing, a notified body has a limited role to check the aspects related to self-testing only. The IVDs not on List A or B, and are not devices for self-testing, are referred to in this report as 'IVD other', and do not require assessment by a notified body. For the tests for HIV, HTLV and hepatitis a so-called common technical specification was developed to lay down the requirements for such products [4]. Following a successful conformity assessment procedure, a CE-mark will be affixed to the IVD to indicate conformity to the applicable directive and to show that the device can be marketed freely in the European Economic Area.

Because of the use of limitative lists with higher risk IVDs in the IVDD, newly developed tests not mentioned in these two lists, by default do not require scrutiny by a notified body. This is irrespective of their risk. An example of such a development was a test for Creutzfeldt-Jakob disease (CJD). To resolve this issue, an addition to the common technical specification for CJD was developed [5]. Rule-based classification systems for *in vitro* diagnostic medical devices have been proposed by several parties (RIVM, the Global Harmonisation task force (GHTF), Canada) [6-8]. A classification system based on rules, as is being used for medical devices [9], will allow new IVDs to be assigned to the appropriate risk class and subsequently to the appropriate conformity assessment procedures. Such a system is robust to changes in products and allows for an increasing involvement of the notified body with increasing associated risks to IVDs.

The new European regulation on *in vitro* diagnostic medical devices (IVDR) introduces a rule based classification system. Annex VIII of the IVDR addresses seven classification rules (see also Annex II in this report). Using these classification rules, an IVD can be assigned one of four risk classes (A-D), A being the lowest risk class and D the highest (see figure 1). The classification rules take into consideration factors such as purpose of the test (e.g. assessment of suitability of blood for transfusion or monitoring the stage of a disease), the risk of propagation, the nature of the disease or agent (e.g. cancer or sexually transmitted agent), and the type of specimen (i.e. blood or urine) to establish the risk class. Devices classified in class A can be self-certified by the manufacturer. For IVDs in Class B, C or D, assessment by a notified body is required for market authorisation.

Figure 1: IVDR risk classes, examples and notified body involvement

1.1.3   *Registration of devices in the Netherlands*
The Dutch decree on IVDs requires that manufacturers that are located in the Netherlands register themselves and their IVDs to the Central Information Unit on Health Care Professions (CIBG). Registration is also required when an IVD is not marketed in the Netherlands but elsewhere in the European Union. The database of the CIBG contains product names, product descriptions and whether the IVDs are categorised as list A, list B, self-test or other in the IVDD.

1.2   Aim

The new classification system of the IVDR is expected to result in a shift from IVDs from low to higher risk classes. Classification in these higher risk classes requires assessment by a notified body in order to achieve market access for an IVD. The IVDR requires notified bodies to have responsibilities in the vigilance process. The IGJ will have to adapt their policy to the changed procedures and new situation.

The IGJ requested RIVM to perform a study to assess the distribution of IVDs registered in the Netherlands over the different risk classes of the IVDR, and the shift from the categories of the IVDD to the IVDR classes.

To do so, a representative sample of all IVDs registered in the CIBG database was classified according to the classification rules of the IVDR (Annex VIII of the IVDR and Annex II of this report) and compared to categorization under the IVDD.

2   Methods

2.1   Database and preparations

RIVM was provided with the information from the registration database of the CIBG via the IGJ. The registration database of the CIBG, comprising all IVDs that are registered in the Netherlands (updated until January 2018), contains 5390 entries. Each entry represents one or several IVD and includes the category of the IVD in the IVDD (List A; List B; Self-test; IVD other), a product name, product description and group name. The product name and product description could contain details about the type of product (e.g. blood glucose meter), specific substances, markers or organisms that can be tested by the particular IVD (e.g. Human immunodeficiency virus (HIV)), or even the disease that is related to a specific marker (e.g. prostate cancer). The content of the fields product name and product description varied widely between the different IVDs. For part of the IVDs there was no product description provided.

The following fields were added to the database for the study as described in this report: Class IVDR, classification rule, organ/disease/marker/organism, remark, and assessor. Besides the actual classification in class A-D of the IVDR in the field 'class IVDR', the specific classification rule that applied was registered. The field organ/disease/marker/organism was used to register the specific purpose of an IVD when this could be derived from the information provided.

2.2   Classification

Three assessors independently worked through the database, using the information from the fields product name, product description and group name to assess which classification rule applied, and correspondingly, which IVDR class. When the information provided allowed this, the specific organ/disease/marker/organism tested by the IVD was entered. Each subsequent entry was classified by one of the assessors after which the assessor added his/her initials in the relevant column. When there was uncertainty about the class or the classification rule that applied, the entry was marked to discuss it within the project team. In weekly project meetings, the marked entries were discussed to reach consensus. In some cases, the team did not reach consensus, for example because the classification rules could be interpreted in different ways or because the information in the database was insufficient. In these cases, it was checked whether more information was available or input from experts from authorities was used.

In the case insufficient information was provided, the IGJ checked whether more information was available on these specific IVDs within their databases, to facilitate the classification. If no further information was available, the entry was excluded. In some cases, IVDs concerned tests for drugs of abuse. Based on the description provided, it was checked whether the test was to be used by health care professionals or for a specific substance. If this was the case, it was classified as an IVD.

In other cases, or if information was insufficient to judge, the entry was excluded.

For interpretation issues, the entry was discussed with a representative of the Dutch or Belgian authorities, who also participated in the European IVD Technical Group. This Technical Group is amongst others responsible for developing guidance on the IVDR classification rules for IVDs.

The organ/disease/marker/organism tested by the IVD was used for a final check on the database and classifications on inconsistencies, performed by two assessors.

2.3 Analysis

The complete dataset consisted of 5390 entries. It was decided that at first a sample of 1000 entries would be used, after which no further classification would be done if the uncertainty of the results was less than a limit of 5%. All data analyses were performed in Microsoft Excel.

To avoid possible sources of bias in the sample, the 5390 entries were put in a randomized order. The first 1000 entries were classified and the proportions (percentages) of the IVDs over the IVDD categories and IVDR classes were determined. Additionally, the 95% confidence intervals for the proportions were calculated using the binomial distribution. It was established that the margin of error was less than 4% for each of the IVDR risk classes. It was concluded that the analysed entires provided a reliable overview of the occurrence of the four IVDR risk classes in the database. Therefore, no further entries were classified, as it would not substantially increase the accuracy of the results. In the report, the number of entries in the different risk classes or categories is tabulated to allow an insight into the shift in the classification from IVDD to IVDR.

3   Results

3.1   Distribution of IVDs: IVDD categories and IVDR risk classes

Following the classification of 1000 entries, the analysis indicated that no further entries needed to be classified to obtain a reliable overview of the occurrence of the four IVDR risk classes in the database. After exclusion of entries from the assessment due to insufficient data (n=30) or because they were not considered to be IVDs (n=24), a total number of 946 entries was analysed. The distribution of the IVDs over the different risk classes (IVDR) and categories (IVDD) is presented in table 1.

Table 1a: distribution of database entries over IVDD categories and notified body approval

Authorisation procedure	Registered database entries (n = 946)	
	IVDD categories, % (n)	
Self-certification	**IVD other**	93.1 (881)
Notified body approval required	**List A**	0.9 (9)
	List B	4.2 (40)
	Self-test	1.7 (16)

Table 1b: distribution of database entries over IVDR risk classes and notified body approval

Authorisation procedure	Registered database entries (n = 946)	
	IVDR classes, % (n)	
Self-certification	**A**	15.9 (150)
Notified body approval required	**B**	51.7 (489)
	C	31.0 (293)
	D	1.5 (14)

Among the 946 random database entries that were assessed, currently 1.7% of the IVDs are categorized as self-tests, 4.2 % as List B devices, 0.9% as List A devices and 93.1% are not classified in a specific category ('IVD other'). When the entries were classified according to the rules in the IVDR, 1.5% of all devices are Class D, 31,0% Class C, 51,7% are Class B and 15.9% Class A.

3.2   Shifts from IVDD categories to IVDR risk classes

The above data indicate that the percentage of IVDs not requiring a notified body for market access decreases from 93% (IVD other in IVDD) to 16% (Class A in IVDR). Accordingly, the percentage of IVDs that do require a notified body for market access increases from 7% (List A, List B and self-test in IVDD) to 84% (Class A in IVDR). Figure 2 shows the distribution of classified IVDs over the IVDR classes separately for each of the IVDD categories.

All IVDs that are on List A of the IVDD, shift to highest risk class (D) of the IVDR. All List B IVDs are reclassified as Class C. The self-tests were reclassified as Class B (62.5%) or C (37.5%), according to IVDR classification rules. The IVDs that were in the category 'IVD other' were distributed over all IVDR risk classes, but were predominantly classified in Class B (54.4%). The five tests reclassified from 'IVD other' to Class D included two tests for transmissible agents (West Nile and Epstein Barr virus), specifically intended to test blood samples for suitability for donation or transplantation; two tests for pandemic influenza; and one HIV control.
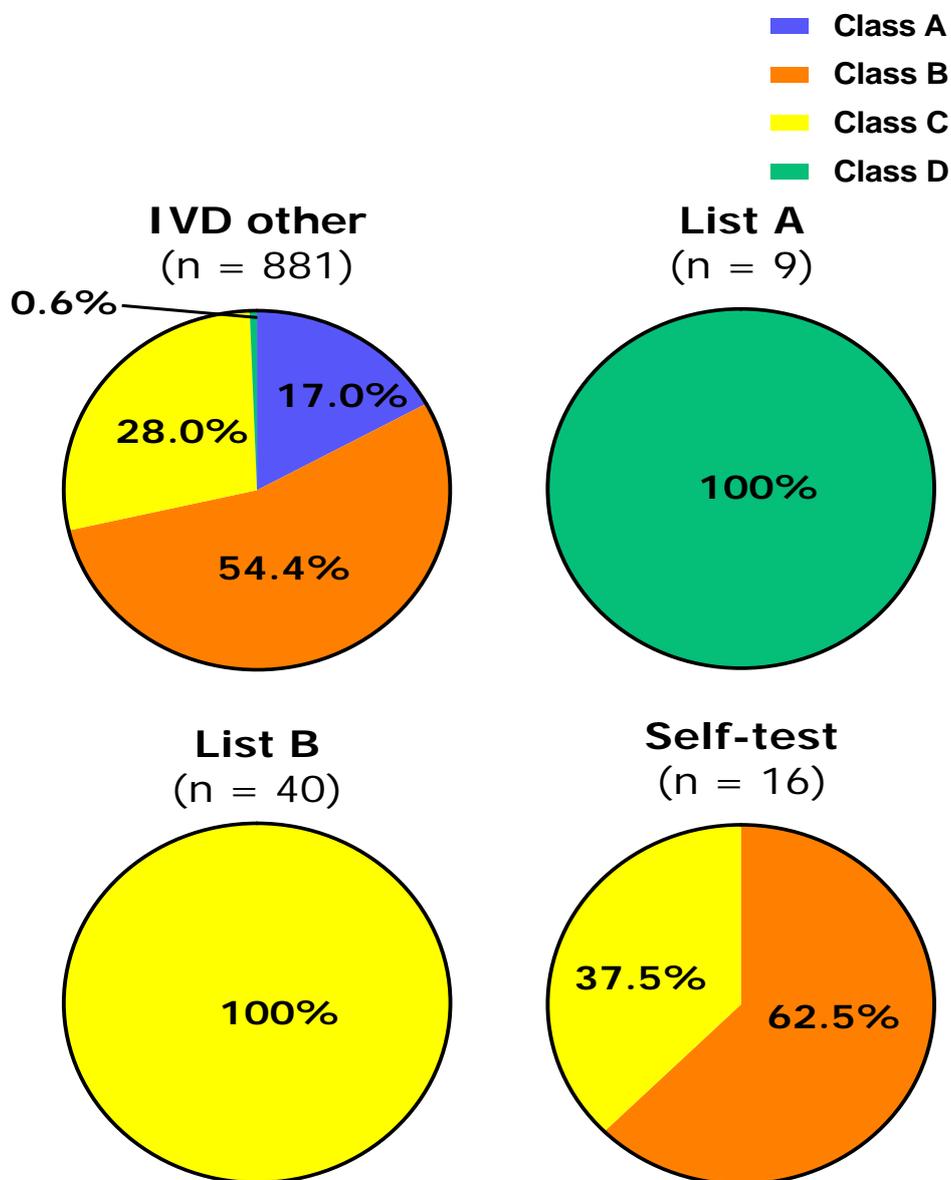

Figure 2: distribution of classified IVDs over the IVDR classes separately for each of the IVDD categories

4 Discussion and conclusions

4.1 Discussion

4.1.1 *Overall*
In this study the classification rules of the IVDR were used to classify the IVDs registered in the Netherlands into risk classes A-D. The classification was hampered by multiple possible interpretations of some of the classification rules and by a lack of detailed information for part of the IVDs. For these reasons, the results provide an overall picture of the distribution of IVDs over risk classes and not a reference of classification of specific registered IVDs.

The study shows that under the IVDR, the notified body involvement in the market authorisation procedure will increase from 7% to 84%. Under the IVDR, the majority of the IVDs will become Class B and C devices. Although both classes require assessment by a notified body, the distinction between class B and C is relatively large for manufacturers, since considerably more effort is needed for the conformity assessment procedures for Class C IVDs than for Class B IVDs. Classification should therefore be performed carefully and clear guidance on the classification is of utmost importance.

4.1.2 *Interpretation of terminology and specific classification rules*
During the classification of IVDs, the project team faced a number of recurring discussion points and interpretation issues in the classification rules. The main problems encountered are addressed below.

Classification rules and description of IVDs
While several classification rules of the IVDR refer to applications, such as genetic testing and disease staging, the descriptions of the IVDs in the database often only indicate markers to be tested by the IVD. This meant that the marker had to be matched to an application. However, a marker may be one of a subset to diagnose a certain condition, or may be a marker for multiple diseases/conditions. In some cases, an IVD could be classified in different classes, depending on the interpretation of the product description.

Terminology in classification rules
Used terminology lacked guidance on the definition and resulted in ambiguity in the classification. This was the case for the terms "life threatening", and for "high risk of propagation", "substances and biological components", and "general laboratory use".

In the classification rules, the term life threatening is used in several instances. Whereas for certain diseases it may be clear that an erroneous test result could lead to a life-threatening situation (e.g. for malaria), this is often less clear and open for multiple interpretations. The following interpretation of the term life threatening disease was used: *"diseases resulting in death or long-term disability, that are often*

limited in their treatment options, untreatable, or require major medical interventions".[1]

The term high risk of propagation was also considered ambiguous and resulted in uncertainty in the classification of certain IVDs. The following interpretation of this term was used for this study:

"Several factors contribute to the risk of propagation of a pathogen within a population, namely:

1. *the transmissibility (i.e. the probability of infection when there is contact between a susceptible and an infected individual). Transmission includes zoonosis and vector-mediated transmission.*
2. *the contact rate of infected and susceptible individuals (i.e. the number of contacts per time), and*
3. *the duration of infectiousness*

The risk of propagation of a pathogen within a population is estimated in a population where there is no enhanced risk, with respect to propagation and disease outcome, due to an underlying disease or condition, or due to specific housing and sanitation conditions".[2]

These definitions are helpful for the classification. However, even though the terms are clearly defined, the decision whether a situation is applicable for a certain IVD is still a matter of discussion.

Rule 3j addresses *monitoring of levels of medicinal products, substances or biological components*. The distinction between a substance and a biological component is often unclear. For example, it was assumed that glucose was either a substance or a biological component and that erroneous results can lead to a life threatening patient management decision. Therefore tests for glucose were considered to be Class C according to rule 3j. Another interpretation issue for this rule is the fact that the tests are intended for monitoring. Often this was not mentioned in de available description of the test and glucose test were considered to be covered by rule 3j. For one test, glucose was mentioned with several other compounds as a urine test, and this was not considered as a test for monitoring, in line with rule 3j. In this case, the test was classified as B.

To facilitate common interpretation of the classification rules and terminology used, guidance should be available, as is currently available for interpretation of the classification rules in the MDD [10].

4.1.3   *Methodology*

As there is no central system for the registration of medical devices or IVDs, using the notification database from the Dutch authorities was the best option to obtain an overview of the shift in distribution of IVDs from the IVDD categories to IVDR classes. The database contains all registrations for IVDs to the Dutch authorities. However, there is no information about the completeness of the IVDs registered.

[1] Guidance for the Risk-based Classification System for *In vitro* Diagnostic Devices (IVDDs), Health Canada, 2016
[2] Jones, J. H. (2007). Notes on R0. From http://web.stanford.edu/~jhj1/teachingdocs/Jones-on-R0.pdf

It is a limitation that the information in the database, provided by the suppliers varied considerably, from very detailed descriptions to entries containing nearly no information about the product. In some cases, lack of detailed information in the database resulted in difficulties with the classification. For example, in rule 1, first indent and rule 3b), it is indicated that the diagnosis is done in a specific type of specimen, e.g. blood or cerebrospinal fluid. The type of specimen is thereby decisive for the classification of the IVD. However, information on the intended type of specimen was often lacking in the database. Classification was also difficult when classification rules indicated that a test should be for a specific purpose (e.g. disease staging in rule 3g, monitoring in rule 3j and use for transfusion, transplantation in rules 1 and 2). Information on the specific purpose of an IVD was often lacking in the database.

Another difficulty was that some entries fields contained incorrect information, e.g. a blood glucose meter being classified as a self-test under the IVDD, although this is a list B IVD under the IVDD. For some IVDs included in the database, there was uncertainty about whether it concerned IVDs. This was the case for e.g. a lancet, which is a medical device. Furthermore, the database included entries for tests for drugs of abuse.

Finally, the assessment was done based on the classification rules, for which no final guidance exists. Because part of the classification rules may be subject for multiple interpretations, the results of the classification may differ when other decisions are made or when guidance on the interpretation would have been available. However, a large shift is not expected, especially since the entries where there was doubt were discussed with experts that are working on the guidance document.

Due to the methodological concerns listed above, the results of this study only give an indication of the situation that will occur when the IVDR is fully implemented. The discussion points for which there was uncertainty in the interpretation of the classification rules could provide input for developing the guidance document on the classification of IVDs under the IVDR, which is currently undertaken by the IVD Technical Group, that assists the European Commission in relation to the implementation of existing Union legislation, programmes and policies.

4.2 Conclusions

This study aimed to assess the distribution of IVDs registered in the Netherlands over the different risk classes of the IVDR, and the shift from the categories of the IVDD to the IVDR classes. Under the IVDR, more IVDs shall require a notified body approval in order to obtain market access. The assessment and classification of a random sample of all IVDs registered in The Netherlands showed that under the IVDD, 7% of the IVDs require assessment by a notified body for market access. Under the IVDR, 84% of the IVDs that are currently registered in the Netherlands will require a notified body assessment for market access. Approximately 50% of all assessed IVDs are classified in risk class B and over 30% in Class C in IVDR. For the application of the classification

rules in the IVDR, a guidance document is needed to facilitate consistent application of the classification rules.

5 References

1. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices. OJ L 331, 7.12.1998. Amended by Regulation (EC) No 596/2009 of the European Parliament and of the Council of 18 June 2009. OJ L 188, 18.7.2009.

2. Besluit van 22 juni 2001, houdende regels met betrekking tot het in de handel brengen en het toepassen van medische hulpmiddelen voor *in-vitro* diagnostiek (Besluit *in-vitro* diagnostica).

3. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. OJ L 117, 5.5.2017.

4. COMMISSION DECISION (2009/886/EC) of 27 November 2009 amending Decision 2002/364/EC on common technical specifications for *in vitro* diagnostic medical devices*.

5. COMMISSION DECISION (2011/869/EU) of 20 December 2011 amending Decision 2002/364/EC on common technical specifications for *in vitro* diagnostic medical devices.

6. RIVM Report 360050007 *In vitro* Diagnostic Medical Devices. Decision rules for IVD-classification, Hollestelle ML, de Bruijn ACP, 2006.

7. Global Harmonisation task force, SG1, Principles of *In vitro* Diagnostic (IVD)Medical Devices Classification, 19 February 2008.

8. GUIDANCE DOCUMENT: Guidance for the Risk-based Classification System for InVitro Diagnostic Devices (IVDDs), Minister of Public Works and Government Services Canada 2016.

9. COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices, as amended by Directive 2007/47/EC of the European Parliament and of the council of 5 September 2007.

10. MEDDEV 2. 4/1 Rev. 9: MEDICAL DEVICES: Guidance document - Classification of medical devices, EUROPEAN COMMISSION DG HEALTH AND CONSUMER, June 2010.

Annex I: lists A & B from IVDD

List A
- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell,
- reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.

List B
- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd,
- reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies,
- reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis,
- reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria,
- reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia,
- reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups: DR, A, B,
- reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA,
- reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy 21,
- the following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar.

Annex II: Classification rules from IVDR

1 IMPLEMENTING RULES

1.1. Application of the classification rules shall be governed by the intended purpose of the devices.

1.2. If the device in question is intended to be used in combination with another device, the classification rules shall apply separately to each of the devices.

1.3. Accessories for an in vitro diagnostic medical device shall be classified in their own right separately from the device with which they are used.

1.4. Software, which drives a device or influences the use of a device, shall fall within the same class as the device. If the software is independent of any other device, it shall be classified in its own right.

1.5. Calibrators intended to be used with a device shall be classified in the same class as the device.

1.6. Control materials with quantitative or qualitative assigned values intended for one specific analyte or multiple analytes shall be classified in the same class as the device.

1.7. The manufacturer shall take into consideration all classification and implementation rules in order to establish the proper classification for the device.

1.8. Where a manufacturer states multiple intended purposes for a device, and as a result the device falls into more than one class, it shall be classified in the higher class.

1.9. If several classification rules apply to the same device, the rule resulting in the higher classification shall apply.

1.10. Each of the classification rules shall apply to first line assays, confirmatory assays and supplemental assays.

2. CLASSIFICATION RULES

2.1. Rule 1
Devices intended to be used for the following purposes are classified as class D:
- detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration;
- detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation;

- determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management.

2.2. Rule 2

Devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration, are classified as class C, except when intended to determine any of the following markers:
- ABO system [A (ABO1), B (ABO2), AB (ABO3)];
- Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)];
- Kell system [Kel1 (K)];
- Kidd system [JK1 (Jka), JK2 (Jkb)];
- Duffy system [FY1 (Fya), FY2 (Fyb)];

in which case they are classified as class D.

2.3. Rule 3

Devices are classified as class C if they are intended:
a. for detecting the presence of, or exposure to, a sexually transmitted agent;
b. for detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation;
c. for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring;
d. for pre-natal screening of women in order to determine their immune status towards transmissible agents;
e. for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring;
f. to be used as companion diagnostics;
g. to be used for disease staging, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring;
h. to be used in screening, diagnosis, or staging of cancer;
i. for human genetic testing;
j. for monitoring of levels of medicinal products, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring;
k. for management of patients suffering from a life-threatening disease or condition;
l. for screening for congenital disorders in the embryo or foetus;

m. for screening for congenital disorders in new-born babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities.

2.4. Rule 4
a. Devices intended for self-testing are classified as class C, except for devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine, which are classified as class B.
b. Devices intended for near-patient testing are classified in their own right.

2.5. Rule 5
The following devices are classified as class A:
a. products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for *in vitro* diagnostic procedures relating to a specific examination;
b. instruments intended by the manufacturer specifically to be used for *in vitro* diagnostic procedures;
c. specimen receptacles.

2.6. Rule 6
Devices not covered by the above-mentioned classification rules are classified as class B.

2.7. Rule 7
Devices which are controls without a quantitative or qualitative assigned value are classified as class B.