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A.W. van Drongelen | C.G.J.C.A. de Vries | J.W.G.A. Pot

Assessment of files of in vitro diagnostic devices for self-testing

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RIVM Report 360050017/2008

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A.W. van Drongelen
C.G.J.C.A. de Vries
J.W.G.A. Pot

Contact:
Arjan W. van Drongelen
Centre for Biological Medicines and Medical Technology
Arjan.van.Drongelen@rivm.nl

This investigation has been performed by order and for the account of Dutch Health Care Inspectorate, within the framework of V/360050 'Supporting the Health Care Inspectorate on Medical Technology'

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Abstract

Assessment of files of in vitro diagnostic devices for self-testing

An increasing number of people are now using medical diagnostic devices without having consulted a physician. Incorrect results could be obtained using these devices because they are not always suitable for the user and the instructions for use are not always clear. This is the outcome of an RIVM investigation into medical diagnostic self-tests, based on the documentation submitted by their manufacturers. The investigation concerned ovulation tests, blood glucose meters for diabetics and a self-test for the sexually transmitted disease Chlamydia. Manufacturers of such devices are required to systematically identify and analyse the risks associated with these devices. The product has to be improved or information about its use and related risks provided to the user wherever necessary.

Shortcomings were found in the way that the risk analyses were carried out by the manufacturers. An issue is that experiences with the product and related incidents have been insufficiently incorporated into the risk analyses. Moreover, risks mentioned in the instructions for use were not always present in the risk analysis, as they should be. Vice versa, the residual risks, identified in the risk analysis for incorporation into the instructions for use, were not always included in the instructions for use. A further shortcoming related to the fact that lay user studies performed by the manufacturer did not always appear suitable for testing the usability of the self-test for the Dutch market.

The quality of files of eight medical diagnostic self-tests was assessed by the RIVM. Of the requested high risk self-tests (e.g. HIV, prostate cancer and Chlamydia) only one file (a Chlamydia self-test) was received. The total response was only 57% of all included manufacturers. This investigation was conducted by order of the Dutch Health Care Inspectorate.

Key words:
IVD, self-test, assessment, Chlamydia self-test, ovulation test, blood glucose meter

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Rapport in het kort

Beoordeling van dossiers van in-vitro diagnostische zelftesten

Steeds vaker voeren mensen medisch-diagnostische testen uit zonder begeleiding van een arts. De testen en de gebruiksaanwijzing zijn echter niet altijd goed afgestemd op de gebruiker, wat kan leiden tot onjuiste testuitslagen. Dit blijkt uit onderzoek van het RIVM naar medisch-diagnostische zelftesten, gebaseerd op door de desbetreffende fabrikanten aangeleverde documentatie. Het gaat om ovulatietesten, bloedglucosemeters voor diabetici en een test voor de geslachtsziekte Chlamydia. Fabrikanten van dergelijke testen zijn verplicht de risico's van hun producten systematisch te signaleren en analyseren. Zonodig moeten zij hun product verbeteren of informatie verstrekken over risico's die samenhangen met het gebruik van het product.

Tekortkomingen zijn gevonden in de manier waarop fabrikanten de risicoanalyse uitvoeren. Zo worden ervaringen met een product en incidenten onvoldoende in de risicoanalyse verwerkt. Daarnaast staan in de gebruiksaanwijzing risico's die niet in de risicoanalyse zijn vermeld maar daarin wel horen te staan. Omgekeerd staan niet alle risico's die volgens de risicoanalyse in de gebruiksaanwijzing moeten staan, er daadwerkelijk in. Verder bleek de opzet van studies onder leken niet altijd geschikt om de bruikbaarheid van het product voor de Nederlandse markt te testen.

Het RIVM heeft de kwaliteit van dossiers van acht medisch-diagnostische zelftesten onderzocht. Van de opgevraagde dossiers voor zogeheten hoogrisicotesten (HIV, prostaatkanker en Chlamydia) is slechts één dossier voor Chlamydiatesten ontvangen en beoordeeld. De totale respons was 57 procent van de in het onderzoek opgenomen fabrikanten. Het onderzoek is uitgevoerd in opdracht van de Inspectie voor de Gezondheidszorg.

Trefwoorden:
IVD, zelftest, dossierbeoordeling, Chlamydiatest, ovulatietest, bloedglucosemeter

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Summary

Major shortcomings were observed in documentation of in vitro diagnostic devices for self-testing, in particular in relation to the analysis and communication of risks. This was concluded in a study performed by the Dutch National Institute for Public Health and the Environment.

An increasing number of people are now using diagnostic devices without having consulted a physician. Incorrect results could be obtained using these devices because they are not always suitable for the user and the instructions for use are not always clear. A similar conclusion was drawn after a previous investigation of over-the-counter medical devices.

In order to assess the availability and quality of technical documentation several types of in vitro diagnostic devices for self-testing were selected (HIV-tests, prostate tumor marker (PSA) tests, ovulation tests, blood glucose meters for diabetics and a Chlamydia test). Several manufacturers of these devices were requested to submit a specified set of documentation.

The response of the manufacturers was low. From fourteen manufacturers included in this study, only eight manufacturers sent in their file. Four manufacturers were excluded from this investigation, as they claimed that the selected test was not a self test or they claimed not to supply the selected test to the Dutch market. Documentation sets of high-risk tests (HIV self-tests and PSA self-tests) were not received. This could be related to the fact that the companies addressed for the high risk devices were all based outside the Netherlands.

Due to the unavailability of documentation of high-risk tests, the results of this investigation could not be extrapolated to all in vitro diagnostic self-tests. Moreover, the results were influenced by the fact that half of the submitted documentation concerned blood glucose meters, which have been widely used for many years, and for which it could thus be expected that the documentation is of better quality than average.

Although almost all assessed files were complete, major shortcomings were observed. For the risk analyses, a considerable number of risks were lacking, e.g. risks related to lay use, the risk of supplying insufficient information and the risk of interfering substances. Furthermore, there was a lack of coherence between the risk analysis and the instructions for use. In only two out of eight files, all residual risks mentioned in the risk analysis were mentioned in the instructions for use, which is the desired situation as the user has to be aware of all residual risks. Moreover in half of the files, less than 50% of the warnings and precautions in the instructions for use were addressed in the risk analysis. Apparently, many precautions and warnings mentioned in the instructions for use were added without any systematic analysis in the risk assessment procedure. The last major shortcoming was observed in updating the risk analysis to account for experiences from post market surveillance and vigilance activities.

The findings of this investigation indicated that a cycle for continuous improvement has not been fully implemented by these manufacturers, which might have implications for patient safety.

Abbreviations

AR	Authorised Representative
DHCI	Dutch Health Care Inspectorate
FDA	Food and Drug Administration (USA)
FMEA	Failure mode and effects analysis
FSCA	Field Safety Corrective Action
HIV	Human Immunodeficiency Virus
IFU	Set of Instructions for Use (i.e. user manual)
IVD	In-Vitro diagnostic Device
IVDD	Directive on In Vitro Diagnostic Medical Devices (EU)
ISO	International Organization for Standardisation
MDD	Medical Device Directive (EU)
NAAT	Nucleic Acid Amplification Test
NB	Notified Body
OTC	Over-The-Counter
PSA	Prostate-Specific Antigen
RA	Risk Analysis
RIVM	Dutch National Institute for Public Health and the Environment (Rijks-instituut voor Volksgezondheid en Milieu)
RVZ	Dutch Council for Public Health and Health Care (Raad voor de Volks-gezondheid & Zorg)

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1 Introduction

1.1 General

Limited information is available about the use and diagnostic value of in vitro diagnostic devices (IVDs) for self-testing. However, the number of diseases for which these so-called self-tests are available has risen and nowadays, self-tests are available on the internet and in drugstores in the Netherlands for approximately 25 diseases and/or disorders (1, 2).

According to a study on self-tests by the Dutch Health Council (Gezondheidsraad), tests should perform in accordance with the following criteria: proven diagnostic value, proven effectiveness, positive risk-benefit ratio, accurate test results when used by lay users and adequate information to users (3). The diagnostic value is determined by examining the results of the self-test in a relevant test group. When the balance between health benefit of a self-test and the risk or cost is favourable, the test could be eligible for use as a preventive measure (3).

Recently, the Dutch Health Care Inspectorate (DHCI) investigated procedures and the method of working of the company MiraTes, and took legal action against this company based on their findings (http://www.igz.nl/actueel/nieuwsberichten/mirates). Furthermore, the RIVM was asked by the DHCI to perform an assessment of 16 files of over-the-counter (OTC) medical devices (IR-thermometers and wound dressings). It became clear that the manufacturers of these devices did not take lay use sufficiently into account. Also an assessment of the technical documentation of several cholesterol self-tests revealed major shortcomings in both the risk analysis and the user information (unpublished results, see annex I). Moreover, several incidents with 'point of care' blood glucose meters – which are similar to blood glucose self-testing devices - were reported to the DHCI (http://www.igz.nl/actueel/nieuwsberichten/bloedglucosemeters). Their technical documentation was assessed and revealed several shortcomings. Due to these combined findings, the DHCI requested the RIVM to perform an assessment of files of several types of IVDs for self-testing to investigate whether the previous findings are applicable to IVDs for self-testing in general.

1.2 Legislation

IVDs are regulated by the directive on in vitro diagnostic medical devices (IVDD) (4). A device for self-testing is defined in the IVDD as *any device intended by the manufacturer to be used by laypersons in a home environment* (4). IVDs for self-testing receive special attention in this directive. Specific requirements for devices for self-testing are (4):

- The information and instructions provided by the manufacturer should be easy for the users to understand and to apply. The suitability of these instructions should be substantiated by studies carried out with laypersons.
- The conformity assessment procedure always requires the intervention of a notified body; self certification is not an option.

Moreover, the Dutch decree on IVDs prohibits to sell high risk devices for self-testing (e.g. HIV self-tests, tumor marker tests) without the intervention of a health care professional (sales channels regulation) (3, 5).

1.3 Aim

The aim of this investigation was to assess the availability and quality of technical documentation of several types of IVDs for self-testing. Specifically, the following questions were to be answered:

- What is the availability of the technical documentation for IVDs for self-testing, as required in the IVDD?
- What is the quality of the technical documentation for IVDs for self-testing?
- Did manufacturers perform studies with lay users to show that the devices are suitable as devices for self-testing?

2 Methods

2.1 Selection of products

An internet search was performed and several chemist's and pharmacies were visited to make an inventory of self-tests available to the Dutch public.
Based on this inventory, in close collaboration with the DHCI, the RIVM selected five product groups. Approximately five manufacturers per product group were selected. The following criteria were applied:

- One or more high risk self-tests and one or more low risk self-tests had to be included.
- Multiple inclusion of the same product, marketed under different brand names, has to be prevented (i.e. own-brand labeling).
- MiraTes self-tests were excluded (MiraTes was under investigation by the DHCI at the time of initiation of this investigation).
- Cholesterol self-tests were excluded, because these tests had already been studied by the RIVM (see 1.1).
- Because incidents with point of care blood glucose meters had been reported to the DHCI and the DHCI has been receiving a considerable number of reports for blood glucose meters for self-testing, blood glucose meters for self-testing had to be included in this study.
- At least one self-test for a sexually transmissible disease had to be included.
- At least one Dutch manufacturer of self-tests had to be included.
- A maximum of two products from one manufacturer.

After selecting the products groups, a limited internet search was performed to obtain more information about these products and the risk associated with their use.

2.2 Request for technical documentation to manufacturers

Manufacturers of the selected self-tests received a letter from the DHCI (see Annex II) with the request to submit documents described in Annex III, points 3 and 6.1 of the IVDD:

- a general description of the product, including any variants planned;
- design information, including the determination of the characteristics of the basic materials, characteristics and limitation of the performance of the devices, methods of manufacture and, in the case of instruments, design;
- the descriptions and explanations necessary to understand the above-mentioned characteristics, drawings and diagrams and the operation of the product;
- the results of the risk analysis and, where appropriate, a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the Directive if the standards referred to in Article 5 have not been applied in full;
- adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available);
- with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used; such data should originate from studies in a clinical or other appropriate environment or result from relevant bibliographical references;
- test reports including, where appropriate, results of studies carried out with laypersons,
- data showing the handling suitability of the device in view of its intended purpose for self-testing;
- the labels and the set of instructions for use (IFU).

Three additional items, not mentioned in Annex III, points 3 and 6.1 of the IVDD, were also requested:
- the post market surveillance procedure;
- the vigilance procedure;
- a copy of the correspondence concerning the conformity assessment procedure of the above-mentioned product between as the manufacturer and the notified body. This should at least include the assessment report of the above-mentioned product by the notified body.

Finally, the manufacturers were requested to supply one (for expensive instruments) or two samples of the product.

On 31 March 2008, the letters were sent to the manufacturers. Both samples and documentation were to be sent directly to the RIVM. On 24 April 2008, the first reminder was sent by the DHCI. The second reminder was sent mid May 2008 by the DHCI and the closing date was 31 May 2008.

2.3 Assessment

2.3.1 Availability of the technical documentation items

Upon receipt of the documentation, an availability check concerning the requested technical documentation items was carried out.
Results were entered in a database (Microsoft Access); 'yes' when documentation was received and 'no' when no documentation was received. The score was changed accordingly, when missing information was received following reminders to the manufacturer.

2.3.2 Assessment of technical documentation

The assessors used the received samples, general description and design information to gain knowledge about the devices. Further assessment was not performed on these three items.
Two assessors reviewed, independently from each other, the technical documentation of each IVD using a checklist (Annex III) and entered the scores into the above mentioned database. As assessors may subject the technical documentation to different interpretations, guidance was written, facilitating objective and consistent assessment (see Annex III). For each IVD the two assessments were compared. Inconsistencies were checked and resolved. A final version was drafted and the assessment was completed. The final assessment scores are presented in Annex IV.

Apart form the review of the contents on the IFU, each IFU was also checked for the presence of the risks, which should be reported to the user in the IFU, based on the results of the risk analysis. Similarly, a check was performed to establish whether all warnings and precautions mentioned in the IFU were addressed in the risk analysis. The coherence was rated as less than 50%, 50-75%, more than 75%, and 100%.

The data on the analytical performance, present in the submitted documents, were assessed using the following analytical parameters (1):
- Specificity is the percentage of people without a condition being correctly identified.
- Sensitivity is the percentage of people with a condition being correctly identified.
- Reproducibility is the extent to which the test gives the same outcome if repeated under the same conditions.

- Accuracy is the extent to which the mean of repeated measurements, conducted on a given sample, approaches the mean of the samples measured by the comparative method designed by the manufacturer.
- Interfering substances are substances, potentially present in the sample to be tested, which can influence the test results.

The specific requirements for the analytical performance of blood glucose meters were derived from the standard EN ISO 15197 Determination of performance criteria for in vitro blood glucose monitoring systems for management of human diabetes mellitus.

3 Results

3.1 Risks of self-tests

Table 1 shows the risks associated with the use of self-tests.

Table 1 Examples of risks of self-tests

In vitro diagnostic self-tests	Risks
General[a]	Diagnostic sensitivity: – No positive result in the presence of the target marker (false-negative result) – Positive result in absence of the target marker (false-positive result) Analytical sensitivity: – Risk that false-negative results are obtained during the period between infection and seroconversion (e.g. HIV). This gives a false sense of safety, potentially promoting risky behaviour. Accuracy : – Accuracy depends on the performance of the test and the ability of a (lay) person to collect the sample and interpret the test results (e.g. Chlamydia, PSA).
Blood glucose meters[b]	– Effect of imprecision of the blood glucose meter can lead to insulin-dosage error. – Use errors (e.g. not enough blood on the test strip, inserting a wrong test strip, inserting the test strip incorrectly, and using expired strips) which are likely to result in incorrect values, potentially followed by an incorrect insulin-dose. – Instrument error (insufficient analytical precision, display failure).
Ovulation tests[c]	One type of ovulation tests determines the fertile time of a woman's menstrual cycle by observing saliva or cervical-vaginal mucus ferning patterns with a hand-held microscope. The following risks were identified for this type of ovulation test: – No identifiable beginning or end of the fertile period can be found with the ferning pattern method. – Insufficient quality and resolution of the microscopes could lead to misinterpretation of the pattern. Additionally, the reading skills of a layperson can lead to misjudgement. – Interference of food, as the ferning pattern is caused by the salt present in saliva.

a. (6-11)
b. (12-15)
c. (16, 17)

More information about self-tests included in this investigation is given in Annex V.

3.2 Selection of products and request for documentation

In close collaboration with the DHCI, the RIVM selected the following five product groups (number of identified products between parentheses):
- HIV self-tests (n = 5)
- Prostate-specific antigen (PSA) self-tests (n = 5)
- Chlamydia self-tests (n = 2)

– Blood glucose meters (n = 4)
– Ovulation tests (n = 4)

Eighteen manufacturers were requested to submit technical documentation. Two of them were requested to submit documentation of two types of self-tests.

3.2.1 Response to the initial request

Two letters were returned to sender, because the address was incorrect. As no other information was available, no further action could be undertaken. One of the two returned letters concerned a manufacturer that was requested to send information on two self-tests.

From the sixteen remaining manufacturers, eight manufacturers responded to the initial request:

– Four manufacturers were excluded from this study:
  - Three manufacturers stated that their medical devices were not available in the Netherlands. These devices were therefore excluded from the study.
  - One respondent stated that the medical device was not intended to be used as a self-test but as point-of-care test. This device is therefore excluded from the study.
– Three manufacturers sent their documentation on time.
– One respondent was no longer the EU representative; therefore the letter was forwarded to the correct EU representative, who responded by sending the requested documentation.

3.2.2 Response after first and second reminder

From eight manufacturers who did not respond to the initial request, four manufacturers sent their documentation after the first reminder.

One respondent stated that they were the importer of the device and not the manufacturer. The letter was forwarded to the manufacturer. The manufacturer did not respond.
One respondent stated that they were not the manufacturer or the authorized representative. The letter was forwarded to the manufacturer. The manufacturer did not respond.
Two manufacturers did not respond at all.

Eventually technical documentation sets of eight manufacturers were received for eight self-tests (Figure 1).

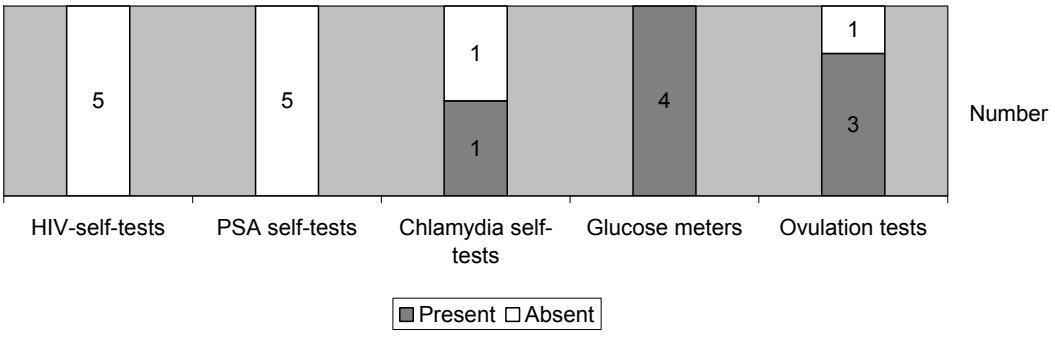

Figure 1 Received documentation

3.3 Availability check

Availability of the requested file items in the received sets of technical documentation was checked. The list of standards, used to show compliance with the essential requirements in the IVDD, was either present as part of the essential requirement checklist or as a separate list. Test reports (analytical performance) and data on handling suitability were requested to evaluate the performance of the test and to investigate whether a test is suitable for use by laypersons. If no correspondence with the notified body was submitted, a declaration of conformity was scored as the correspondence between the manufacturer and the notified body. From one manufacturer, the list of standards, test reports and data on handling suitability were absent. All other files were complete (Figure 2).

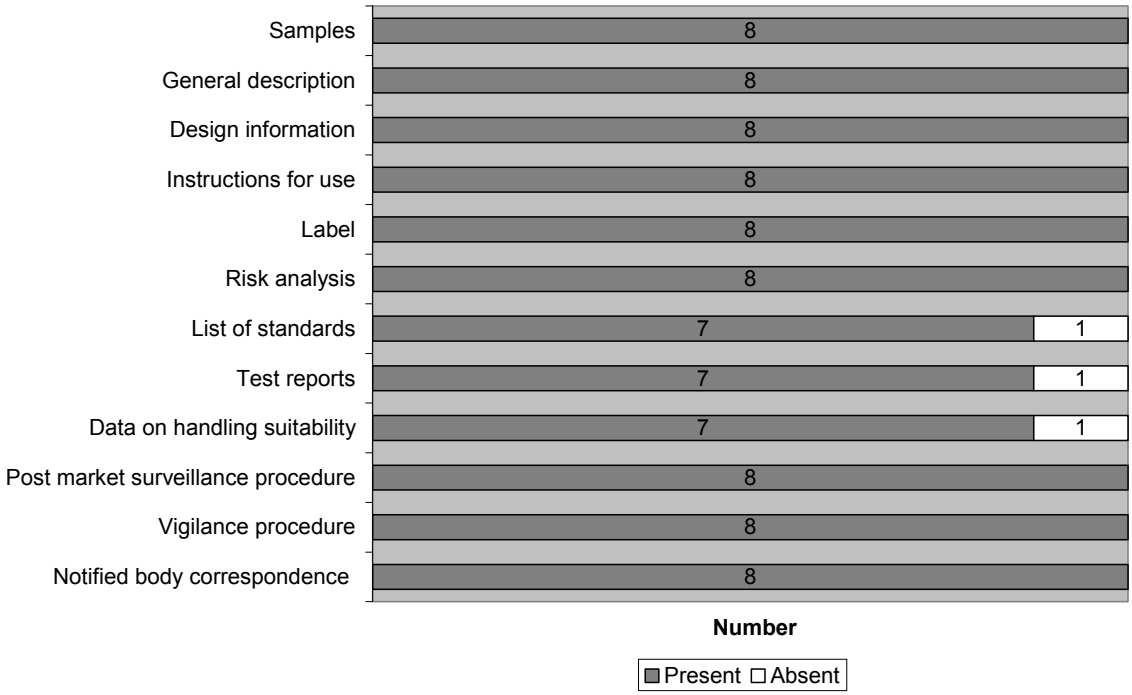

Figure 2 Availability of technical documentation items

3.4 Assessment of technical documentation

The samples, general description and design information were used to gain knowledge about the devices; no further assessment was performed on these items.

3.4.1 Instructions for use

Information for self-testing has to be suitable for laypersons without any specific medical knowledge and/or skills, in a home environment. The following aspects of the instructions for use (IFU) were assessed: editorial aspects of the IFU, content of the IFU, problems/warnings, maintenance/cleaning, and contact information.

Editorial aspects of the IFU

To perform a self-test, clear and simple instructions for use are necessary. Therefore, an assessment of the editorial aspects of the IFU was performed. The results are presented in Figure 3.

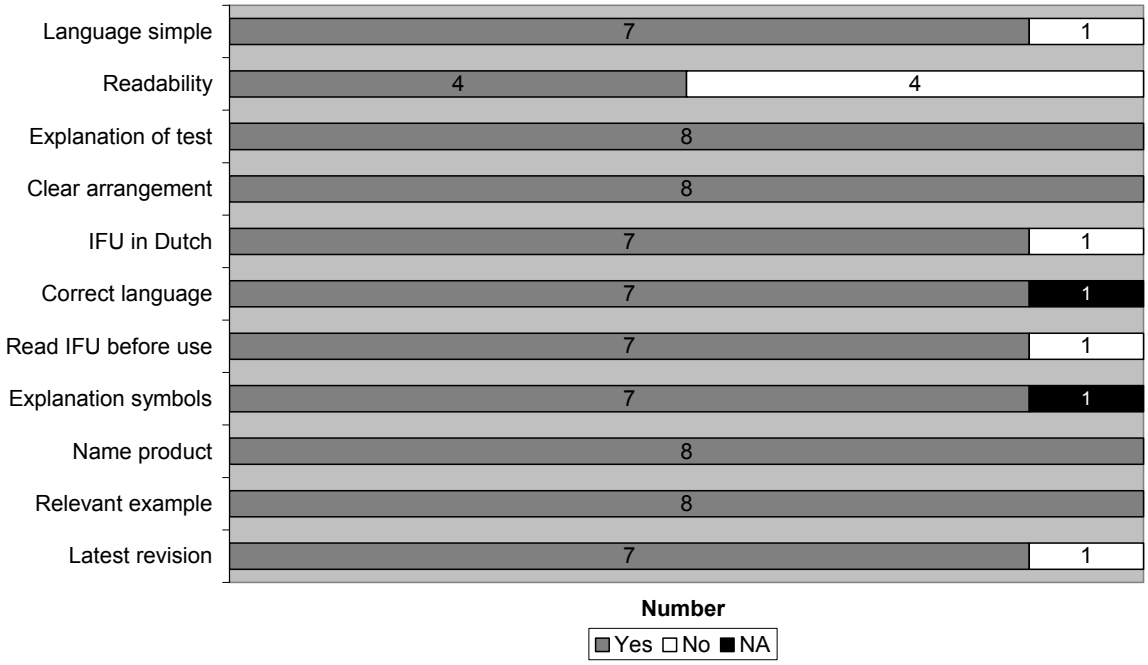

Figure 3 Incorporation of editorial aspects in the IFU (n=8)

For six of the eleven items on editorial aspects, no file showed shortcomings. Readability was insufficient in 50% of the files, as the font size was too small (<9 pt, Times New Roman). Four other aspects were insufficient for a single file. An example of the non-simple language used in one file is given underneath.

Example 1; 'Glucose in the sample reacts with glucose dehydrogenase (reagent component) and then chloride is produced in proportion to the glucose concentration of the blood sample.'

One IFU was not in Dutch; therefore the use of correct language could not be determined and was scored as not applicable. For another IFU, the explanation of symbols was not applicable, because no symbols were used.

Content of the IFU
The results of the assessment on the content of the IFU are presented in Figure 4.

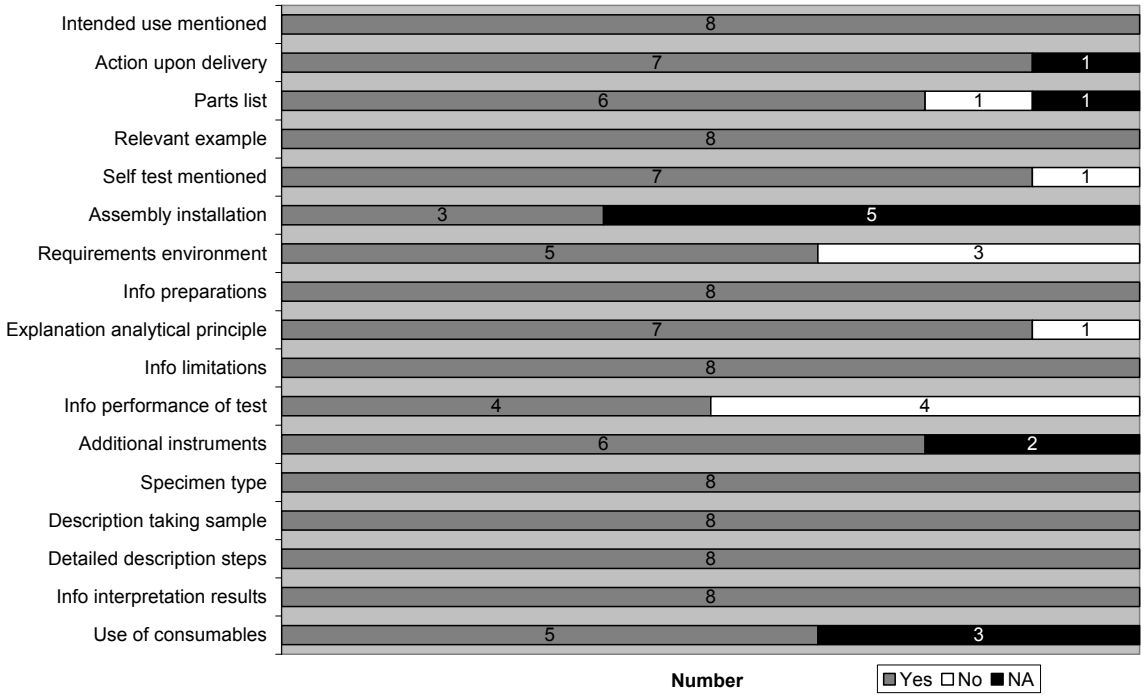

Figure 4 Presence of items in the IFU (n=8)

For twelve of the seventeen items, no file showed shortcomings (n=8), whereas four of these items were not applicable for all files. One product name related to the term self-test, although in the IFU 'self-test' is not explicitly mentioned. This was scored as being insufficient. Five times, instructions for assembly and installation were not applicable, because these tests were ready to use. Consumables could be either test strips for blood glucose meters or a pipette to administer the sample to the device.

Precautions and warnings in the IFU
The IFUs were checked for the presence of precautions and warnings (see Figure 5).

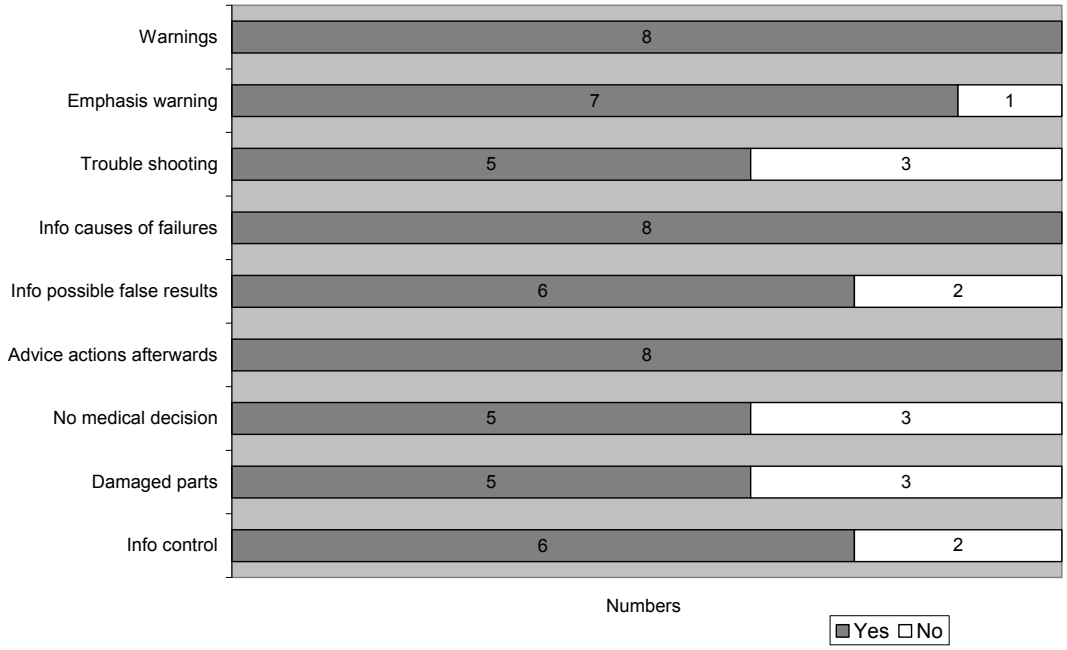

Figure 5 Presence of problems and warnings in the IFU (n=8)

With regard to precautions and warnings, some IFUs were not complete. The missing information can lead to use errors.

Maintenance and cleaning in the IFU
The IFUs were checked for the presence of instructions for maintenance and cleaning (see Figure 6).

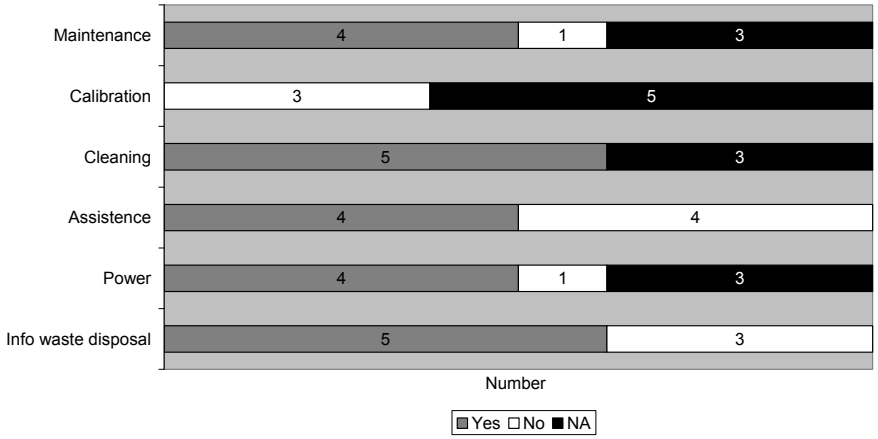

Figure 6 Presence of maintenance and cleaning items in the IFU (n=8)

Three devices were intended for single use, so maintenance and cleaning were not applicable. For other devices, calibration was not mentioned. Several times, checking the performance using a control solu-

tion was mentioned for blood glucose meters. This is, however, not a calibration. According to the information submitted, the manufacturer did not consider calibration to be important. For the ovulation tests and the Chlamydia test, calibration was not applicable and for one blood glucose meter, the IFU stated explicitly that calibration was not necessary. For the three other blood glucose meters, there was no information about calibration.
The four IFUs of the blood glucose meters contained information about the power supply. One other self-test contained a battery, but the power supply was not mentioned in its IFU. It was not clear what to do when the battery does not work or how to replace the battery. For the remaining three devices, power supply was not applicable, because no power was necessary for the operation of the test.
In some IFUs, information about waste disposal was missing. The authors considered information about waste disposal applicable, as one test had a battery and for all tests different chemicals were used.
When information is not clear for a layperson, contact information should be present for assistance. This information was missing in four cases.

Contact information
According to the IVDD (essential requirements 8.7) the IFU must contain the name or trade name and address of the manufacturer. For devices imported into the community intended for distribution in the community, the label, the outer packaging or the IFU shall also state the name and address of the authorized representative (AR) of the manufacturer. Results of the assessment of this aspect are presented in Table 2. The visiting address was considered to be the complete address. A postal address was scored as an incomplete address.

Table 2 IFU; availability of contact information (n=8)

Name and visiting address	Present complete	Present incomplete	NA
Manufacturer	6	2	0
Authorized representative	4	1	3

NA= not applicable

All IFUs contained an address. The visiting address of the manufacturers and AR's were printed on four IFUs. The address of the AR was not applicable for three self-tests, because the manufacturers were based in Europe. Twice the postal address instead of the visiting address of the manufacturer was used and once this was the case for the address of the AR.

3.4.2 Label

Several aspects of the labels of the received self-tests were assessed (see Figure 7).
Almost all labels (n=8) comply with all assessed items. One label does not mention or refer to warnings. This can lead to incorrect use of the self-test which can be prevented by printing warnings on the label.
According to the IVDD, a device intended for self-testing must be labeled 'self-test'. As mentioned before in the paragraph 'content of the IFU', one product has a product name related to the term self-test. However, 'self-test' is not explicitly mentioned on the label and this was scored as not present.

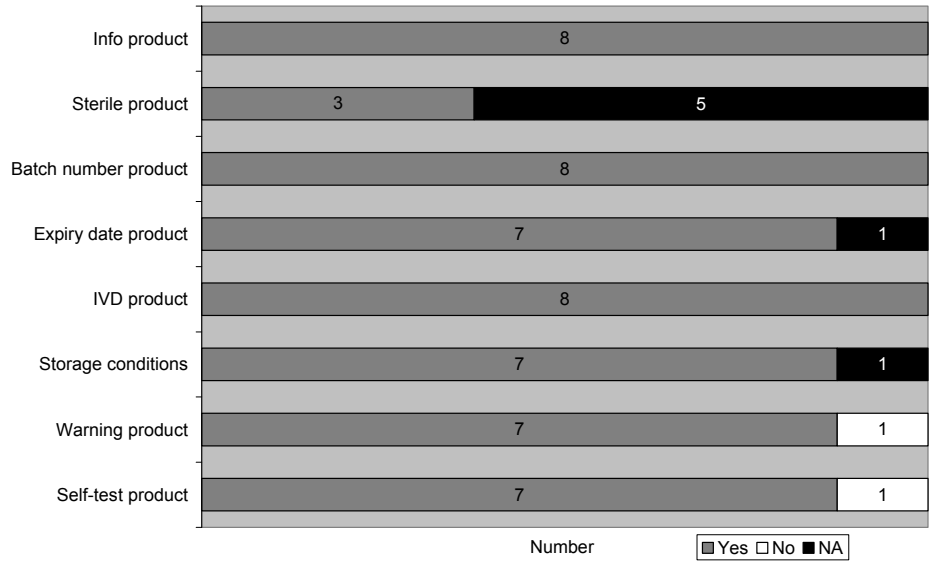

Figure 7 Presence of information on labels (n=8)

Contact information

For devices imported into the community and intended for distribution in the community, the label, the outer packaging or the IFU shall also state the name and address of the AR of the manufacturer. Results of the assessment of this aspect are presented in Table 3. The full visiting address is considered to be the complete address. A postal address was scored as an incomplete address.

Table 3 Label; availability contact information (n=8)

Name and visiting address	Present	Incomplete	Absent	NA
Manufacturer	5	2	1	0
Authorized representative	3	1	1	3

NA= not applicable

Most labels state the address of the manufacturer. According to the IVDD, absence of the address on the label is acceptable as long as it is stated in the IFU, which is always the case. However, in several cases, the address given on the label is not the full visiting address**.**

3.4.3 Risk analysis

Aspects of the risk analysis were assessed as shown in Figure 8. For blood glucose meters, additional aspects, which are not applicable for the other devices (see Figure 9), were included in the assessment.

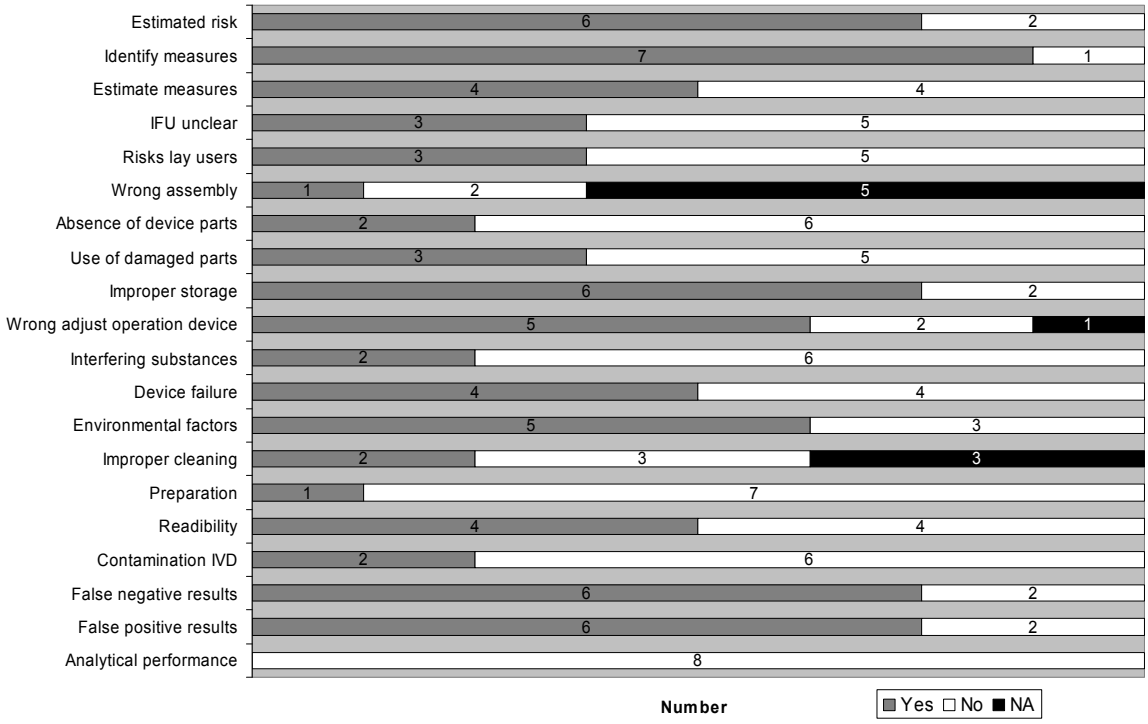

Figure 8 Presence of aspects in risk analyses (n=8)

In general, the risk analyses are of moderate quality. Important aspects as the risk for wrong preparation, interfering substances, risk for using damaged parts, absence of device parts, risks of lay use, unclear IFU, contamination of the IVD, and insufficient analytical performance were not mentioned in more than half of the risk analyses. Seven of the risk analyses referred to the risk management standard EN ISO 14971. One file did not refer to any risk management standard.

Two of the eight risk analyses did not contain information about the estimated risks. One of these risk analyses (for an ovulation test) contained the following remark: 'Wrong result in the test has no effect on the health of the patient. …….Therefore, no further examinations have been carried out by Failure mode and effects analysis (FMEA) or another risk analysis methodology. Although a more thorough risk analysis may reveal interesting information for the quality of the product and the causes of poor quality and its detectability, it would never reveal causes of serious risk for the patient'.

Wrong assembly of the device was not applicable for five self-tests, because these devices consist of one piece. Three self-tests were for single use only, therefore improper cleaning was not applicable for these tests. One of these risk analyses was a brief statement instead of a risk assessment, only addressing use errors.

Most specific aspects of blood glucose meters were addressed in the risk analyses for these devices (see Figure 9). However, only two risk analyses contain the risk for using the wrong strip or using the wrong unit, which can lead to erroneous results.

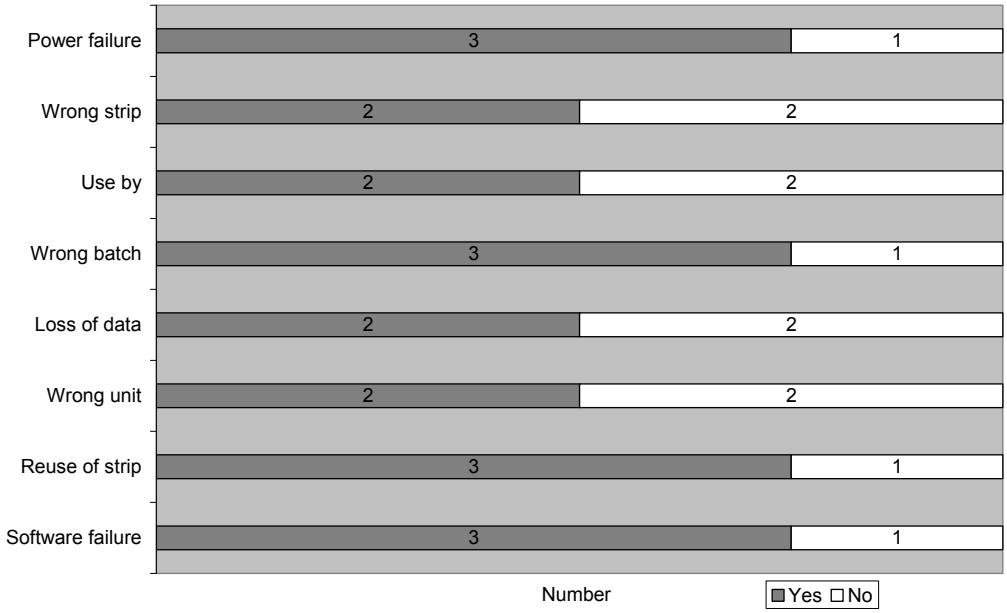

Figure 9 Presence of additional aspects in risk analyses of blood glucose meters (n=4)

3.4.4 Coherence between risk analysis and instructions for use

Mitigation of risks through changes to the design or alarms are preferred over communicating residual risks to the user as warnings and precautions. It was assessed whether these risks to be included in the user information were included in the IFU or on the label. It was also assessed whether the warnings and precautions in the IFU were included in the risk analysis. The results are presented in Table 4.

Table 4 Coherence between risk analysis and instructions for use (n=8)

	<50%	50-75%	>75%	100%	Undeterminable
Risks described in RA, also described in IFU	1	0	4	2	1
Risks described in IFU, also described in RA	4	3	1	0	0

RA = risk analysis
IFU = Instructions for use

In general, most risks described in the risk analyses were mentioned in the IFU as warnings, precaution and /or contra-indications. Vice versa, there was less coherence between the documents.
As stated before (paragraph 3.4.3), one risk analysis did not contain information about risks, so the coherence between this specific RA and IFU is undeterminable. However, there are some risks presented as warnings and/or precautions in the instructions for use. This was scored as < 50% for the coherence between the IFU and the RA.

3.4.5 Post market surveillance procedures and vigilance procedures

The post market surveillance (PMS) procedures and the vigilance procedures were checked for availability of procedures for handling complaints, performing corrective and preventive actions (CAPA) and updating the risk analysis (RA). In addition, the vigilance procedure was checked for availability of the procedure for notifying the competent authority, and for the procedure for recall or Field Safety Corrective Action (FSCA). See Figure 10.

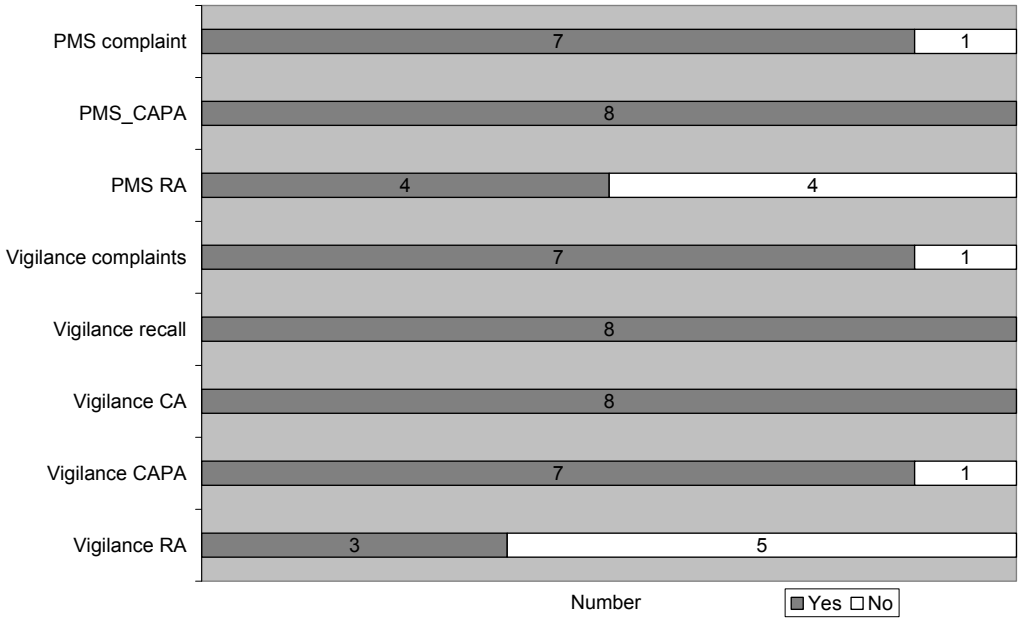

Figure 10 Post market surveillance procedures and vigilance procedures (n=8)

All PMS procedures and almost all vigilance procedures contain information about the CAPA procedure. Only four PMS procedures and three vigilance procedures contain information about updating the risk analysis as a result of PMS and vigilance activities.

In addition, the PMS procedures were also checked for the number of sources used to collect active and/or non-active complaints. All manufacturers used three or more sources to collect experiences. They used both active methods (e.g. customer survey) and passive methods.

3.4.6 Analytical performance and handling suitability

The fertility tests and Chlamydia test are qualitative tests. This means that test results can be either positive or negative. The blood glucose meters are quantitative tests. This means that the results will be presented in units (quantity of glucose in blood). As described in the IVDD (Essential requirements 8.7(h), see Textbox 1) an assessment of the analytical performance of self-tests is compulsory and, must be described in the instructions for use, where appropriate.

Textbox 1 Specific analytical performance according to the IVDD

> ***8.7 Where appropriate, the instructions for use must contain the following parameters:***
> (h) The measurement procedure to be followed with the device including as appropriate*:*
> – *the specific analytical performance characteristics (e.g. sensitivity, specificity, accuracy, repeatability, reproducibility, limits of detection and measurements range, including information needed for the control of known relevant interferences), limitations of the method and information about the use of available reference measurements procedures and materials by the users about the use of available reference measurements.*

The set-up of investigations to determine the analytical performance of a test was assessed, as well as the conditions (e.g. in a laboratory or at home) under which the test was performed.

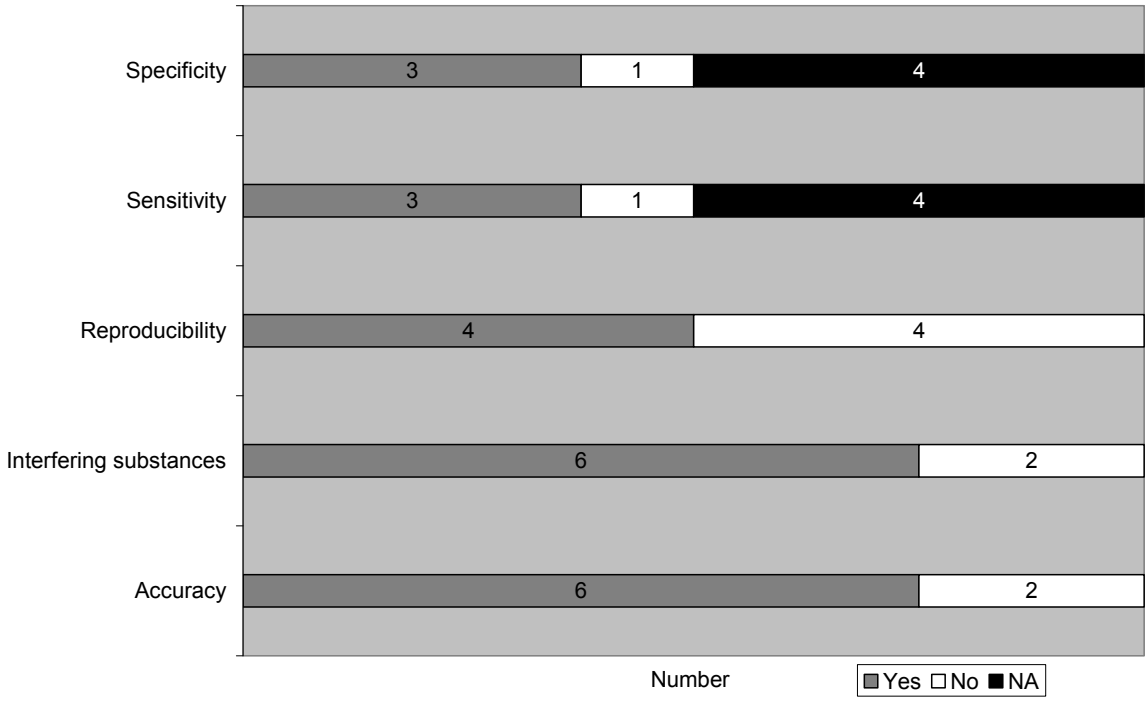

Figure 11 Analytical performance (n=8)

The requirements for the analytical performance of blood glucose meters are described in an international standard (EN ISO 15197). All blood glucose meters met the requirements for the analytical performance in EN ISO 15197. Specificity and sensitivity testing were not assessed for blood glucose meters (n=4) and were scored as not determined (ND).
Lay use has been tested for three blood glucose meters. In these studies, laypersons tested the self-test using their own blood and blood samples were obtained from these patients to be tested using a reference method in a clinical setting. One self-test was tested by technicians in a clinical setting only. The data contained no specific reference to the use of the self-test by laypersons.

From one manufacturer of the other tests, there was no information available to determine the analytical performance of the test, except for information on accuracy and interfering substances. However, the submitted information on accuracy and interfering substances was inconsistent.
Specificity and sensitivity were determined three times. In all cases, samples were tested by lay users with the self-test and samples were analyzed in a laboratory. The number of participants in these studies varied from 76 to 197 persons. In one study, samples were taken by the layperson and a physician and were analyzed by using the self-test and in a laboratory test. The results of the laboratory were comparable with the results obtained by the lay users in the different studies (e.g. specificity and sensitivity results between 95-100%). Overall, these data suggested good correlation between laboratory results and self-test results.

Only half of the files of the investigated tests contained information on reproducibility.

3.4.7 Notified body correspondence

All manufacturers have sent their declaration of conformity certificate. This is in compliance with the IVDD. However, the specifically requested correspondence with the notified body was not submitted by any manufacturer. Two manufacturers submitted the conformity assessment report of the self-test concerned and once a general surveillance audit report (dated 1999) was submitted. Due to the limited information received, no assessment of the correspondence was performed.

4 Discussion and conclusions

4.1 Discussion

General
The response of the manufacturers was low; from the fourteen manufacturers included in this investigation, only eight supplied the requested files. Documentation of high-risk tests (e.g. HIV self-tests and PSA self-tests) was not received, therefore the quality of these files could not be assessed. The results presented in this report are from blood glucose meters, fertility tests and one Chlamydia test. As 50% of the files assessed were for the blood glucose meters, this creates a bias in the results. As blood glucose meters have been widely used for many years and there is an international standard for these devices, it can be expected that the files for blood glucose meters are of better quality than average.

Almost all files that were received were complete. Shortcomings in the documentation were found mainly in the risk analysis (RA); experiences with the product and related incidents were insufficiently incorporated into the RA. The instructions for use were not always clear. Unclear instructions can lead to wrong results and eventually can have a negative effect on the health of the user (e.g. wrong insulin dose). Also the results of lay user studies performed by the manufacturer did not always appear suitable for testing the usability of self-tests for the Dutch market.

The results of the investigation will be discussed in more detail below, in relation to the specific research questions.

What is the availability of the documentation for IVDs for self-testing, which manufacturers should have available?

General
The response of the manufacturers was low; however almost all documentation that was received was complete.

Response
Four manufacturers were excluded from this investigation following the initial request. One manufacturer replied that the selected device was not a self-test but a point-of-care test. Three other manufacturers stated that the selected device was not available to Dutch customers, although the websites did not indicate that. One of these company stated '*This product has not been notified, distributed, or marketed in the Netherlands*'. The response of remaining fourteen manufacturers and their authorized representatives on the request for technical documentation of self-tests was low. Following the initial request, the four excluded manufacturers responded and four other manufacturers or European representatives (57%) responded and sent the requested documentation. For two companies, the letters were returned to sender. Apparently, the contact details of the companies on the internet were not correct, which means that there are no easy means to contact these companies.
After the first and second request, four of the remain eight manufacturers sent their documentation. Two other companies replied that they were not the manufacturer, authorized representative or importer of the device and the letter was forwarded to the manufacturers, who did not respond to the request. Eventually, 86% (n=12) of the included companies responded, although some responses were non-cooperative. One of the companies indicating that they were not the manufacturer of the product was not cooperative and stated: '*I am not interested in this request. We only sell products from other com-*

panies, (...) so please contact the respective manufacturers'. When the DHCI requested the names of the manufacturers, no response was received, but an internet search by one of the assessors provided the address. The request was subsequently sent to this address. Finally, eight sets of documentation were received form fourteen included companies.
No documentation was received from manufacturers of HIV and PSA self-tests. These self-tests are not marketed in the Netherlands through the channels allowed (pharmacies), but the visited websites gave the impression that these products could be ordered from and shipped to the Netherlands.
As it was difficult to find data on the products and the manufacturer and/or distributors on the internet, it is possible that several requests were not addressed to the appropriate company. This could have contributed to the low response. Moreover, the companies addressed for the high risk devices were all based outside the Netherlands. Most of the companies that sent in their information were either based in the Netherlands or the initial contact was made through a Dutch distributor. The apparent reluctance to cooperate with a request of a competent authority and the impossibility to obtain correct contact information on manufacturers and or distributors on internet, are factors that could hamper the surveillance activities of competent authorities.

Availability
Overall, the received documentation was mostly complete. The items test reports, list of standards and data on handling suitability) were each missing once. Because the missing information was limited, it was decided not to exclude the devices concerned from the investigation.

What is the quality of the documentation for IVDs for self-testing, which manufacturers should have available?

General
A major shortcoming was observed for the risk analyses, which were lacking a considerable number of risks, e.g. risk of lay use, the risk of supplying insufficient information and the risk of interfering substances. Another major shortcoming was the lack of coherence between the risk analysis and the instructions for use. In most cases, 75% or more of the risk mentioned in the risk analysis were addressed in the instructions for use, whereas less than 50% of the warnings and precautions in the instructions for use were addressed in the risk analysis of four out of eight submitted files. The last major shortcomings were, updating the risk analysis to account for experiences from post market surveillance and vigilance activities. This indicates that a cycle for continuous improvement has not been fully implemented by these manufactures.

Assessment of the instructions for use and labels
Overall, the **editorial aspects** of the IFUs were assessed to be sufficient. One IFU was not in Dutch, which is in conflict with the Dutch decree on IVDs. The decree states that every IVD marketed in the Netherlands should be accompanied by a Dutch IFU. The IVDD specifically mentions the right of the member states to require the official language of that member state. Half of the IFUs were printed in a type font considered too small (less than 9 pt. Times New Roman). This was always the case for the simple test devices. This is most likely due to the fact that the IFU need to contain a considerable amount of information, whereas the size of the leaflet is too small to print this information in a larger type font. On the other hand, there is no reason why this information cannot be printed on a larger leaflet.

Overall, the **contents** of the IFU showed some shortcomings that can and should be improved. Not all items were applicable for all devices. Some items, mainly information about the performance of the test and requirements for the test environment, were missing. The performance of the tests is mentioned as a part of the instructions for use in the essential requirements in de IVDD. The introductory sentence to

the requirement starts with 'Where appropriate', so it can be argued that it is not appropriate for all the IVDs assessed, especially the qualitative tests. Three out of four devices, for which performance information was missing, were qualitative tests. For these tests intended for lay users, extensive information about the analytic performance might not be necessary. However, there should be basic information about the analytical performance in the IFU, notably the uncertainty. The test environment (e.g. humidity, temperature) is a requirement from the harmonized European Standard EN 592 on the instructions for use for self-test IVDs. Although it is strictly speaking not a requirement in the IVDD, it is an important aspect of the appropriate application of the device.

In general, the majority of precautions and warnings were addressed in the IFUs, although for some items, extra attention would be appropriate. Information regarding the proper function of the device, and warnings not to use the product if damaged refer to situations that can influence the outcome of the test and should always be addressed. This is one of the areas were improvements should be made.
It is remarkable that none of the IFUs of the blood glucose meters contain information about the calibration, although these meters are used frequently for a prolonged period of time. In most cases, checking the meters using a reference solution was mentioned in the IFUs. For this application, this was considered sufficient. When deviations are discovered during these checks, other options (replacement) will be chosen.

Addresses of manufacturers and authorized representatives (if applicable) were present in the IFUs. However, these addresses were not always correct. In several cases, the postal address was given. This is in contradiction with the view of the DHCI that the visiting address should be given. The IVDD and standards on the instructions for use for self-test IVDs (EN 592 'Instructions for use for in vitro diagnostic instruments for self-testing') state that the name and address of the manufacturer shall be given, without any further specification. The standard EN 1041 'Information supplied by the manufacturer of medical devices', although not applicable to IVDs, assumes that the address is the postal address and even indicates that a trade name, postal code and country is sufficient. Apparently, there are different opinions on this subject, which can explain the different choices of the manufacturers.
Most labels contain the applicable addresses. However, the addresses were already mentioned in all IFUs, and the IVDD does not require the addresses to be both on the label and in the IFU. Therefore, the address not being present on the label is not a shortcoming in these cases.

Assessment of the risk analyses

The risk analyses are of moderate quality, as approximately 40% of applicable risks are only mentioned in half or less of the risk analyses. It is remarkable that only three out of eight risk analyses for self-tests addressed the risks related to lay use or unclear IFU. This is consistent with a recent assessment by the RIVM of files of 16 over the counter (OTC) medical devices (IR-thermometers and wound dressings), which revealed that the manufacturers of these devices did not take lay use sufficiently into account (18).
For IVDs, interfering substances have to be considered. Although this has been addressed in some way in most files, it has only been addressed in two risk analyses.
For the blood glucose meters, it was remarkable that the risks of using wrong strips and the expiration date were addressed in only half of the analyses, although these were items addressed in the IFU of the meters and the strips and in the literature survey (Table 1).
Apparently, the RA is not perceived as an integral part of the design process. On the other hand, some issues were addressed in other ways (e.g. in the design) and might no longer be considered risks and thus are no longer included in the RA. Our opinion is that such risks, including the way they are controlled or mitigated, should still be included in the RA.

Coherence between RA and IFU

For most of the devices, the residual risks that are to be addressed in the IFU according to the risk analyses, were addressed in the IFU for 75% or more. However, 100% was achieved in only two files, which is the desired situation, as the user has to be aware of all residual risks.
In nearly all files, 75% or less of the residual risks mentioned in the IFU can be found in the RA. This might be due to the fact that some risk analyses are more focused on the manufacturing process than on the risks of use of the product. Another reason might be that the parties responsible for performing the RA and the IFU are not fully aware of their mutual interest.
Apparently, many precautions and warnings mentioned in the instructions for use and on the labelling were added without any systematic analysis in the risk assessment procedure. This is opposed to sound risk management principles, and indicates that manufacturers have not implemented a cycle of continuous improvement as prescribed by current risk management and quality management systems.
Coherence between residual risks in the risk analysis and the user information is lacking in a considerable number of files and needs improvement. If manufacturers implement a cycle of continuous improvement and ensure that the residual risks in the RA cohere with warnings and precautions in the instructions for use, users, who will read the instructions for use and labelling, will be aware of the hazards identified.

PMS and vigilance procedures
The most striking finding for the PMS and vigilance procedures was that more than 50% did not require an update of the RA following PMS/vigilance reports. Following reports of problems with a device or changes in the state-of-the-art, the RA documents should be reviewed to determine if the failure modes and their level of severity have previously been correctly identified, and if current methods for mitigation are effective. The results of this review could support whether immediate action is required and if additional mitigation steps are needed to improve the quality and safety of the medical device, the accompanying information for the user, or training of user. As the coherence between the risk analyses and the IFUs also shows shortcomings, this is an area that requires improvement, as the RA plays a crucial role in guaranteeing a continuous safe use of the devices. Apart from this, the PMS and vigilance procedures showed no other major shortcomings.

Do manufacturers have studies with lay users available to show that the devices are suitable as devices for self-testing?

General
The analytical performance was not fully investigated for all devices assessed.
None of the studies with lay users for testing the usability of self-tests is performed using the devices as marketed in the Netherlands. The extrapolation of these results to the products as marketed in the Netherlands, including the Dutch IFU, should be elaborated upon.

Analytical performance
It is remarkable that the reproducibility is not determined for 50% of the assessed devices. Additionally, the specificity and sensitivity were not determined for one of the four devices for which it was applicable. Furthermore, the influence for interfering substances was not determined in two cases, although it was considered applicable for all devices.

Suitability testing
For most devices, tests involving lay users have been performed. This is different from the results for the cholesterol self-tests (see Annex 1). However, none of these tests have been performed in the Neth-

erlands. One of the submitted studies was performed in China[1]. The Dutch IFUs were not used. Moreover, the set-up of these tests, the translation of the IFU, carefully reading the IFU first before commencement of the test, and the type of lay users involved might be different from the actual use of the devices (in the Netherlands). In reality, lay users may not even read the complete IFU before performing the test. This behavior should be reflected in the set up of lay use tests. This is especially true for a more complicated self-test, like the Chlamydia test. Therefore, a direct extrapolation of the results of the lay use tests submitted to the Dutch situation is not possible.

Other findings
This investigation relies on the information submitted by the manufacturers and their interpretation of the requested information. Possibly, the manufacturer has more information available than they submitted.

The text of the current IVDD contains the wording 'where appropriate' in several places, e.g. for performing tests with laypersons and providing information on analytical performance. This can lead to differences in interpretation between manufacturers and notified bodies or competent authorities.

The results indicate that the manufacturers have not (fully) implemented a cycle of continuous improvement. This could have a negative effect on patient safety, as risks arising from actual use of a device were not evaluated and possible improvements are therefore not made.

4.2 Conclusions

- The availability of requested information is poor: slightly more than half of the included manufacturers supplied the requested information. The products for which no information was supplied were mainly high risk IVDs from manufacturers based outside the Netherlands.
- Shortcomings in the supplied documentation were mainly related to the risk analysis, the coherence between the risk analysis and the instructions for use and updating the risk analysis to account for experiences from PMS and vigilance activities. This indicates a cycle of continuous improvement has not been fully implemented by these manufacturers.
- For most devices, tests involving lay users have been performed to indicate that these devices are suitable as self-tests, although applicability to Dutch lay users can be questioned.
- Due to the absence of a continuous cycle of product improvement, patient safety cannot be fully guaranteed.

[1]When extrapolating the results of studies performed in China to the European situation, several aspects need to be carefully considered. Are the IFUs as used in these studies equivalent to the ones used in Europe? Are there additional differences between both regions (e.g. cultural, behavioral, clinical test setting) that might influence the outcome of lay user testing?

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References

1. Weijden Tvd, Ronda G, Norg R, Portegijs P, Buntinx F, Dinant G-J, et al. Diagnostische zelftests op lichaamsmateriaal. -Aanbod, validiteit en gebruik door de consument-. http://wwwcvznl/zorgpakket/preventie/indexasp?blnPrint=true&size=K. 2007.

2. Spielberg F, Kassler WJ. Rapid testing for HIV antibody: a technology whose time has come. Ann Intern Med. 1996 Sep 15;125(6):509-11.

3. Gezondheidsraad. Jaarbericht bevolkingsonderzoek 2007. Zelftests op lichaamsmateriaal. Den Haag: Gezondheidsraad, 2007; publicatienr. 2007/26; 2007.

4. IVDD98/79/EC. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices, OJ, L331, 1-37, http://ec.europa.eu/enterprise /medical_devices/legislation_en.htm. 1998.

5. Besluit-IVDD. 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, Dutch Deecree on In Vitro Diagnostics). 2001.

6. Moi H. [Handilab C Chlamydia for home testing is not what it claims]. Tidsskr Nor Laegeforen. 2007 Aug 23;127(16):2083-5.

7. NB-MED/2.5.5/Rec4. Assessment of the sensitivity of In Vitro Diagnostic Medical Devices-guidance on the application of the CTS. 2001.

8. Oberpenning F, Hetzel S, Weining C, Brandt B, De Angelis G, Heinecke A, et al. Semi-quantitative immunochromatographic test for prostate specific antigen in whole blood: tossing the coin to predict prostate cancer? Eur Urol. 2003 May;43(5):478-84.

9. Walensky RP, Paltiel AD. Rapid HIV testing at home: does it solve a problem or create one? Ann Intern Med. 2006 Sep 19;145(6):459-62.

10. Wright AA, Katz IT. Home testing for HIV. N Engl J Med. 2006 Feb 2;354(5):437-40.

11. Frith L. HIV self-testing: a time to revise current policy. Lancet. 2007 Jan 20;369(9557):243-5.

12. Boyd JC, Bruns DE. Quality specifications for glucose meters: assessment by simulation modeling of errors in insulin dose. Clin Chem. 2001 Feb;47(2):209-14.

13. Skeie S, Thue G, Sandberg S. Patient-derived quality specifications for instruments used in self-monitoring of blood glucose. Clin Chem. 2001 Jan;47(1):67-73.

14. Skeie S, Thue G, Nerhus K, Sandberg S. Instruments for self-monitoring of blood glucose: comparisons of testing quality achieved by patients and a technician. Clin Chem. 2002 Jul;48(7):994-1003.

15. FDA-CDRH. Reminder: Users of Blood Glucose Meters Must Use Only the Test Strip Recommended For Use With Their meter. http://wwwfdagov/cdrh/oivd/test-stripshtml, 17 March 2008. 2008.

16. Fehring RJ, Gaska N. Evaluation of the Lady Free Biotester in determining the fertile period. Contraception. 1998 May;57(5):325-8.

17. Guida M, Tommaselli GA, Palomba S, Pellicano M, Moccia G, Di Carlo C, et al. Efficacy of methods for determining ovulation in a natural family planning program. Fertil Steril. 1999 Nov;72(5):900-4.

18. Hollestelle ML, Hilbers ESM, Drongelen AWv. Risks associated with the lay use of 'over-the-counter' medical devices. Study on infrared thermometers and wound care products RIVM letter report 360050002/2007.

19. Skolnik HS, Phillips KA, Binson D, Dilley JW. Deciding where and how to be tested for HIV: what matters most? J Acquir Immune Defic Syndr. 2001 Jul 1;27(3):292-300.

20. Haddow LJ, Robinson AJ. A case of a false positive result on a home HIV test kit obtained on the internet. Sex Transm Infect. 2005 Aug;81(4):359.

21. Linn MM, Ball RA, Maradiegue A. Prostate-specific antigen screening: friend or foe? Urol Nurs. 2007 Dec;27(6):481-9; quiz 90.

22. Mahilum-Tapay L, Laitila V, Warwrzyniak J, Alexander S. New point of care Chlamydia Rapid Test bridging the gap between diagnosis and treatment: performance evaluation study. BMJ. 2007 8 december;335:1190-4.

23. Baan C, Wolleswinkel-van den Bosch J, Eysink P, Hoeymans N. Wat is diabetes mellitus en wat is het beloop? Volksgezondheid Toekomst Verkenning, Nationaal Kompas. 2005; Bilthoven: RIVM, <http://www.nationaalkompas.nl> Gezondheid en ziekte\ Ziekten en aandoeningen\ Endocriene, voedings- en stofwisselingsziekten en immuniteitsstoornissen\ Diabetes mellitus, 7 december 2005. .

24. Slingerland R, Muller W, Dollahmoersid R, Witteveen C, Meeues JT, Blerk vI, et al. Vier op de vijf bloedglucosemeters onder de maat van de TNO-richtlijn. diabetesSpecialist. 2006;20:28-30.

25. Guida M, Barbato M, Bruno P, Lauro G, Lampariello C. Salivary ferning and the menstrual cycle in women. Clin Exp Obstet Gynecol. 1993;20(1):48-54.

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Annex I Conclusions from previous IVD-file assessments

In 2006, RIVM assessed the files of four cholesterol self-tests.
Underneath, a short summary of conclusions.

Do the instructions for use and the labeling of cholesterol self-tests fulfill the current legal requirements?
In general, the legal requirements were reasonably well addressed on the label and in the instructions for use. The instructions for use showed a number of shortcomings. The shortcomings were related to the use of jargon, the absence of a (clear) explanation of the analytical principles and insufficient reference to the possibilities of false-positive or false-negative results. The interpretation of the results could be difficult in cases where the instructions for use did not clearly indicate which action the user should take following certain results. The mentioning of 'self-test' on the packaging should be more clear.

Do the test reports pay sufficient attention to the use of the devices by consumers/lay users?
The assessed test reports were mainly aimed at demonstrating the specificity, sensitivity etc. of the test. The test reports did not contain much information about the user friendliness, the comprehensibility of the instructions for use and the interpretation of the results.

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Annex II Letter for requesting information

Dear <**name of contact person**>,

The Dutch Healthcare Inspectorate is the competent authority in The Netherlands for the Directive on in vitro diagnostic medical devices (98/79/EC), IVDD. Currently, the Inspectorate is conducting a study on the completeness and quality of the documentation of In Vitro Diagnostic devices for self-testing. The actual study will be performed by the Dutch National Institute for Public Health and the Environment (RIVM).

Pursuant to the IVDD I request you to send the following documents of <**name of the product(s)**>. These documents, apart from the post market surveillance and vigilance procedures, are required in Annex 3, points 3 and 6.1 of the IVDD.

- a general description of the product, including any variants planned;
- design information, including the determination of the characteristics of the basic materials, characteristics and limitation of the performance of the devices, methods of manufacture and, in the case of instruments, design;
- the descriptions and explanations necessary to understand the abovementioned characteristics, drawings and diagrams and the operation of the product;
- the results of the risk analysis and, where appropriate, a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the Directive if the standards referred to in Article 5 have not been applied in full;
- adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available);
- with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used; such data should originate from studies in a clinical or other appropriate environment or result from relevant biographical references;
- test reports including, where appropriate, results of studies carried out with laypersons,
- data showing the handling suitability of the device in view of its intended purpose for self-testing;
- the labels and instructions for use;
- the post market surveillance procedure;
- the vigilance procedure;
- a copy of the correspondence concerning the conformity assessment procedure of the above mentioned product between yourself as manufacturer and the notified body. This shall at least include the assessment report of the above mentioned product by the notified body.

In order to avoid the risk of misunderstanding, I would appreciate it if you would clearly mark and tab the above mentioned documents. Please note that these documents will be treated confidentially.

You are kindly requested to send the documentation, marked as confidential and accompanied by two samples of your product (one sample in case of blood glucose monitoring systems), to:

The Dutch National Institute for Public Health and the Environment (RIVM)
Section Medical Technology (PB 50)
IVD-Assessment

P.O. Box 1
NL-3720 BA Bilthoven
The Netherlands

If you prefer to submit the information electronically, you can send it to IVD-assessment@rivm.nl. It would be very much appreciated it if you could forward your information before **<date>**. In case you are not the legal manufacturer or European Authorized Representative for the above mentioned product(s), you are requested to send me the name of the manufacturer or European representative of the product(s) by return.

Furthermore, I would like to add that we may ask for additional documents in case our findings give reason tot do so.

Finally, upon finalizing the investigation, I will inform you regarding the findings concerning your product. If you have any questions regarding this letter or our study, please do not hesitate to contact me at the letterhead address or at LM.d.vries@igz.nl.

Yours sincerely,

The Inspector for medical technology

Annex III Checklist

Assessment checklist

General	Description	Remarks
Manufacturer	Manufacturers name	Name of the company manufacturing the IVD (not the consumables)
Autorised_Rep	Name Authorised Representative	State NA if manufacturer as stated above is also the entity placing the product on the market.
Product_name	Product name	Name of the product as stated on the packaging/label
Product_type	Type of product,1= HIV, 2= Chlamydia, 3= glucose, 4= fertility, 5 = PSA	
Samples_rec	Sample(s) received? 1 = yes, 2 = no, 3 = only one (if not glucose monitoring system)	Two samples were requested (one for blood glucose monitoring systems).
Gen_description_rec	General description received? 1 = yes, 2 = no	General description of the product and its intended use.
Design_info_rec	Design information received? 1 = yes, 2 = no	Design of the product, if applicable illustrated with figures.
RA_received	Risk analysis received? 1 = yes, 2 = no	
List_Standards_rec	List of standards received? 0 = NA, 1= yes, 2= no	List of standards used to show compliance with the essential requirements, either as part of the essential requirements checklist or as separate list.
Reports_rec	Test reports received? 1 = yes, 2 = no	Evaluation/testing of the product to confirm the performance of the test.
Data_suitability_rec	Data on handling suitability received? 1 = yes, 2 = no	Investigation to confirm that the test is suitable for use by laypersons.
Label_rec	Label(s) received? 1= yes, 2 = no	The packaging of the test can be considered as label.
IFU_rec	Instructions for use received? 1 = yes, 2 = no	Are explicit instructions for use received? If it is a simple test, instructions may be printed on the packaging, instead of as a separate insert.
PMS_procedure_rec	PMS-procedure received? 1 = yes, 2 = no	A complaint procedure is also considered to be a PMS-procedure.
Vigilance_rec	Vigilance procedure received? 1 = yes, 2 = no	The vigilance procedure can be incorporated in the PMS-procedure. This is scored as 1 (yes).
NB info rec	Notified body correspondence received? 1 =yes, 2 = no	Correspondence between the manufacturer and AR is requested. Ideally this is the evaluation report of the NB. If Annex IV of the IVDD is used, at least the declaration of conformity needs to e submitted.
A_IFU	Description	Remarks
A_language_simple	Simple language used? 1 = yes, 2 = no	The language used shall be comprehensible for laypersons (no jargon, no scientific terminology).
A_readability	Are the IFU readable (letter size, contrast etc)? 0 = NA, 1 = yes, 2 = no	Font size => 9 pt., Times New Roman. Good contrast between text and its background. Figures should be readable.
A_explanation_of_test	Use of figures and illustrations. 0 = NA, 1 = yes, 2 = no	Consideration shall be given to the following aspects of presentation, where appropriate: Overview of operating elements, flow and Block diagrams, integration and arrangement of text/illustrations, graph emphasis of warnings, examples, diagrams of procedural steps (EN 592:2002, paragraph 4)
A_clear_arrangement	Are the IFU clearly arranged? 1 = yes, 2 = no	Different languages clearly separated. Clear/logic lay-out. When appropriate, IFU shall include a table of content and an index (EN592:2000 paragraph 5.1)
A_IFU_in_Dutch	Are the IFU in Dutch? 1= yes, 2 = no	The instructions for use shall be in Dutch.
A_correct_language	Is correct language used? 1 = yes, 2 = no	Note if spelling is incorrect, improper/incorrect translations or ambiguous Dutch words/phrases.

Assessment checklist (continued)

A_IFU	Description	Remarks
A_read_IFU_before_use	Is the statement 'read IFU before use' mentioned in IFU? 1 = yes, 2 = no	Statement/symbol that the IFU are to be read carefully before use(EN592:2002, paragraph 5.1)
A_explanation_symbols	Is the meaning of (non) EN 980 graphical symbols explained? 0 = NA, 1 = yes, 2 = no	Are the symbols used, which are not harmonized in EN 980, explained?
A_name__address_manufacturer	Is the name and visiting address of the manufacturer given? 1 = yes, 2 = no, 3 = yes, but address incorrect	The address shall be the visiting address. When address is post address, choose 3.
A_name_address_AR	Is the name and address of the AR given, if applicable? 0 = NA, 1 = yes, 2 = no, 3 = yes, but address incorrect	The address shall be the visiting address. When address is post address, choose 3.
A_name_product	Is the name of the product mentioned on the IFU? 1 = yes, 2 = no	-
A_storage_requirements	Are the storage conditions given? 1 = yes, 2 = no	Storage conditions can include requirements for temperature, humidity and (sun) light. For temperature, a symbol can be used.
A_warnings	Are warnings given? 1 = yes, 2 = no	-
A_emphasis_warning	Are warnings/precautions graphically emphasised? 0 = NA, 1 = yes, 2 = no	Does the IFU contain warning symbols or are warning printed in another font than the normal text?
A_intend_use_mentioned	Is the intended use mentioned? 1 = yes, 2 = no	
A_action_upon_delivery	Is information about action upon delivery given? 0 = NA, 1 = yes, 2 = no	Information on how to store, unpack, checking for completeness, not getting wet etc.
A_parts list	Do the IFU contain a list of contents? 1 = yes, 2 = no	-
A_damaged_parts	Is a warning given not to use product when (parts are) damaged? 1 = yes, 2 = no	The product of parts of it shall not be used if visibly damaged (e.g. damaged packaging of sterile product). Although one specific item might be mentioned, the general concept needs to be made clear for a score greater than 1.
A_relevant_example	Are relevant examples used? 0 = NA, 1 = yes, 2 = no	Are examples used to explain the proper execution of the test.
A_selftest_mentioned	Is it clearly mentioned that it is an IVD for self-testing? 1 = yes, 2 = no	-
A_assembly_installation	Do the IFU contain instructions for assembly and installation? 0 = NA, 1 = yes, 2 = no	Do the IFU contain information on how to assemble and install the product and, if applicable, how to check that this is properly done. NA for Blood glucose meters.
A_requirements_environment	Do the IFU contain requirements for the test environment? 1 = yes, 2 = no	Are requirements for the test environment given (e.g. hard level surface)?
A_info_preparations	Do the IFU contain information about preparations prior to operation? 1 = yes, 2 = no	E.g. washing and drying hands
A_explanation_analytical_principle	Are the principles explained in such a way lay users can understand? 1 = yes, 2 = no	Is the analytical principle explained (terminology used is not evaluated, this is correct language).
A_info_limitations	Do the IFU contain information about the limitations of the test (eg. influence of diet, pregnancy)? 1 = yes, 2 = no	E.g. influence of contraceptive pill for fertility testing and aspirin and hematocrit for blood glucose.
A_info_performance_of_test	Do the IFU contain information about the performance of the test (e.g. sensitivity, detection limits)? 1 = yes, 2 = no	-
A_additional_instruments	Are additionally required instruments mentioned (e.g. watch)? 1 = yes, 2 = no	Lancet and lancet device for blood glucose meters.
A_specimen_type	Is the type of specimen to be used mentioned? 1 = yes, 2 = no	E.g. blood (and type of blood sample, e.g. whole blood or plasma) or saliva.

Assessment checklist (continued)

A_IFU	Description	Remarks
A_description_taking_sample	Is the procedure for obtaining a (blood) sample described? 1 = yes, 2 = no	-
A_detailed_description_steps	Are the steps in the procedure described in sufficient detail? 1 = yes, 2 = no	Is the text, together with the illustrations etc., sufficient for the lay user to perform the test?
A_info_control	Do the IFU contain information about checking the proper function of the device? 1 = yes, 2 = no	
A_info_interpretation_results	Is explained how to interpret the results? 0 = NA, 1 = yes, 2 = no	Is it stated how the results need to be interpreted (NA if a system is to check the concentration of blood glucose and the system gives this value)
A_info_waste_disposal	Do the IFU contain information about waste disposal? 0= NA, 1 = yes, 2 = no	-
A_info_causes_of_failures	Do the IFU contain information about what can cause to test to fail? 1 = yes, 2 = no	e.g. application of insufficient sample volume.
A_info_possible_false_results	Do the IFU contain information about the possibility of false negative and false positive results? 0 =na, 1 = yes, 2 = no	For blood glucose monitoring systems, an unexpected result is considered as a false result.
A advice_actions_afterwards	Do the IFU contain information on how to deal with the test results? 1 = yes, 2 = no	It should be clear how the results have to be interpreted.
A_no_medical_decision	Is it mentioned that the user should not make any medical decision based on this test result without consulting a physician? 1 = yes, 2 = no	-
A_latest_revision	Is the date of the latest revision or the revision number of the IFU mentioned? 1 = yes, 2 = no	
A_use_of_consumables	Do the IFU contain information about the compatible consumables ? 0 =NA, 1 = yes, 2 = no	(e.g. test strips for blood glucose meters)
A_maintanance	Is information given about the required maintenance? 0 = NA, 1 = yes, 2= no.	Mostly applicable for glucose monitoring system.
A_calibration	Is information given about the required calibration? 0 = NA, 1 = yes, 2= no.	Mostly applicable for glucose monitoring system.
A_cleaning	Is information given about the required cleaning/disinfection? 0 = NA, 1 = yes, 2= no.	Mostly applicable for glucose monitoring system.
A_assistence	Is contact information for assistance given. 1 = yes, 2 = no	A user should be able to contact the manufacturer or a supplier with questions.
A_trouble_shooting	Is there information on trouble shouting 1 = yes, 2 = no	There should be information on the possible causes if the test does not function properly.
A_power	Is information supplied on power supply, if applicable both mains and batteries. 0 = Na, 1 = yes, 2 = no	For active devices, information needs to be present on(the different types of) power supply.
B_Label	Description	Remarks
B_name__address_manufacturer	Is the name and visiting address of the manufacturer given? 1 = yes, 2 = no, 3 = yes, but address incorrect	The address shall be the visiting address. When address is post address, choose 3.
B_name_address_AR	Is the name and address of the AR given, if applicable? 0 = NA, 1 = yes, 2 = no, 3 = yes, but address incorrect	The address shall be the visiting address. When address is post address, choose 3.
B_info_product	Is information provided on the type and function of the product? 1 = yes, 2 = no	Is the name and type of the product mentioned as well as the function of the product (e.g. Abbott freestyle, glucose monitor)
B_info_clear	Is information clear and explicit? 1 = yes, 2 = no	The language used should not be overly complicated.

Assessment checklist (continued)

B_Label	Description	Remarks
B_sterile_product	Is information on the label about sterility? 0 = NA, 1 = yes, 2 = no	The compete product or parts can be supplied sterile. Is this mentioned on the packaging of the complete product or the component package?
B_batch_number_product	Is the batch/lot number visible on the label? 1 = yes, 2 = no	
B_expiry_date_product	Is the expiry date on the label? 0 = NA, 1 = yes, 2 no	Expiry date is often preceded by symbol (sandglass)
B_IVD_product	Is IVD symbol present? 1 = yes, 2 = no	
B_storage_conditions	Are the storage conditions present? 0 = NA, 1 = yes, 2 = no	Storage conditions can include requirements for temperature, humidity and (sun) light. For temperature, a symbol can be used.
B_warning_product	Are there any warnings/precautions on the label? 0 =NA, 1 = yes, 2 = no	E.g. interfering substances, when not to use product.
B_selftest_product	Is 'self-test' mentioned on the label? 1 = yes, 2 = no	
C_Risk analysis	Description	Remarks
C_1441	IS EN 1441 mentioned or used? 1 = yes, 2 = no.	Is the analysis performed using the old risk management standard EN1441 or is this standard referenced in the risk analysis?
C_14971	Is EN/ISO 14971 mentioned or used? 1 yes, 2 no	Is the analysis performed using the current risk management standard EN ISO 14971 or is this standard referenced in the risk analysis?
C_estimated_risk	Is the risk quantified? 1 = yes, 2 = no	Risks can be quantified, taking into consideration the likelihood, the severity of consequences and the change of detection.
C_risks	Risks, 1 = use errors, 2 = instruments errors, 3 = both, 4 = unknown	Are both use errors and products failures addressed?
C_identify_measures	Are measures taken to minimise risk described? 1 = yes, 2 = no	Design, precautions, warnings.
C_estimate_measures	Is the risk reduction due to measures taken quantified? 1 = yes, 2 = no	Same as for risks, but either likelihood, severity of consequences and the change of detection is reduced.
C_IFU_unclear	Is the risk of unclear IFU addressed? 1 = yes, 2 = no	If it is stated that the IFU needs to be clear for the intended users, this is also acceptable (score 1)
C_risks_lay_users	Is the risk of use by laypersons addressed? 1 = yes, 2 = no	Is the absence of knowledge and skills for the lay user addressed?
C_wrong_assembly	Do the risk analysis contain information about wrong assembly of the device? 0 = NA, 1 = yes, 2 = no	Risk of wrong assembly, incompatibility of parts. NA for Blood glucose meters.
C_absence_of_device_parts	Is the risk of missing parts addressed? 1 = yes, 2 = no	The test system can not function properly if part of the system are absent or if consumables (e.g. lancet) are not present. Although one specific item might be mentioned, the general concept needs to be made clear for a score greater than 1.
C_use_of_damaged_parts	Is the risk of damaged device parts addressed? 1 = yes, 2 = no	Although one specific item might be mentioned, the general concept needs to be made clear for a score greater than 1.
C_improper_storage	Is the risk of improper storage addressed? 1 = yes, 2 = no	Improper storage can lead to deviations.
C_wrong_adjust__operation_device	Is the risk of improper operations or set up of the device? 0 = NA, 1 = yes, 2 = no	E.g. wrong unit for glucose concentration.
C_interfering substances	is the risk of interfering substances addressed? 1 =yes, 2 =no	E.g. salt in saliva sample, aspirin and hematocrit levels for blood glucose. The test result can be influenced by substances in the specimen to be analyzed.
C_device_failure	Is the risk of device failure addressed? 1 =yes, 2 =no, 3 = partially	Device failures can have many causes. Therefore, a fair number of device failures need to be addressed.
C_environmental_factors	is the risk of the influence of environmental factors addressed? 1 =yes, 2 =no	Environmental factor include temperature, humidity, (sun) light, detergents/disinfectant (e.g. alcohol swab)
C_improper_cleaning	Is the risk of improper or no cleaning addressed? 0 = NA, 1 = yes, 2 = no	Reusable devices can require periodic cleaning. The effects of failing to clean need to be assessed.
C_preparation	Is the risk of no/insufficient preparation addressed? 1 = yes, 2 = no	To obtain good results (no interference), hands should be clean and dry.

Assessment checklist (continued)

C_Risk analysis	Description	Remarks
C_readibility	Is the risk of non-readability addressed? 0 = NA, 1 = yes, 2 = no	For glucose monitoring systems, the display should be easily readable. For other tests, the 'readability' of the results should be acceptable for the intended user.
C_glu_ power_failure	Is the risk of power failure addressed? 0 = NA, 1 = yes, 2 = no	NA if not an active device. Power failure can be when connected to mains or when running on battery power.
C_glu_wrong strip	Is the risk of using a wrong type of test strip addressed? 0 = NA, 1 + yes, 2 = no	Glucose monitoring systems are developed for use with a limited number of strips.
C_glu_use_by	Is the risk of using strips after the use by date addressed? 0 = NA, 1 = yes, 2 = no	A test strip is a single use item and should be discarded after use. Reusing can lead to wrong results.
C_glu_wrong_batch	Is the risk of using a wrong batch code addressed? 0 = NA, 1 = yes, 2 = no	Different batches of test strips are calibrated separately. Using a wrong code can lead to improper results. This can be caused by the user or by a manufacturing problem.
C_glu_loss_of_data	Is the risk of losing data addressed? 0 = NA, 1 = yes, 2 = no	Most glucose monitoring systems will have a history of the last measurements.
C_glu_wrong_unit	Is the risk of using different units addressed? 0 = NA, 1 = yes, 2 = no	Blood glucose concentration can be expressed as mmol/l or mg/dL (USA)
C_glu_reuse_of_strip	Is the risk of reusing a strip addressed? 0 = NA, 1 = yes, 2 = no	
C_glu_software_failure	Is the risk of software/control failure addressed? 0 = NA, 1 = yes, 2 = no	Glucose monitoring systems are software controlled, which introduces additional risks, which can not be easily detected.
C_risk_RA_in_IFU	Risks described in the RA are described in the IFU? 1= less than 50%, 2 = 50-75%, 3 = more than 75%, 4 = 100%, 5 = undeterminable	Estimate the percentage of the risks referred to the IFU that is actually present in the IFU.
C_risk_IFU_in_RA	Risks described in the IFU are also described in the RA? 1= less than 50%, 2 = 50-75%, 3 = more than 75%, 4 = 100%	Estimate the percentage of warning in the IFU that are covered in the RA.
C_contamination_IVD	Is the risk of contamination of a reagent addressed? 0 = NA, 1 = yes, 2 =no	Microbiological or chemical contamination (impurity) of reagents of IVDs can cause deviations n the test results. The RA should address this (if applicable).
C_false_negative_results	is the risk of false negative results addressed?	e.g. period between infection and seroconversion in HIV patients
C_false_positive_results	Is the risk of false positive results addressed? 0 =NA, 1 =yes, 2 = no	Ovulation test positive for women during menopause
C_analytical_performance	Is the risk of insufficient analytical performance addressed? 1 =yes, 2 = no	Does the RA consider this risk or does is address the required analytical performance for the intended use?
D_PMS and Vigilance	Description	Remarks
D_PMS_complaint	Is the PMS procedure active (no: only complaints)? 1 = yes, 2 = no	
D_PMS_sources	How many sources are used by the manufacturer? 1 = less than three, 2 = more or equal to three	
D_PMS_sources_txt	Which sources of information for PMS are used? 1 = active, 2= passive, 3 = both	active sources are customer surveys, meeting with users. Passive sources are complaints, media
D_PMS_CAPA	Is the necessity to perform corrective and preventive actions mentioned (refer to)? 1 = yes 2 = no	
D_PMS_RA	Is the need to perform risk analysis mentioned (refer to)? 1 = yes, 2 = no	
D_vigilance_complaints	Is there a procedure present for complaints? 1 = yes, 2 = no	
D_vigilance_recall	Is recall / FSCA part of the procedure? 1 = yes, 2 = no	
D_vigilance_CA	Is notification duty to CA mentioned? 1 =yes, 2 no	
D_vigilance_CAPA	Is the necessity to perform corrective and preventive actions mentioned (refer to)? 1 = yes, 2 = no	
D_vigilance_RA	Is the need to perform risk analysis mentioned (refer to)? 1 = yes, 2 = no	

Assessment checklist (continued)

E_analytical performance	Description	Remarks
E_specificity	Have test been performed to determine the specificity of the self-test? 0=NA, 1=Yes, 2 =No	(Diagnostic) specificity is the percentage of people without a condition being correctly identified using actual samples of body fluids. Answer to be given in %. Use the highest value obtained. Preferably, the specificity given in the user information shall be used. If no data are present, state NA.
E_specificity_txt	Remarks on E_specificity	
E_sensitivity	Have test been performed to determine the sensitivity of the self-test? 0=NA, 1=Yes, 2 =No	(Diagnostic) sensitivity is the percentage of people with a condition being correctly identified. Answer to be given in %. Use the highest value obtained. Preferably, the specificity given in the user information shall be used. If no data are present, state NA.
E_sensitivity_txt	Remarks on E_sensitivity	
E_reproducibility	Have test been performed to determine the reproducibility of the self-test? 0=NA, 1=Yes, 2 =No	Reproducibility is the extent to which the test gives the same outcome if repeated under the same conditions. Answer to be given in %. Use the highest value obtained. Preferably, the specificity given in the user information shall be used. If no data are present, state NA.
E_reproducibility_txt	Remarks on E_reproducibility	Criteria for blood glucose meters; samples <100 mg/dL, than SD <5 mg/dL and samples=>100 mg/dL, than CV% <5%.
E_interfering_substances	Have tests been performed to establish in influence of other substances on the test results? 1 = yes, 2 = no	Extra for blood glucose meter: Hematocrit is the ratio of the volume of red cells to the volume of whole blood. Normal range of hematocrit is approx 45-52% for men and approx. 37-48% for women. Hematocrit levels outside this range are less prevalent. To test the hematocrit sensitivity of the meter whole blood is reformulated with different compositions of red cells and plasma to generate blood samples of desired hematocrit.
E_accuracy	Have test been performed to determine the accuracy of the self-test? 0=NA, 1=Yes, 2 =No	The extent to which the mean of repeated measurements, conducted on a given sample, approaches the blood glucose concentration in the sample as measured by the comparative method designated by the manufacturer (ISO 15197). Results from the reference method (e.g.YSI) compared with the results of the blood glucose meters in one plot (e.g. Clarke's error grid). Criteria total error <20%
E_accuracy	Remarks on E_accuracy	

Annex IV Final assessment score

ID	7	8	9	10	11	12	13	14
Product_type	3	4	4	4	3	3	3	2
Samples_rec	1	1	1	1	1	1	1	1
Gen_description_rec	1	1	1	1	1	1	1	1
Design_info_rec	1	1	1	1	1	1	1	1
RA_rec	1	1	1	1	1	1	1	1
List_standards_rec	1	1	2	1	1	1	1	1
Reports_rec	1	1	2	1	1	1	1	1
Data_suitability_rec	1	1	2	1	1	1	1	1
Label_rec	1	1	1	1	1	1	1	1
IFU_rec	1	1	1	1	1	1	1	1
PMS_procedure_rec	1	1	1	1	1	1	1	1
Vigilance_rec	1	1	1	1	1	1	1	1
NB info rec	1	1	1	1	1	1	1	1
A_Language_simple	1	1	1	1	1	1	2	1
A_readibility	1	2	2	2	1	1	1	2
A_explanation_of_test	1	1	1	1	1	1	1	1
A_clear_arrangement	1	1	1	1	1	1	1	1
A_IFU_in_Dutch	1	1	2	1	1	1	1	1
A_correct_language	1	1	0	1	1	1	1	1
A_read_IFU_before_use	1	1	2	1	1	1	1	1
A_explanation_symbols	1	1	0	1	1	1	1	1
A_name__address_manufacturer	3	1	1	1	1	1	1	3
A_name_address_AR	1	0	0	0	1	3	1	1
A_name_product	1	1	1	1	1	1	1	1
A_storage_requirements	1	1	0	1	1	1	1	1
A_warnings	1	1	1	1	1	1	1	1
A_emphasis_warning	1	1	1	2	1	1	1	1
A_intend_use_mentioned	1	1	1	1	1	1	1	1
A_action_upon_delivery	1	1	0	1	1	1	1	1
A_parts list	2	1	0	1	1	1	1	1
A_damaged_parts	2	1	2	1	1	2	1	1
A_relevant_example	1	1	1	1	1	1	1	1
A_selftest_mentioned	1	2	1	1	1	1	1	1
A_assembly_installation	0	0	1	0	0	1	0	1
A_requirements_environment	2	1	2	1	1	1	1	2
A_info_preparations	1	1	1	1	1	1	1	1
A_explanation_analytical_principle	2	1	1	1	1	1	1	1
A_info_limitations	1	1	1	1	1	1	1	1
A_info_performance_of_test	1	1	2	2	1	2	1	2
A_additional_instruments	1	1	0	1	1	1	1	0
A_specimen_type	1	1	1	1	1	1	1	1
A_description_taking_sample	1	1	1	1	1	1	1	1
A_detailed_description_steps	1	1	1	1	1	1	1	1
A_info_control	1	1	2	1	1	1	1	2

ID	7	8	9	10	11	12	13	14
A_info_interpretation_results	1	1	1	1	1	1	1	1
A_info_waste_disposal	2	1	2	1	1	1	1	2
A_info_causes_of_failures	1	1	1	1	1	1	1	1
A_info_possible_false_results	1	2	2	1	1	1	1	1
A advice_actions_afterwards	1	1	1	1	1	1	1	1
A_no_medical_decision	1	1	1	2	1	1	2	2
A_latest_revision	1	1	1	1	1	2	1	1
A_use_of_consumables	1	1	0	0	1	1	1	0
A_maintanance	1	0	2	0	1	1	1	0
A_calibration	2	0	0	0	2	2	0	0
A_cleaning	1	0	1	0	1	1	1	0
A_assistence	1	2	2	1	1	1	2	2
A_trouble_shooting	1	2	2	1	1	1	1	2
A_power	1	0	2	0	1	1	1	0
B_name__address_manufacturer	2	1	1	3	1	1	1	3
B_name_address_AR	1	0	0	0	2	3	1	1
B_info_product	1	1	1	1	1	1	1	1
B_sterile_product	1	0	0	0	1	1	0	0
B_batch_number_product	1	1	1	1	1	1	1	1
B_expiry_date_product	1	1	0	1	1	1	1	1
B_IVD_product	1	1	1	1	1	1	1	1
B_storage_conditions	1	1	0	1	1	1	1	1
B_warning_product	1	1	1	1	1	2	1	1
B_selftest_product	1	2	1	1	1	1	1	1
C_1441	2	2	2	2	2	2	2	2
C_14971	1	1	2	1	1	1	1	1
C_estimated_risk	1	1	2	1	2	1	1	1
C_risks	3	3	1	4	3	3	3	3
C_identify_measures	1	1	2	1	1	1	1	1
C_estimate_measures	1	1	2	2	2	1	1	2
C_IFU_unclear	1	2	2	2	2	1	1	2
C_risks_lay_users	1	2	2	2	2	1	2	1
C_wrong_assembly	0	0	2	2	0	0	0	1
C_absence_of_device_parts	2	1	2	2	1	2	2	2
C_use_of_damaged_parts	2	1	2	2	1	2	1	2
C_improper_storage	1	1	2	2	1	1	1	1
C_wrong_adjust__operation_device	1	1	2	0	1	1	2	1
C_interfering substances	2	2	2	2	2	1	1	2
C_device_failure	1	2	2	2	1	2	1	1
C_environmental_factors	1	1	2	2	1	2	1	1
C_improper_cleaning	1	0	2	0	1	2	2	0
C_preparation	2	2	2	2	2	1	2	2
C_readibility	1	2	2	1	1	2	2	1
C_glu_ power_failure	1	0	0	0	1	2	1	0
C_glu_wrong strip	2	0	0	0	1	2	1	0
C_glu_use_by	2	0	0	0	2	1	1	0
C_glu_wrong_batch	1	0	0	0	1	1	2	0

ID	7	8	9	10	11	12	13	14
C_glu_loss_of_data	1	0	0	0	2	2	1	0
C_glu_wrong_unit	1	0	0	0	1	2	2	0
C_glu_reuse_of_strip	2	0	0	0	1	1	1	0
C_glu_software_failure	1	0	0	0	1	2	1	0
C_risk_RA_in_IFU	3	4	1	5	4	3	3	3
C_risk_IFU_in_RA	2	1	1	1	2	1	2	3
C_contamination_IVD	1	2	2	2	1	2	2	2
C_false_negative_results	1	2	1	1	1	2	1	1
C_false_positive_results	1	2	1	1	1	2	1	1
C_Analytical_performance	2	2	2	2	2	2	2	2
D_PMS_complaint	1	1	2	1	1	1	1	1
D_PMS_sources	2	2	2	2	2	2	2	2
D_PMS_sources_txt	3	3	3	3	3	3	3	3
D_PMS_CAPA	1	1	1	1	1	1	1	1
D_PMS_RA	2	1	1	1	1	2	2	2
D_vigilance_complaints	1	1	2	1	1	1	1	1
D_vigilance_recall	1	1	1	1	1	1	1	1
D_vigilance_CA	1	1	1	1	1	1	1	1
D_vigilance_CAPA	1	2	1	1	1	1	1	1
D_vigilance_RA	2	2	1	2	1	1	2	2
E_specificity	0	1	2	1	0	0	0	1
E_sensitivity	0	1	2	1	0	0	0	1
E_reproducibility	1	1	2	1	2	1	2	2
E_interfering_substances	1	2	1	1	2	1	1	1
E_accuracy	1	2	1	1	1	1	1	2

Annex V Literature survey

HIV self-tests

HIV counselling and testing is primarily a prevention method to facilitate timely initiation of antiretroviral therapy, and to reduce the risk of onward transmission. Therefore it is important to detect asymptomatic HIV infection in an early stage. In 1986, the idea for home HIV testing was first presented to the US Food and Drug Administration (FDA). The idea was that the availability of a rapid home HIV test would dramatically increase rates of disease detection, especially in communities that had been proven to be difficult to reach. However, there are some disadvantages of HIV self-testing, such as costs and the performance of rapid HIV tests. Not everybody can afford to buy a HIV self-test. Using a home HIV test contains some risks in interpretation of the results. For instance, obtaining a false-positive result can cause emotional distress and a false-negative result could provide a person a false sense of security and potentially promote risky behaviour. HIV tests available on the market are rapid HIV blood tests, oral sample tests, urine sample tests, and a home specimen collection test kit. These tests are all based on detecting HIV antibodies in the different body fluids. With the home specimen collection test kit, a sample can be collected and send to a laboratory for analysis. With the other tests a sample is collected on a test strip followed by adding a buffer. The results can be read after a fixed period. A positive result is obtained when a colored line appears beside the control line (9, 19, 20). In the Netherlands it's prohibited to sell high risk devices, such as HIV self-tests, without intervention of a healthcare professional, e.g. a pharmacist. This means that a lay user can not buy a HIV self-test without the intervention of a healthcare professional.

Prostate-Specific Antigen self-tests

Prostate cancer is the most frequently diagnosed cancer among men in the Netherlands. The progress of the disease is often unpredictable and men can get old without even knowing they have got the disease. A screening method to detect prostate cancer is the prostate–specific antigen (PSA) method. PSA is excreted by cells in the prostate. It causes the liquefaction of congealed seminal fluid and is a normal product of the prostate gland. A small amount of PSA in blood can be detected with several chemical assays. An increase of PSA in blood can be an indication for prostate cancer. When the PSA value is increased, a biopsy of the prostate is taken to confirm the onset of prostate cancer, which is a very unpleasant intervention. Due to the low specificity of the PSA tests, three out of four of these interventions are unnecessary. Another disadvantage of the PSA self-test is that the test does not make any distinction between latent tumors and aggressive tumors (3, 21). A study to determine the handling suitability of a PSA (self-)test is described by Oberpenning et al. (2003). In this study 301 men (156 volunteers and 145 referred patients, mean ages 57 years and 64 years) performed the PSA self-test according to leaflet instructions. The first step in performing the test was to take a blood sample by using a lancet device. Two drops of blood are inserted in the sample chamber of the test system, after which five drops of diluents were added immediately. If PSA is present in the blood sample, it forms a complex with anti-PSA antibody dye conjugate on the membrane strip. This complex migrates by capillary forces and is captured by another fixed anti-PSA antibody, resulting in a pink line. Among the 156 volunteers, 38 (24%) experienced difficulties to produce sufficient amounts of blood from a lancet puncture. The rate of false-positive and false-negative test results increases considerably for PSA concentrations close to the cutoff value. The overall conclusion was that test handling and interpretation was difficult (8). Like HIV self-tests, PSA self-tests are high risk devices, which can not be sold without intervention of a healthcare professional in the Netherlands.

Chlamydia self-tests

Chlamydia trachomatis infection is the most prevalent sexually transmitted bacterial infection worldwide. The infection is common among sexually active women and, when left untreated, it can result in complications such as pelvic inflammatory disease, ectopic pregnancy, and infertility. Chlamydia infec-

tions occur in many cases without any symptoms and therefore remain undetected. With screening programs, these infections can be detected and treated. A test to detect Chlamydia infection is the nucleid acid amplification test (NAAT). This test can only be performed in a laboratory (22) with associated high costs. Self-tests for detecting Chlamydia are available, however the performance and reliability of these tests is rather questionable based on available literature. A study to determine the handling suitability of a Chlamydia self-test is described by Moi [2007]. In this study 157 women were asked to perform a Chlamydia self-test. A second sample was tested in a laboratory. The Chlamydia self-test contains a swab to take a vaginal sample. After the sample is taken, the swab is in contact with reagents for a fixed period. The last step is a short contact between the swab and coloring reagent. The swab shows a dark color when positive. No color appears when the person is negative for Chlamydia. The results showed that sixteen women were positive according to NAAT, four of these were interpreted positive by the self-test and nine as uncertain. Thirteen women who had a negative NAAT interpreted the self-test as positive. Most women had no problem taking the vaginal swab test, however the interpretation of the results was difficult (6).

Blood glucose meters

Diabetes mellitus is a disorder of the glucose metabolism, which can lead to several other complications like hypertension, hart disease, etc. Diabetes patients have abnormally high blood sugar (hyperglyceamia) resulting from insufficient levels of the hormone insulin. Insulin, produced by the pancreas, is involved in the blood glucose regulation. It induces the cellular uptake of glucose from the blood. When insulin levels are too low, blood glucose levels are increased which can lead to the diverse symptoms, like blurred vision, poor wound healing, cardiac arrhythmia, coma and eventually even death. Diabetes is diagnosed when blood glucose levels exceed normal glucose levels. There are two types of diabetes; patients with type 1 diabetes produce no or little insulin, whereas type 2 diabetes patients have problems with their insulin receptors. Patients with type 2 diabetes can control their disease by diet and oral medicines. Patients with type 1 diabetes control their disease by insulin injections, after determining their blood glucose level with a glucose meter (23). Blood glucose meters are quantitative tests and can be used by the patient as a monitoring self-test. The tests detect the glucose level in one drop of blood. The blood drop is placed on a test strip, which contains glucose-oxidase. The glucose in the blood plasma reacts with the glucose-oxidase, which leads to the production of hydrogen peroxide. Due to the peroxide, the coloring agent on the test strip will be activated and the color intensity can be measured with a blood glucose meter. The imprecision of a blood glucose meter can lead to insulin-dosage error, leading to medical complications. According to the International standard EN ISO 15197, a deviation of 20% of the actual blood glucose value is allowed. When the volume of the blood droplet is too small, an unreliable result can be obtained. The glucose meter calculates the glucose concentration according to normal plasma levels. When a patient is anemic, the blood droplet contains more plasma than cells and the risk that the glucose meter miscalculates the glucose concentration increases (24).

Ovulation self-tests

Ovulation self-tests are developed to determine the fertile period in a woman's menstrual cycle and are used as instruments for family planning. There are two types of ovulation self-tests, urine tests and saliva tests. With the urine ovulation test the luteinizing hormone (LH) level can be measured. An acute rise of the luteinizing hormone (LH) is an indication for ovulation (17). For the saliva tests small handheld microscopes have been developed. With this microscope ferning (or crystallizations) patterns can be observed. The ferning is caused by NaCl, which cyclically increases under the influence of the female hormone estrogen. The user of this saliva tests, licks or smears saliva on the plastic slide of the microscope. After drying for a few minutes, the pattern in the saliva can be observed through the lens in front of a light source. When there is a clear ferning pattern the women is fertile. A study to determine the fertile period with a self-test for saliva ferning patterns is described by Fehring and Gaska

(1998). In this study, a small group of 12 female volunteers (age 30-44) were included. They tested their urine for LH, and observed salivary ferning patterns for two menstrual cycles. The results showed that there was a strong correlation between the LH in the urine and the peak in self-observed ferning. Limitations of the saliva (or cervical-vaginal mucus) tests were the non-specificity of the method (clear ferning patterns were found in male saliva (25)) and difficulties to assess the beginning and end of the fertile time based on the ferning patterns (16). Meals before taking a saliva sample can have a profound effect on the ferning pattern, as the salt in saliva is causing ferning.

RIVM

National Institute
for Public Health
and the Environment

P.O. Box 1
3720 BA Bilthoven
The Netherlands
www.rivm.com