



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport



Point-of-care

Point-of-care diagnostic devices

diagnostic

An assessment of safety related technical documentation items

devices



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and the Environment
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Colophon

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Abstract

Point-of-care diagnostic devices An assessment of safety related technical documentation items

The European regulatory framework requires that manufacturers of point-of-care diagnostic devices prepare technical documentation containing data demonstrating the safety and performance of the device.

In a study performed by the RIVM, commissioned by the Health Care Inspectorate of the Netherlands (IGZ), several shortcomings in this documentation have been observed. Shortcomings in the technical documentation do not necessarily mean that the quality and safety of the devices is insufficient.

Point-of-care diagnostic tests are devices that can be used near or at the site of patients for a relatively fast diagnosis. In the majority of the technical documentation sets, the required education of the intended user and the type of health care setting in which the devices can be used, were not clearly specified. An indication like 'for professional use', which was often encountered, is not sufficient.

In addition, important information on the performance of the point-of-care diagnostic devices was not always present. Also, it was often not clear whether these products have been tested in a group of intended users before they were placed on the market. Most manufacturers do offer training to the users of their products when they are on the market.

Furthermore, shortcomings in the risk management process were encountered frequently. To minimize the risks involved in the use of the device, all known or foreseeable risks should be identified, estimated and eliminated or reduced. In the investigation it was found that the technical documentation was often lacking some items. For example, risks that were not eliminated, were not always addressed as warnings in the instructions for use. Also, it was found that manufacturers paid insufficient attention to risk management activities after their product was placed on the market.

Key words: IVD, point-of-care diagnostic medical device, technical documentation, risks, risk management process, performance, for professional use.

Rapport in het kort

Point-of-care diagnostische testen Een beoordeling van technische documentatie items gerelateerd aan veiligheid

Europese regelgeving vereist dat fabrikanten van point-of-care diagnostische testen technische documentatie opstellen waaruit blijkt dat het product veilig en functioneel is. In een onderzoek door het RIVM in opdracht van de Inspectie voor de Gezondheidszorg (IGZ) zijn verschillende tekortkomingen geconstateerd in deze documentatie. Tekortkomingen in de technische documentatie hoeven overigens niet te betekenen dat de kwaliteit en veiligheid van de testen onvoldoende is.

Point-of-care diagnostische testen zijn apparaten die aan het bed van patiënten of in de huisartspraktijk kunnen worden gebruikt zodat relatief snel een diagnose kan worden gesteld. In het merendeel van de technische documentatie sets staat onvoldoende duidelijk gespecificeerd welke opleiding de beoogde gebruiker dient te hebben gehad, en in welk type gezondheidszorginstelling het apparaat kan worden gebruikt. De term 'voor professioneel gebruik', die vaak werd aangetroffen, is niet afdoende.

Daarnaast is belangrijke informatie over de prestaties van de point-of-care diagnostische testen niet altijd aanwezig. Ook is het vaak niet duidelijk of de fabrikant de producten heeft laten testen door beoogde gebruikers voordat ze op de markt komen. De meeste fabrikanten leveren wel trainingen aan de gebruikers van hun producten als deze al op de markt zijn.

Verder zijn er regelmatig tekortkomingen in het risicomanagementproces gevonden. Om de risico's die gerelateerd zijn aan het gebruik van het apparaat gedurende de gehele levenscyclus te minimaliseren, moeten alle bekende of te verwachten risico's worden geïdentificeerd, geschat en geëlimineerd of verminderd. Uit het onderzoek bleek dat een aantal zaken in de technische documentatie ontbraken. Bijvoorbeeld: risico's die niet waren geëlimineerd, waren niet als waarschuwingen in de gebruiksinformatie opgenomen. Verder bleken de fabrikanten onvoldoende aandacht te hebben voor risicomanagementactiviteiten nadat hun product op de markt was gebracht.

Trefwoorden: IVD, point-of-care diagnostisch medisch hulpmiddel, technische documentatie, risico's, risicomanagementproces, prestatie, voor professioneel gebruik.

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Summary

Point-of-care diagnostic medical devices are in vitro diagnostics used by health care professionals to obtain results rapidly near or at the site of a patient. These products can be useful to quickly determine a marker responsible for a certain disease, e.g., at a doctor's office. Following incidents with point-of-care blood glucose meters, an assessment of the National Institute for Public Health and the Environment (RIVM) revealed several shortcomings in the quality of technical documentation items of the involved devices. Therefore, the Health Care Inspectorate (IGZ) of the Netherlands requested the RIVM to perform an investigation into technical documentation of point-of-care diagnostic devices used for other analytes.

The objective of the study was to assess the availability and quality of technical files of point-of-care diagnostic devices available in the Netherlands, focusing on risk analyses and instructions for use (IFU). Special attention was paid to how manufacturers addressed the suitability of the product and the user information for health care professionals who have no or limited professional education in clinical chemistry.

An overview of point-of-care diagnostic devices on the Dutch market was compiled and subsequently, a number of devices with varying characteristics were selected. The manufacturers of the selected devices were requested to submit items of the technical documentation, as required in the In Vitro Diagnostic medical devices Directive (IVDD). Furthermore, they were asked to fill in a short questionnaire on training offered to customers. Upon receipt, the documentation and questionnaires were checked for completeness. For the assessment, a manual was written based on the IVDD, supplemented with items from the Summary Technical Documentation format developed by the Global Harmonization Task Force and from EN-ISO 14971. Eventually, twenty-one technical files of point-of-care diagnostic devices were assessed. The devices themselves were not examined.

One third of items in the documentation was of good quality and one third was of moderate quality. One quarter of the items is either insufficient or absent. The remaining items were not applicable. Shortcomings were found both in the risk analyses and in the user information. Shortcomings in the submitted technical documentation do not necessarily mean that the quality and safety of the devices is insufficient. However, if for example the risk analysis is insufficient or if important warnings or precautions are not included in the instructions for use, this could imply that product safety and safe use of the device is insufficiently guaranteed.

Comprehensive and contra-dictionary phrasing by the manufacturers makes it difficult to determine whether manufacturers pay sufficient attention to the use of their device by health care professionals who have no or limited professional education in clinical chemistry. It is recommended that in their technical documentation, manufacturers of point-of-care diagnostic devices give clear indications of the required educational level of the intended users and of the health care settings.

Only for an HIV test it was possible to establish that the required performance characteristics were addressed. Lack of specific standards hampered a full assessment of the performance evaluation of the other point-of-care diagnostic devices. It was found, however, for several of these point-of-care diagnostic devices that relevant information (e.g., analytical and diagnostic performance) was lacking. In nearly half of the performance evaluation studies, information on the persons who had executed the tests was lacking. We believe that performance tests should be tested by intended users, like physicians or nurses, to check whether the results obtained in a controlled environment can be reproduced in daily practice.

The coherence between the instructions for use and the risk analyses was moderate. Warnings in the user information were not always linked to risks evaluated in the risk analysis. Furthermore, most manufacturers did not include links to risk management activities in the post market surveillance procedure or vigilance procedure. This raises questions on the proper functioning of the risk management process.

The technical documentation of a wide variety of point-of-care diagnostic devices was assessed, differing in application and features. Although some differences in the results were observed, the general outcome was relatively consistent. Products from a large proportion of manufacturers (estimated at least 55%) who market point-of-care diagnostic devices in the Netherlands were included in the study. Therefore, the results of this study are probably indicative for the quality of the technical documentation of the point-of-care diagnostic devices on the Dutch market.

Abbreviations

| | |
|------|--|
| AR | Authorized Representative |
| CAPA | corrective and preventive actions |
| CE | Conformité Européenne |
| CTS | common technical specification |
| EC | European Commission |
| EN | European Standard |
| IFCC | International Federation of Clinical Chemistry and Laboratory Medicine |
| IFU | instructions for use |
| IGZ | The Netherlands Health Care Inspectorate |
| ISO | International Organization for Standardisation |
| IVD | in vitro diagnostic medical device |
| IVDD | in vitro diagnostic medical devices directive |
| NEN | Dutch Normalisation Institute |
| NVKC | The Netherlands Society for Clinical Chemistry and Laboratory Medicine |
| NVVM | The Netherlands Society for Medical Microbiology |
| PMS | post market surveillance |
| POC | point-of-care |
| POCT | point-of-care testing |
| RIVM | Dutch National Institute for Public Health and the Environment |

1 Introduction

1.1 General

In vitro diagnostic (IVD) medical devices are used by a variety of users in various settings. Currently, three groups of IVDs can be discerned: IVDs for use in a clinical laboratory, IVDs used by consumers at home (self-tests) and IVDs used by health care professionals near or at the site of a patient: the point-of-care (POC) devices. POC diagnostic devices offer health care professionals the opportunity to obtain results rapidly near or at the site of a patient. POC tests, also referred to as on-the-spot testing, rapid tests and near-patient tests, can be helpful in life threatening situations, for instance when a patient arrives at a hospital with cardiac distress and immediate and frequent measurements may be necessary. POC diagnostic devices can also be a useful tool at a doctor's office for a quick scan to determine a marker of a certain disease.

In 2007, the Health Care Inspectorate (IGZ) of the Netherlands received several reports on incidents involving POC diagnostic devices for blood glucose level measurements. In these particular cases, blood glucose values measured at the site of the patient were different compared to the values obtained in the clinical laboratory. This has led to administration of unnecessary or wrong doses of insulin, which in some cases resulted in severe hypoglycaemia. Investigation of these incidents revealed that the problems were most probably caused by incorrect use of the POC diagnostic devices rather than by the POC diagnostic devices themselves. During the course of this investigation, IGZ requested the National Institute for Public Health and the Environment (RIVM) to perform an assessment of the quality of technical documentation items of the involved POC diagnostic devices for blood glucose monitoring. Although they could not be linked to the incidents, several shortcomings in the documentation were found. For this reason IGZ requested RIVM to perform an additional study on technical documentation of POC diagnostic devices used for other analytes than blood glucose, in order to assess the quality of technical documentation of POC diagnostic devices in general.

1.2 Legislation

The European directive 98/79/EC (1), also referred to as the in vitro diagnostic medical device directive (IVDD), applies to all in vitro diagnostic medical devices including the POC tests. The directive gives a definition for devices for self-testing and specifies additional requirements for these devices. The directive does not specifically mention POC diagnostic devices. However, in 2006 a standard for quality and competence of point-of-care testing (POCT) was published (2). In this document, POCT is defined as:

'Testing that is performed near or at the site of a patient with the result leading to possible change in the care of the patient.'

1.3 Objective

The objective of the study is to obtain information on the availability and quality of technical files of POC diagnostic devices available in the Netherlands, focusing on the risk analyses and the instructions for use (IFU). During the assessment special attention will be paid to how manufacturers address the suitability of the product and the user information for health care professionals who have no or limited professional education in clinical chemistry.

For this purpose the following questions are to be answered:

1. Are the requested technical files available?
2. What is the quality of the requested technical files, focusing on the following aspects:
 - Do the manufacturers perform the required analytical performance tests to determine the analytical reliability of the device, as referred to in various reference documents?
 - Are the IFUs sufficiently adapted to health care professionals who have no or limited professional education in clinical chemistry?
 - Is this aspect sufficiently addressed in the risk analyses of the POC diagnostic devices?
 - Is there sufficient coherence between the risk analyses and the IFUs of the POC diagnostic devices?
 - Do the manufacturers pay sufficient attention to active collection of field experiences and improvement of their products in their post-market surveillance (PMS) and vigilance procedures?
3. Do the manufacturers and/or distributors offer training to the users of their POC diagnostic devices?

2 Methods

2.1 Selection of POC diagnostic devices

For the purpose of this investigation the following definition for POC diagnostic devices has been formulated in collaboration with IGZ:

'point-of-care diagnostic devices are in vitro diagnostic devices and equipment to be used outside the clinical diagnostic laboratory by health care professionals who have had no or limited professional education in clinical chemistry (self-tests are excluded).'

For the selection of POC diagnostic devices eligible for the study, RIVM checked the websites of suppliers in the Netherlands and consulted experts from the Netherlands Society for Clinical Chemistry and Laboratory Medicine (NVKC) as well as from the Netherlands Society for Medical Microbiology (NVMM). This resulted in the identification of the majority of manufacturers (estimated at least 90%) who market POC diagnostic devices in the Netherlands.

Subsequently, a non-exhaustive overview was compiled of POC diagnostic devices of these manufacturers. RIVM, in consultation with IGZ, selected POC diagnostic devices for inclusion in the study. To obtain an overall picture, the selection included a wide variety of techniques, types of markers (e.g., markers for infections, diabetes markers), and types of specimens (e.g., blood, urine). POC diagnostic devices measuring one type of marker or multiple types of markers (multi-analysers) were included. Products that had already been subject of previous RIVM studies (e.g., blood glucose meters) were excluded from the selection.

Eventually, approximately 70% of the identified manufacturers or their authorized representatives (ARs) (n=25) were requested to submit the technical documentation of 26 products.

2.2 Request for technical documentation

In September 2009, IGZ sent a letter to all manufacturers or their AR requesting specified parts of the technical documentation of the selected POC device (Appendix 1). These items are required according to Annex 3, point 3 of the IVDD (1), whereas the need for PMS and vigilance is mentioned in point 5. For multi-analysers technical documentation of one type of reagent or assay was requested.

In addition, the manufacturers were asked to fill in a short questionnaire regarding training offered to customers (Appendix 2). Within one week after receipt of the request, the manufacturers had to submit contact details of the person in charge of supplying the requested information. The manufacturers were asked to submit the information to the RIVM within six weeks.

Upon receipt, RIVM checked the documents for completeness. If the submitted documentation and/or questionnaire was incomplete, RIVM sent a request for additional documentation to the contact person.

If a manufacturer did not respond to the request, IGZ sent a reminder. The deadline for submission was 30 June 2010.

2.3 Exclusion

A manufacturer or POC device was excluded from the study if at least one of the following issues was applicable:

- The manufacturer refused to submit available documentation¹
- POC device was not marketed in the Netherlands
- POC device was not yet CE marked
- IVD was not used in a point-of-care setting in the Netherlands.

2.4 Assessment of technical documentation

2.4.1 Availability of the technical documentation items

RIVM checked the received technical documentation and questionnaire for completeness and entered this information in a database (Microsoft Excel). The score was 'present' when documentation was received and 'absent' when no documentation was received. For some items, e.g., sterilisation, the option 'not applicable' could be chosen. If additional documentation was received, the scores were adjusted accordingly.

2.4.2 Assessment of the quality of the technical documentation items

Two assessors reviewed, independently from each other, the technical documentation of each POC device and the questionnaire and entered the scores into a database (Microsoft Access). As assessors may subject the technical documentation to different interpretations, a manual was written based on the in vitro diagnostic medical device directive (IVDD(1)) (annex I, point 8; annex III, points 3 and 5), supplemented with items from the Summary Technical Documentation format developed by the Global Harmonization Task Force (3), facilitating objective and consistent assessment and EN ISO 14971(4) (see Appendix 3 and 3A). For each product, the two assessors compared their scores and resolved any inconsistencies.

A selection of the performance characteristics mentioned in the IVDD (1), the common technical specifications (CTS (5)) and several standards (4, 6, 7) were used for the assessment of the performance evaluation studies.

The directive only presents a list of examples of performance characteristics. In most standards it is not specified which performance tests are required for the performance evaluation of the POC diagnostic devices concerned. Because international regulation and standardisation is limited, an inventory was made of the types of performance characteristics that were evaluated by the manufacturers and of the reference documents that were used for the performance evaluation. The complete assessment scores are presented in Appendix 4.

¹ Competent authorities of member states where these manufacturers are located will be informed about their identity.

Risk management should be a continuous process, described as a set of repeatable steps throughout the entire life cycle of medical devices (4). The coherence between the risk analysis and the IFU and label is a useful tool to obtain an indication of the quality of the risk management process of the manufacturer. For this study the IFU and labels of the POC diagnostic devices were assessed on residual risks² and/or hazards mentioned in the risk analysis. Vice versa, the risk analyses of the POC diagnostic devices were assessed on risks underlying the warnings, precautions and contraindications mentioned in the IFU or on the label.

² A risk, remaining after risk control measures have been taken, is called a residual risk (NEN-EN-ISO 14971:2009).

3 Results

3.1 Selection of POC diagnostic devices

During selection of POC diagnostic devices eligible for this study, several problems were encountered:

- An overview of POC diagnostic devices marketed in the Netherlands was not publicly available.
- Products presented in documentation or on websites of manufacturers or suppliers represented in the Netherlands were sometimes not (yet) CE marked and not (yet) on the Dutch or European market.
- Devices recommended for POCT were not always used as such in the Netherlands.
- NVMM suggested a number of microbiological rapid tests used in the clinical diagnostic laboratory, which were also suitable for POCT. The actual POC use of these devices in the Netherlands could not be confirmed beforehand.

These uncertainties caused the need for replacement of some products initially selected for this study by other POC diagnostic devices from the same manufacturer.

The tests selected were considered to be POC diagnostic devices based on a diversity of phrasings encountered in the information about these devices available on websites (see Textbox 1).

Textbox 1. Examples of phrases indicating the potential for POC use

"...in a variety of settings, including physician's offices..."
 "...clinical and non-clinical settings..."
 "...for any medical environment..."
 "...in your office or at your patient's home..."
 "...on-the-spot-testing..."
 "...while your patients wait..."
 "...by any physician or medically trained person..."
 "...available in minutes for rapid follow-up..."
 "...even with non-laboratory personnel..."
 "...does not require specially trained people..."

Eventually, twenty-five manufacturers or their ARs were requested to submit the technical documentation of 26 products.

3.2 Response of manufacturers or ARs

All the approached manufacturers or their ARs (n=25) responded. Based on the information they provided, seven products were excluded for the following reasons:

- Five devices were not or no longer on the Dutch market;

- One device appeared to be a POC device (advertising) but was intended for laboratory use only;
- One test was not yet CE marked.

In three cases, the excluded product could be replaced by another product from the same manufacturer. In total, 22 devices were included in this study.

Ten sets of technical documentation were received upon the initial request; the other twelve technical files were received after the second request.

This left 22 products of which the completeness of the documentation was checked. In one case, the manufacturer refused to submit several parts of the requested documentation (e.g., complete risk analyses, PMS procedure, vigilance procedure) and therefore this manufacturer was excluded from the study as well.³

Finally, 21 technical files from 20 manufacturers could be assessed (Figure 1). However, some of them were incomplete at first. In these cases additional information was requested from the manufacturer or AR.

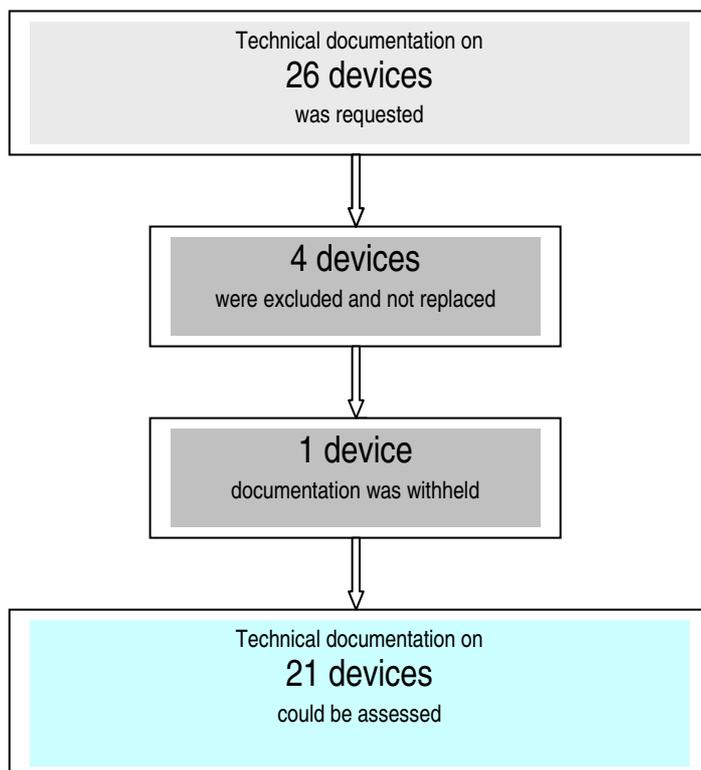


Figure 1. Number of technical files assessed

As shown in Table 1, the technical documentation comprised a wide variety of POC diagnostic devices with various characteristics. Three types of measurements were identified: qualitative, quantitative and semi-quantitative. Qualitative tests are intended to detect the presence or absence of a marker in a specimen. Quantitative tests are intended to determine the amount or concentration of a marker in a specimen. With semi-quantitative tests it is possible to screen specimens on certain markers in a certain concentration range.

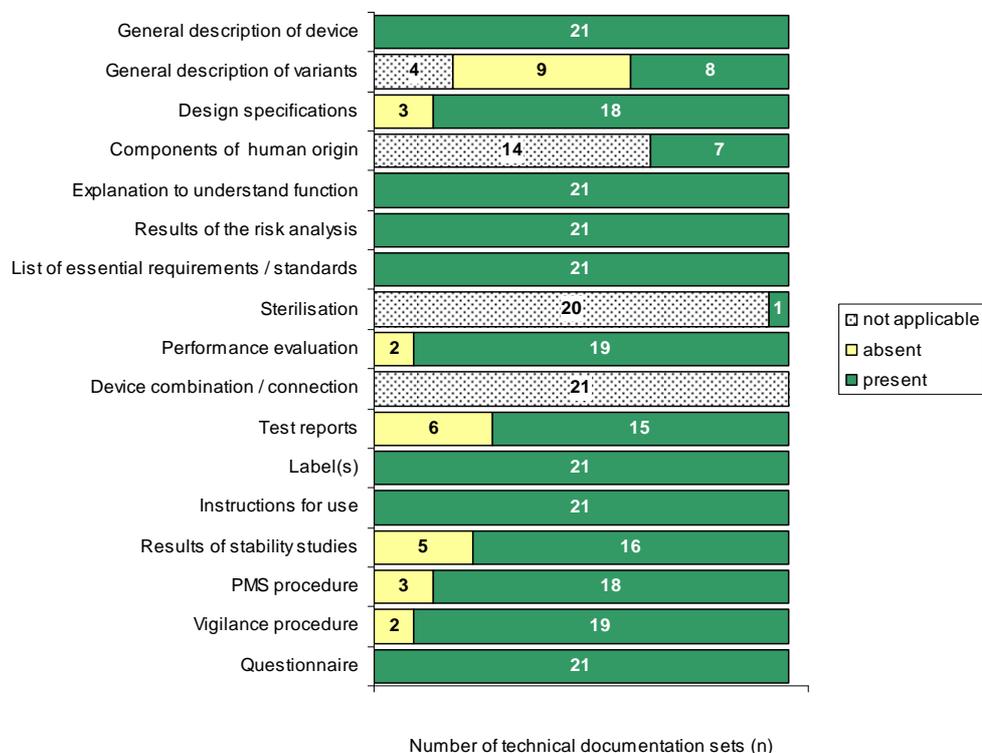
³ The competent authorities of the member state where this manufacturer is located will be informed about the identity of the company.

Table 1. Characteristics of the devices of which the technical documentation was reviewed

| Substance to be measured | Type of measurement | Specimen | Number of devices |
|---|---------------------|--------------------------------------|-------------------|
| Faecal occult blood (FOB) | qualitative | faeces | 1 |
| Diabetes Marker HbA1c | quantitative | blood | 1 |
| C-reactive protein (CRP) | quantitative | blood, serum, plasma | 1 |
| Cardiac Marker h-FABP | qualitative | blood, serum, plasma | 1 |
| Allergy specific IgE | qualitative | blood | 1 |
| Epstein Barr Virus (EBV) IgM antibodies | qualitative | serum | 1 |
| HIV-1/2 antibodies | qualitative | blood, plasma, saliva | 1 |
| Chlamydia | qualitative | endocervical swab/ cytology brush | 1 |
| Influenza A & B | qualitative | nasal wash swab/ throat swab | 2 |
| Lipids cholesterol glucose creatinin | quantitative | blood | 3 |
| Multi analytes (e.g., blood gas, cholesterol) | quantitative | blood, serum, plasma | 6 |
| Multi analytes (e.g., albumin) | semi-quantitative | urine | 2 |
| | | Total | 21 |

3.3 Availability of requested documents

Upon receipt of the technical files from the manufacturers, their completeness was checked (Figure 2).

**Figure 2. Availability of the requested technical documentation**

In all files, the general description, the explanation to understand the function of the device, the results of the risk analysis, the list of essential requirements, the label(s), the IFU and the questionnaire were present. The subject of the test reports varied from clinical studies to the quality of transportation of a device or electrical safety of the device.

Not every file was complete, which was in some cases due to misinterpretation of the request by manufacturers. For instance, some manufacturers did not send the results of the stability studies of the test strips and/or reagents and stated that these studies were not applicable for the POC diagnostic device. However, information on the total test system, meaning the POC diagnostic device including test strips and reagents, was requested.

In some cases an item was not applicable, for example:

- The item 'general description of variants' was scored as not applicable if the technical file contained a statement by the manufacturer that there were no variants of the devices available.
- For none of the POC diagnostic devices a combination with other medical devices was applicable. For the assessment, POC diagnostic devices including test strips or test cassettes were considered as one device.

An overview of the complete availability scores is presented in Appendix 4, Table A1.

3.4 Assessment of documentation content

The identification numbers of the notified body were available in those cases where the device was on list A or B of the IVDD(1) (e.g., HIV-testing) or when the product or a comparable variant was also suitable for self testing.

The quality of the technical documentation was determined by assessment of the general description of the device, the general description of variants, the design specifications, information on components of human origin, results of the risk analysis, label(s), IFUs, the PMS procedure and the vigilance procedure.

Figure 3 shows the overall results of the quality assessment. The results of the performance evaluations are presented in Table 2 (see paragraph 3.4.5).

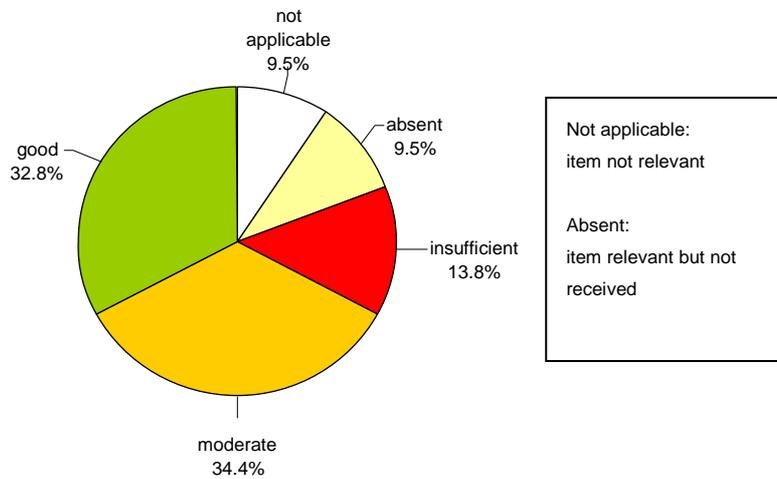


Figure 3. Overview of quality of items in technical files of POC diagnostic devices

The documents on explanation of the function of the device, list of essential requirements/standards, information on sterilisation, test reports and results of stability studies were used as background information. No quality assessment was performed on these items because this was outside the focus of the study. An overview of the complete assessment scores is presented in Appendix 4, Table A2. In the subparagraphs below, the assessment is described in more detail.

3.4.1 Application and materials

A clear description of the device is required, including information on variants (if applicable), the design specifications and the materials used. The results of the assessment are presented in Figure 4.

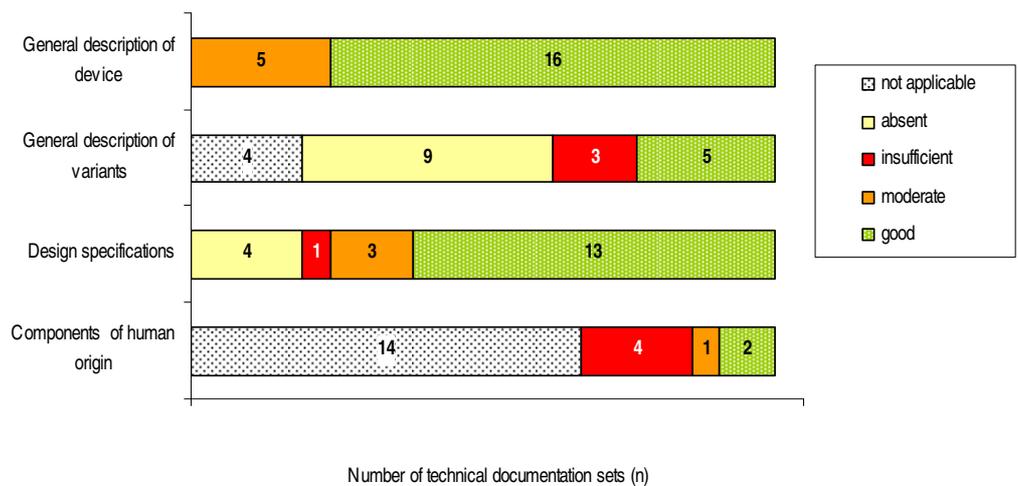


Figure 4. Quality assessment of the technical files regarding application and materials

More than half of the general descriptions and design specifications were complete and scored as good. However, some items were scored as moderate or insufficient because not all issues were addressed in the technical files, for example:

- The physical description of the device or a description of the intended users was lacking in some general descriptions.
- Some files did not contain information on variants like size, colour, model no., etcetera.
- Design specifications like the design drawings, etcetera, were lacking in several cases.
- In some cases, information regarding components of human origin, like information on the origin of the material, etcetera, was lacking.

In the general description, a variety of intended users was mentioned by the manufacturer, as shown in Textbox 2.

Textbox 2 Intended users of POC diagnostic devices

"Professionals"
"Laboratory personnel"
"Users with various levels of work experience and educational background"
"Healthcare practitioners"
"Only for use by an agent of a clinical laboratory"
"Laboratory professionals"

3.4.2 Risk analysis, labels and instructions for use

An important part of the technical documentation is the risk analysis. In the risk analysis the manufacturer should address all the risks that may arise from the design, manufacturing and use of the device and specify the measures that have been taken to prevent or mitigate risks of the device during its entire lifecycle. For the use of the device, the label and the instructions for use should be suitable for the intended users and should contain all the necessary information for the safe use of the devices, including warnings, precautions, storage conditions, etcetera. Results of the assessment of the risk analysis, labels and instructions for use are shown in Figure 5.

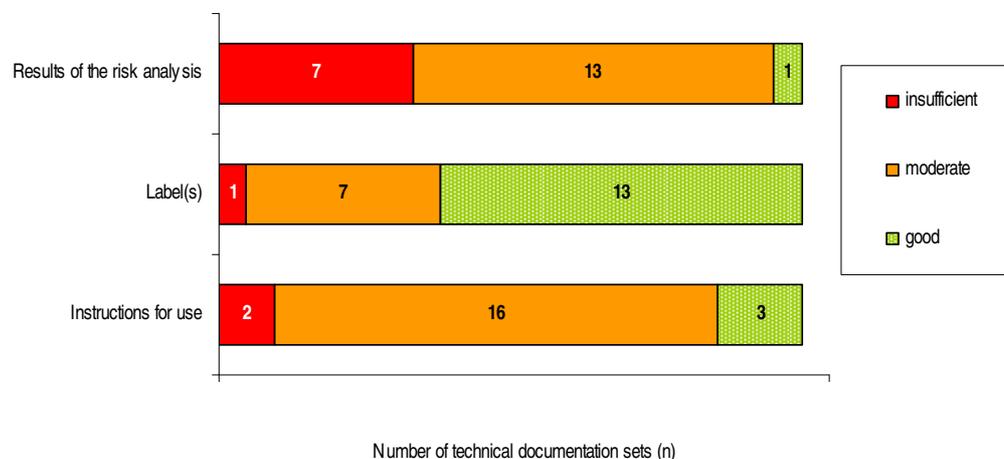


Figure 5. Quality assessment of the technical documentation regarding risk analysis, labels and IFU.

Risk analysis

Only one risk analysis was scored as good (Figure 5). Although more than half of the risk analyses contained information on important items like action taken to reduce or eliminate risks, they were scored as moderate because not all applicable categories of foreseeable hazards were addressed. The risk analyses that were scored as insufficient lacked information on several items (e.g., whether residual risks/hazards were justified in relation to anticipated benefits).

Labels

More than half of the labels were of good quality (Figure 5). Several labels were scored as moderate because they did not comply with all the essential requirements described in the IVDD (1). A shortcoming frequently encountered was a PO Box number printed on a label instead of the visiting address of the manufacturer. One label was scored as insufficient because no standardised symbols were used and the symbols used were not explained on the label. Moreover, the lot number and expiry date were missing on this label.

For one product, two box labels were received. One box label was from the manufacturer and one from the European AR. A striking difference between the two labels was the use of symbols. On one of the labels, the symbols 'keep away from sunlight' and 'consult instructions for use' were present, while these symbols (or text) were lacking on the other label. Moreover, one box label was labelled with the name of the European AR as if it was own-brand labelling, i.e., the European AR became the manufacturer. However, on the label the name and address of the manufacturer and European AR were both printed, according to essential requirements of Annex I, point 8.4a of the IVDD (1).

IFU

The majority of the IFUs were a copy or scan of the original and in some cases consisted of a compressed file. Therefore, their readability in terms of layout, e.g., font size, size of the pictures, could not be assessed.

During the assessment it became clear that not all essential requirements were applicable for every device and not all requirements were formulated specifically enough to be usable as an assessment criterion. Therefore, some essential requirements were further specified for the purposes of the assessment, for example:

- The IVDD (1) mentions that precautions are to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, etc. However, as this list is not exhaustive and aspects such as temperature, humidity, etc. may also influence the performance of the device, they were therefore scored as part of this requirement;
- The name or trade name and address of the manufacturer must be on the label and in the IFU, however it is not specified whether a PO box number is sufficient or not. Neither the IVDD (1) nor the European standards concerning IVDs give specific information regarding this issue. However, according to the guidance in the European Standard EN 1041 (8) for medical devices: 'the full postal addresses may not be necessary if the information is sufficient to contact the manufacturer, e.g., name or trade name, postal code, country. However, the address needs to be sufficient to contact the physical location of the manufacturer or the authorized representative, if applicable. To this end, the PO box number alone is not sufficient'.

For this study the above mentioned idea was adapted and the visiting address was used as the requirement for the assessment.

Only three IFUs were of good quality (see Figure 5). Furthermore, the majority of the IFUs were scored as moderate because they did not comply with one or more essential requirements as described in the IVDD (1). Required items which were lacking in the IFUs, were for instance the performance evaluation and the necessary instructions in the event of damage to the protective packaging. IFUs scored as insufficient lacked compliance with one or more essential requirements. Additionally, less than 80% of the residual risks mentioned in the risk analyses were mentioned as warnings, precautions and contraindications in these instructions for use.

Almost all the use related risks which IGZ indicated in a warning letter (9) sent to users of POC diagnostic devices (blood glucose meters) after reports of incidents were received, were described in the instructions for use (IFU), see Figure 6.

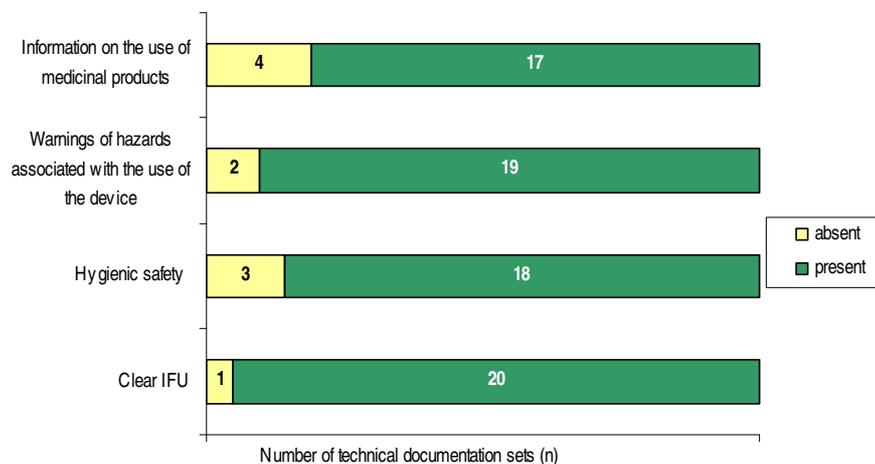


Figure 6. Assessment of use related risks items which IGZ indicated in a letter.

Clear IFU was scored as absent for one IFU because the descriptions of specimen collection and test procedure was unclear. The hygienic safety (e.g., chemical hygiene), warnings of hazards associated with the use of the device and information on the use of medicinal products, diet, etcetera, were not always addressed.

3.4.3 Coherence

The coherence between the risk analysis and the IFU and label is a useful tool to obtain an indication about the quality of the manufacturer’s risk management process. The results of the assessment of coherence of the twenty-one technical documentation sets are presented in Figure 7.

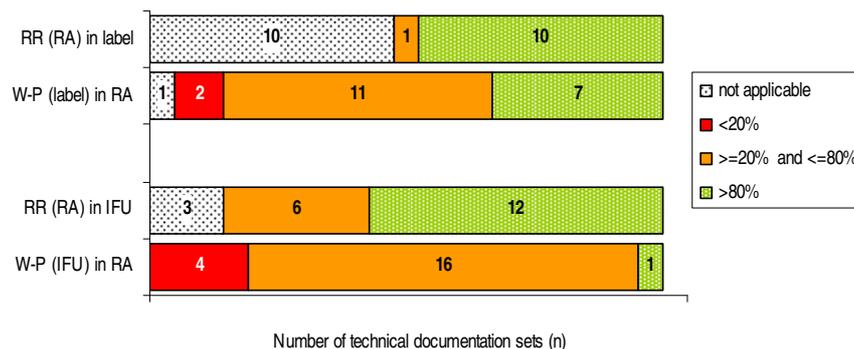


Figure 7. Coherence between risk analysis (RA) and label and between risk analysis and IFU. RR. – residual risks; W-P. – Warning, precautions and contraindication

In several risk analyses, reference was made to the term labelling, which covered both the label and the instructions for use. As a practical approach, the term labelling was interpreted as label and/or instructions for use. Warnings, precautions and contraindications are in many cases not specifically addressed in IFUs (e.g., bold, italic, other font type).

For the purpose of this assessment, only warnings, precautions and contraindications presented with specific typographical characteristics (e.g., bold, italic or other font type) were assessed, because only these are likely to attract the attention of a user.

Risk analysis and label

In almost half of the files, more than 80% of the residual risks identified in the risk analysis were mentioned on the label (Figure 7). Vice versa for only seven files more than 80% of the warnings, precautions and contraindications mentioned on the label were addressed in the risk analysis.

In only one file, between 20%-80% of the residual risks in the risk analysis were mentioned on the label (Figure 7). While vice versa in more than half of the files 20%-80% of the warnings, precautions and contraindications on the label were addressed in the risk analysis.

In two files even less than 20% of the warnings, precautions and contraindications were mentioned as residual risks in the risk analysis.

In some cases the coherence between the risk analysis and the label was scored as not applicable because no residual risks were identified in the risk analysis which should be printed on the label as warnings, precautions and contraindication and vice versa.

Risk analysis and instructions for use

In more than half of the files, 80% or more of the residual risks identified in the risk analysis were mentioned in the IFU (Figure 7). But vice versa: in only one risk analysis 80% or more of the warnings, precautions, contraindications of the IFU were mentioned as residual risks. In the majority of the risk analyses, between 20-80% of the warnings, precautions, contraindications of the IFU were mentioned as residual risks and in four cases this was even less than 20%.

The coherence between the risk analysis and the IFU was scored as not applicable in some cases because no residual risks were identified in the risk analysis which should be incorporated in the IFU as warnings, precautions, and contraindications.

3.4.4 PMS procedures and vigilance procedures

The PMS procedure should contain both active (e.g., customer satisfaction) and passive (e.g., complaints) elements for gathering the experiences of users of the device. In addition, descriptions of corrective and preventive actions (CAPA) and a link to risk management activities should be included as part of a systematic approach for improving the quality of the product. A description on incident reporting and the obligation to notify competent authorities are two aspects which should be described in the vigilance procedure. Furthermore, the manufacturer should have a systematic procedure describing how vigilance findings are used as input for a review of the risk analysis and for CAPA, as is also required for the PMS procedure.

Figure 8 shows the results of the assessment of the quality of the PMS and vigilance procedures.

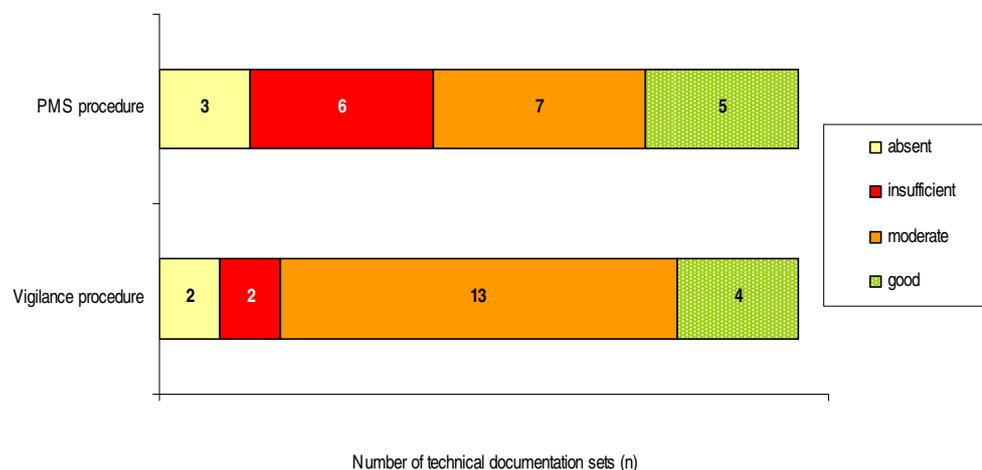


Figure 8. Assessment of the PMS procedures and vigilance procedures.

PMS procedures

Only five of the eighteen PMS procedures were scored as good (Figure 8). Thirteen PMS procedures were scored as moderate or insufficient because one or more important items, like active sources, CAPA or a description of risk management's activities were missing.

Vigilance procedures

A large part of the vigilance procedures was of moderate quality, because the link to risk management activities was not addressed (Figure 8). Two vigilance procedures were scored as insufficient because only the procedure for incident reporting was available.

3.4.5 Performance evaluation

According to the IVDD (1) the technical documentation of IVD devices should contain adequate performance evaluation data showing the performance claimed by the manufacturer and supported by a reference measurement system (when available). Data should originate from studies in a clinical or other appropriate environment or result from relevant bibliographical references. Manufacturers have to execute several performance tests before the device can be placed on the market. A selection of performance characteristics was made, based on examples of performance characteristics mentioned in the IVDD (1), the common technical specifications (CTS (5)) and several standards (4, 6, 7). Table 2 shows an inventory of which of these performance tests were executed by the manufacturers of the POC diagnostic devices. An extra column is added for other performance characteristics than mentioned in IVDD (1), CTS (5) and standards (4, 6, 7).

Table 2. Inventory performance tests executed by the manufacturers

| ID | Type of measurement | Performance characteristic tests performed by the manufacturers (selection of performance characteristics based on examples in the IVDD (1), CTS (5) and several standards (4, 6, 7)) | | | | | | | | | |
|------|---------------------|--|------------------------|----------|---------------|-----------------|---------------------|------------------------|------------------------|------------------------|---|
| | | Analytical sensitivity | Analytical specificity | Trueness | Repeatability | Reproducibility | Limits of detection | Interfering substances | Diagnostic sensitivity | Diagnostic specificity | Other performance characteristics |
| 10* | qualitative | no | no | no | no | yes | no | yes | yes | yes | - |
| 11 | qualitative | no | no | no | no | no | yes | yes | yes | yes | Assay linearity, equivalence with other marketed device, precision |
| 12 | qualitative | yes | yes | no | no | yes | yes | yes | yes | yes | Assay readability, lot-to-lot consistency, accuracy, cytobrush validation, cross-reactivity, compared with reference method |
| 17 | qualitative | no | yes | no | yes | yes | no | yes | no | no | Detection range, correlation with other reference test |
| 18 | qualitative | no | no | no | yes | yes | no | yes | yes | yes | Threshold value/cut-off value |
| 19 | qualitative | no | no | no | no | yes | no | yes | yes | yes | - |
| 22 | qualitative | yes | yes | no | no | yes | no | yes | yes | yes | Cross-reactivity (interfering organisms) |
| 25 | qualitative | yes | yes | no | no | yes | no | yes | yes | yes | - |
| 13 | quantitative | no | no | yes | yes | yes | yes | yes | no | no | Specified reference method, intermediate imprecision, total system error |
| 14 | quantitative | yes | yes | yes | yes | yes | yes | yes | no | no | Linearity, accuracy, calibration to IFCC standard |
| 15 | quantitative | no | no | no | no | no | yes | yes | no | no | Within run precisions, day to day precision, linearity, accuracy |
| 16 | quantitative | yes | yes | yes | yes | yes | yes | yes | no | no | Linearity |
| 23* | quantitative | no | no | yes | yes | yes | no | yes | no | no | Linearity in measurement range |
| 26 | quantitative | yes | no | yes | yes | yes | yes | yes | no | no | - |
| 27 | quantitative | no | no | no | no | no | yes | yes | no | no | Precision, accuracy |
| 29 | quantitative | no | no | yes | no | no | yes | yes | no | no | Precision |
| 31 | quantitative | no | no | yes | no | no | no | yes | no | no | Precision |
| 32 | quantitative | yes | yes | yes | yes | yes | yes | yes | no | no | Linearity, traceability, precision, carry over, reference interval, comparison plasma-serum, limit of blank |
| 33 | quantitative | yes | yes | yes | yes | yes | yes | yes | no | no | Comparison with other equivalent analysers from competitors (trueness); precision, linearity, reference range, |
| 28** | semi-quantitative | yes | no | no | no | yes | yes | yes | no | no | Cut of values |

IFCC – International Federation of Clinical Chemistry and Laboratory Medicine

* Assessment according to the CTS

** Performance evaluation was not available but the performance characteristics were described in the leaflet of the test strips

In twenty of the twenty-one technical files, information on the performance evaluation was available.

For only one POC device, an HIV test (list A of annex II of the IVDD (1)), a specific assessment of the performance evaluation was possible within the scope of this investigation because list A devices have to conform with the Common Technical Specifications (CTS (5)). The results of the performance evaluation of this product showed compliance with the CTS (5).

Besides the performance characteristics, the technical files were assessed on two other aspects:

1. Whether the manufacturer has performed the tests with a proper test population, e.g., test for the determination of faecal occult blood in a patient population with and without colorectal cancer;
2. And whether POC diagnostic devices were tested by the intended user group (e.g., physicians, nurses).

Information on the proper test population was available in more than half of the technical files. But information regarding the persons who tested the POC diagnostic devices was only available in nine technical files. Tests were executed by laboratory professionals, medical personnel, lay users and even students. In some cases, the POC device was also available in a self-test version, which explains the lay user tests. In one of the technical files, performance tests were executed by students, despite the fact that the test was intended to be used by qualified personnel only (see Appendix 4, Table A3).

In the majority of the files the manufacturers referred to documents like: the CTS (5), international standards (EN 375 (6), ISO 13485 (10), EN 13612 (7)), The National Committee for Clinical Laboratory Standards (NCCLS), and IFCC standards. One manufacturer had an internal standard operating procedure for the performance evaluation and in two cases manufacturers referred to a standard for self-testing (ISO 15197 (11)). In eight files, information on reference documents was lacking (see Appendix 4, Table A3).

3.5 Training for users

Because POC diagnostic devices are used by health care professionals who have not been extensively educated in the performance of clinical diagnostic tests, it is important that manufacturers of POC diagnostic devices offer training to an adequate extent to the users of their devices. The manufacturers in this investigation were asked to fill in a short questionnaire concerning instruction and training. The results are presented in Table 3.

Table 3. Results of the questionnaire concerning instruction and training (n=21)

| Aspects of the training | Number of manufacturers |
|---|-------------------------|
| Manufacturers that offer training to users | 17 |
| If manufacturers did offer training to users (n=17), training was given to: | |
| hospital users | 17 |
| non-hospital users | 11 |
| the training was given by*: | |
| Personal instruction or training | 17 |
| Written or digital instruction | 9 |
| Hands-on training | 16 |
| the training was given*: | |
| As part of the purchase and/or | 13 |
| Upon request for free | 12 |
| Upon request at a fee | 4 |

* The manufacturers could choose more than one answer

More than 80% of the manufacturers offer training to users of their POC diagnostic devices. Most manufacturers provide training by personal instruction. In more than 50% of cases, training is given as part of the purchase and upon request for free. Only 20% of the manufactures requested a fee for the training.

4. Discussion and conclusions

General

The objective of this study was to obtain information on the availability and quality of technical files of point-of-care (POC) diagnostic devices marketed in the Netherlands, focusing on safety related items, mainly in the risk analysis and user information. During the assessment, special attention was paid to how manufacturers addressed the suitability of the product and its information for users who have no or limited professional education in clinical diagnosis.

The investigation was based on technical documentation by manufacturers of POC diagnostic devices. The POC diagnostic devices themselves were not examined.

To assure consistent assessments, a manual for the assessment was written, based on international reference documents (1, 3, 4).

Some products are complex due to multiple applications, combination with several accessories, elaborate sample preparations and/or sophisticated techniques. This implies that their use needs a substantial level of training and experience. This is reinforced by the frequent use of the term 'professional use'. In several standards on in vitro diagnostic (IVD) medical devices, professional use is defined as 'use by personnel who have received special education and training with regard to procedures utilizing IVDs' (12-15). However, for POC diagnostic devices the 'professional' who uses the devices may be a physician, a nurse, a doctor's receptionist, a ward orderly, etc., which are professions with major differences in the underlying education levels and fields of expertise in using in vitro diagnostic devices.

Some POC diagnostic devices seem to be offered on the borderline between clinical laboratory setting and point-of-care setting or are recommended for use in both settings. The actual use of these products may differ from one country to another. In general, the descriptions of intended users of POC diagnostic devices are sometimes ambiguous.

Below, the results of this study are discussed in relation to the questions mentioned in the objective (paragraph 1.3).

Are the requested technical files available?

In some cases the technical documents received upon initial request were not complete. It appeared that the description of the content of the technical documentation in the letter, which was largely in accordance with the IVDD wording, was not always clear to manufacturers. In these cases, additional clarification was provided. After the reminder, almost all documents of the technical files were received. Sometimes relevant instructions for use (IFU) were not submitted (e.g., leaflet for the test strips). And in some cases either the risk analysis of the test strips or of the measuring instrument were received. In other cases only a summary of the risk analysis was received. One manufacturer was excluded from this study, because he refused to submit several parts of the requested documentation.

Conclusion:

The manufacturers or authorised representatives included in this investigation cooperated in sending the technical documentation of their POC diagnostic device and most of the requested technical documentation is available.

What is the quality of the requested technical documentation?

General

The quality of the technical documentation was assessed by checking the presence of relevant items, as mentioned in our manual (Appendix 3). Some essential requirements needed to be specified because they were not sufficiently specific to be usable as assessment criteria (e.g., point 8.7r. of the IVDD (1) important environmental factors like temperature, humidity, were included for the assessment).

Although most items were present, the technical documentation often showed several shortcomings. In the majority of the risk analyses not all foreseeable categories of hazards, as derived from EN ISO 14971 (4), were addressed (e.g., no information regarding disposal). And in most of the IFUs items related to the essential requirements of the IVDD (1) were lacking (e.g., not addressing the necessary instruction in the event of damage to the protective package).

Shortcomings in the submitted technical documentation do not necessarily mean that the quality and safety of the devices is insufficient. However, if for example the risk analysis is insufficient or if important warnings or precautions are not included in the instructions for use, this could imply that product safety and safe use of the device is insufficiently guaranteed.

Conclusion:

One third of the documentation items is of good quality and one third is of moderate quality because important documents like the risk analysis and IFU show shortcomings in the information regarding foreseeable hazards and essential requirements, respectively. One quarter of the items is either insufficient or absent. The remaining items were not applicable. Shortcomings in the submitted technical documentation do not necessarily mean that the quality and safety of the devices is insufficient.

Do the manufacturers perform the required analytical performance tests to determine the analytical reliability of the device, as referred to in various reference documents?

Information regarding the performance characteristics was in many cases available in the instructions for use and in the technical documentation.

The available legislation and most of the European standards do not specify the relevant performance tests in detail. According to the IVDD (1), the technical documentation should contain 'adequate performance evaluation data' and the specific analytical performance characteristics should be addressed in the instructions for use. General descriptions of the diverse performance characteristics are available in several European standards (e.g., EN 13612 (7), EN 375 (6)).

Documents with specific information on performance tests are only available for a limited number of tests, like the common technical specification (CTS (5)) for in vitro-diagnostic medical devices for products on List A in Annex II of the IVDD(1), the EN-ISO 15197 (11) for blood glucose meters and Annex H of the EN-ISO 14971 (4). Moreover, the definitions of single performance characteristics are different in various documents, e.g., the IVDD uses 'accuracy' synonymously with 'trueness', whereas the term 'accuracy' includes both 'trueness' and 'precision', according to ISO 3534-1 (16) and ISO 5725-1 (17) (EN 375 (6)). These factors complicated the assessment of the performance evaluations submitted by the manufacturers.

For only one of the POC diagnostic devices included in this study, an HIV test which is on list A of the IVDD, specific assessment of the performance evaluation was possible. The results showed that performance was evaluated in accordance with the applicable reference document, i.e., CTS (5).

Within the scope of this investigation it was not possible to determine whether all the relevant performance evaluation tests were executed for the other twenty POC diagnostic devices because no specific (inter)national reference documents were available for these tests.

Therefore, a survey was made of the performance characteristics evaluated by the manufacturers. Although results regarding various performance characteristics were available, information on important characteristics like analytical performance and diagnostic performance was lacking in several cases. Data on the analytical performance of a POC device provides information on the limits of detection (sensitivity) and the ability of the test to solely determine the target marker (specificity). A falsely high or falsely low result can lead to an incorrect diagnosis or delayed treatment and harm to the patient.

The diagnostic performance of POC diagnostic devices provides information on how the test performs in a patient population, i.e., on the probability that the device gives a positive result in the presence of the target marker and a negative result in the absence of the target marker. A higher probability value means better diagnostic performance of a POC device, resulting in more reliable test results (4). Therefore, it is important to determine not only the analytical performance but also the diagnostic performance of POC diagnostic devices.

Furthermore, in nearly half of the performance evaluation studies information on the persons who had executed the tests was lacking. We believe that performance tests should not only be tested by employees in the laboratory of the manufacturer, but also by a group of intended users, like physicians or nurses, to check whether the results obtained in the controlled environment can be reproduced in daily practice.

Conclusion:

Performance characteristics are presented in different ways.

For only one POC device, an HIV test, it could be established that the required performance characteristics were addressed.

Lack of specific standards hampered a full assessment of the performance evaluation of the other POC diagnostic devices. It was found, however, for several of these POC diagnostic devices, that relevant information (e.g., analytical and diagnostic performance) was lacking. In nearly half of the performance evaluation studies, information on the persons who had executed the tests was lacking.

Are instructions for use sufficiently adapted for health care professionals who have no or limited professional education in clinical chemistry? And is this aspect sufficiently addressed in the risk analysis of the POC diagnostic devices?

It was very common for POC diagnostic devices and their accessories, that more than one set of instructions for use were applicable (e.g., packaging inserts for consumables like test strips and calibration solutions, user manual for the analyser, instructions for users, etc.). The necessity of reading several IFUs complicates the correct use of the device, especially for persons with no or limited professional education in clinical chemistry.

Almost all IFUs contained detailed information on the procedure to be followed and a remark that particular training was required. This could be interpreted as an indication that manufacturers pay attention to the use of their POC device by health care professionals who had no or limited professional education in clinical chemistry. However, in many cases the general description or the IFU mentions that the intended users of the POC diagnostic devices are health care professionals who have had professional education in clinical chemistry. This seems to be in contradiction with the use in a POC setting. It can therefore be debated whether such devices are truly POC diagnostic devices. Unfortunately, POC diagnostic devices are not mentioned in the IVDD(1) and therefore, no specific requirements for the IFUs and intended users are available. This complicates the assessment of whether the IFUs are sufficiently adapted for health care professionals who have no or limited professional education in clinical chemistry.

The language in which the information is provided is also an important issue. Provided that safe and correct use of the device is ensured, Member States may authorize the information to be in one or more official Community languages according to the IVDD(1).

All received IFUs and labels for the POC assessment study were available in English and several other languages (e.g., French, Spanish, etcetera). Only a few were also available in Dutch. The use of the English language is allowed according to the Dutch IVD decree, if the intended use is for professionals. However, because for POC diagnostic devices the term 'professional' may refer to a variety of professions with major differences in education levels, this allowance does not guarantee a sufficient command of the English language.

Most of the use-related risks as described in a letter (9) from the Health Care Inspectorate of the Netherlands were sufficiently addressed in the instructions for use. This was also the case for use-related risks addressed as residual risks in the risk analyses. However, not all other applicable risks were indeed addressed in the risk analyses.

Conclusion:

POC diagnostic devices are not mentioned in the IVDD and therefore no specific requirements for the IFUs and intended users are available. The IFUs appear to be adapted for their intended users, however, in many cases it is specified that the users should have a professional education in clinical chemistry. This is in contradiction with the general understanding of 'point of care'.

Most use-related risks are addressed in the IFUs and risk analyses.

Is the coherence between the risk analysis and the instructions for use of the POC diagnostic devices sufficient?

Risks should be evaluated in the risk analysis and information on residual risks should be made available in the instructions for use and/or the label as a warning, precaution or contraindication. The coherence between the instructions for use and the risk analysis and between the label and risk analysis was moderate. Especially risks related to warnings, precautions and contraindications mentioned on the label and in the instructions for use could not always be found in the risk analyses. The lack of coherence between the risk analysis and the instructions for use raises questions about the thoroughness of the risk mitigation procedure followed by the manufacturers of the POC diagnostic devices and the accuracy of the communication of the residual risks to the user. This may indicate that the 'continuous cycle of product improvement' is not working adequately.

Conclusion:

The coherence between the instructions for use and the risk analyses was moderate. Warnings in the user information were not always evidently based on risks evaluated in the risk analysis. The lack of coherence between the risk analysis and the instructions for use raises questions about the thoroughness of the risk mitigation procedure followed by the manufacturers.

Do manufacturers pay sufficient attention to active collection of field experiences and improvement of their products in their post-market surveillance (PMS) and vigilance procedures?

The majority of manufacturers did not refer to risk management activities in their PMS procedure or vigilance procedure. Risk management should be a continuous process, described as a set of repeatable steps throughout the entire life cycle of the product. Surveillance findings can lead to the re-assessment of a risk, for example, in cases where corrective actions or preventive actions are initiated. Therefore, a link to the risk management activities should be included in the PMS and vigilance procedures.

Conclusion:

The management of risks reported after experiences with POC devices is insufficiently included in the PMS procedures and vigilance procedures.

Do manufacturers or distributors provide training to the users of their POC diagnostic devices?

Most manufacturers offer training to users of their POC diagnostic devices. The majority of the manufacturers gave training to hospital users and training was mostly given by personal instruction or as hands-on training. In more than half of the cases, training was given as part of the purchase. The majority of the manufacturers offered training for free.

Conclusion:

Most manufacturers offer training to users of their POC diagnostic devices.

Extrapolation of results

Technical files of a selection of POC diagnostic devices were assessed. This selection comprised products that included a wide variety of techniques, types of markers (e.g., markers for infections, diabetes markers), types of specimens (e.g., blood, urine) to obtain an overall picture. POC diagnostic devices measuring just one type of marker as well as more complex devices, e.g. multi-analysers for multiple types of markers were included. Although some differences in the results were observed, the general outcome is relatively consistent. The selection was made using a list of POC diagnostic devices on the Dutch market, which was compiled from an internet survey. Although the list was not exhaustive, consultation of several experts in the field enabled the inclusion in this study of products from a large proportion of manufacturers (estimated at least 55%) who market POC diagnostic devices in the Netherlands. Therefore, the results of this study are probably indicative for the quality of the technical documentation of the POC diagnostic devices on the Dutch market.

5. Recommendations

For Manufacturers

- The technical documentation should give clear indications of intended users, including educational level and health care setting. An indication like 'for professional use' is not sufficient.
- To maintain the quality and safe use of a POC device, all risks underlying warnings, precautions and contraindications communicated to the user via the instructions for use or label should have been evaluated in the risk analysis.
- To maintain and improve the quality and safety of POC diagnostic devices, links to the risk management activities should be incorporated in the procedures for PMS and vigilance.

For Regulators

- Several essential requirements of the IVDD should be phrased more clearly and illustrated with examples, or be accompanied by guidance.
- The IVDD should emphasise the necessity of the manufacturer's specifications of the intended use of IVDs that are (also) meant for non-laboratory settings.
- A clear definition for 'POC devices' should be mentioned in the IVDD and general requirements on appropriateness of product design and accompanying information for intended use location and education/training of intended user should be considered.

For Standardising Institutions

- In IVD standards, reference to the informative annex H of EN ISO 14971 "Guidance on risk management for in vitro diagnostic medical devices" should be considered.

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Appendix 1. Letter to the manufacturers

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

The Dutch Healthcare Inspectorate is the competent authority for the Directive on in vitro diagnostic medical devices, 98/79/EC (short: IVDD) in the Netherlands. As such, the Inspectorate is charged with the surveillance and enforcement of the regulations for in vitro diagnostic medical devices.

As part of the vigilance process regarding previously reported incidents involving point-of-care (POC) equipment, the technical files of the involved products were assessed. This assessment showed several shortcomings in the technical files. In order to investigate whether these shortcomings are more widespread, technical files of other manufacturers and several other types of POC diagnostic devices are now requested for assessment. The objective is to investigate whether the available documentation fulfils the (essential) requirements. However, this study does not concern the benefit, necessity or efficacy of POC testing.

The actual study will be performed on our behalf by the Dutch National Institute for Public Health and the Environment (RIVM). The device(s) mentioned below, marketed by your company, is one of the devices selected for inclusion in this study. Therefore, you are requested to send a copy of the following documents for: **<name of the product(s)>**.

1. a general description of the product, including any variants planned;
2. 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;
3. in the case of devices containing tissues of human origin or substances derived from such tissue, information on the origin of such material and on the conditions in which it was collected;
4. the descriptions and explanations necessary to understand the above-mentioned characteristics, drawings and diagrams and the operation of the product;
5. the results of the risk analysis and, where appropriate, a list of the standards referred to in Article 5 of the IVDD, 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;
6. in case of sterile products or products with a special microbiological state or state of cleanliness, a description of the procedures used;

7. 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;
8. if the device is to be combined with other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when combined with any such device(s) having the characteristics specified by the manufacturer;
9. test reports;
10. the labels, instructions for use and other instructions, e.g., associated with consumables like strips, cartridges or cuvettes, as marketed in the Netherlands;
11. the results of stability studies (if applicable);
12. the post-market surveillance procedure;
13. the vigilance procedure.

The above-mentioned documents are required in Annex 3, point 3 of the IVDD, whereas the need for post-market surveillance and vigilance is mentioned in point 5. If the device mentioned above is no longer marketed in the Netherlands and a newer version is available, you are requested to send in the documentation for the latest version of the device.

In order to avoid the risk of misunderstanding, I would appreciate if you clearly mark and tab the above-mentioned documents. If one of them is not applicable for your device(s), you are requested to clearly state the reason. Please note that these documents will be treated confidentially and will be destroyed after completion of the investigation.

Additionally, you will find a short questionnaire on training and instruction activities enclosed with this letter. You are requested to fill in this form and to send it together with the documents mentioned above. If preferred, you can request an electronic version of this questionnaire from the e-mail address below.

Furthermore, you are requested to provide the contact details (including name, e-mail address and telephone number) of the person who will be in charge of handling the request within your company, within one (1) week after receiving this letter.

You may e-mail the contact details to: POC-assessment@rivm.nl

You are requested to send the documentation, marked as confidential, to:

**The Dutch National Institute for Public Health and the
Environment (RIVM)
Section Medical Technology (PB 50)
POC-Assessment, AvD
P.O. Box 1
NL-3720 BA BILTHOVEN
The Netherlands**

If you prefer to submit the information electronically, you can send it to:
POC-assessment@rivm.nl

It would be very much appreciated if you could forward your information
before:

1 December 2009

Additional documents may be requested in case our findings indicate that
additional documentation is necessary for a proper assessment of your
device or if information is considered to be incomplete.

Upon finalising 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,

Ms L.M. de Vries, M.Sc.,
Inspector

Appendix 2. Questionnaire

Questionnaire on Instruction and training

1. Do you offer training to users of your point-of-care device?

No

Yes: To hospital users
 To non-hospital users

2. If you offer training:

Is the training given by:

Personal instruction or training and/or

Written or digital (e.g., CD, web-based) instruction or training and/or

Hands on training

(more than 1 answer possible)

3. Is training given:

As part of the purchase and/or

Upon request? Free
 At a charge

(more than 1 answer possible)

Appendix 3. Manual for the assessment of technical documentation

This manual gives information for the availability and quality assessment of technical documentation items of CE marked point-of-care (POC) diagnostic devices complying with the In Vitro Diagnostic Medical Devices Directive 98/79/EC (IVDD) (1).

A. General description of the medical device

Availability options

Absent: the technical documentation does not contain any documentation related to a specific item.

Present: the technical documentation contains information related to a specific item. (Information on a specific item can also be found in other parts of the documentation (e.g., IFU, risk analysis))

Contents (items absent/present):

1. (generic) name of the medical device,
2. physical description of the medical device,
3. (schematic) drawing, diagram or photograph of the medical device,
4. diagnostic mode of action. This should include specimen type, parameter(s) to be measured, detection principle, chemical reactions (if applicable).
5. intended user
6. intended use
7. limitations of the method.

Assessment score concerning general description of the medical device

| | |
|---------------|--|
| Absent | |
| Insufficient: | any combination with \leq four items present |
| Moderate: | any combination of five-six items present |
| Good: | all items present |

B General description of any variants of the POC device

Availability options:

Test strips or test cassettes used in combination with devices with a measuring function are not considered as variants of the POC device.

Not applicable: manufacturer states that there are no variants (and items 1 and / or 2 below are absent).

Absent: any information on variants (including statement) is absent.

Present: technical documentation mentions variants.

Contents (items absent/present/not applicable):

1. variants are implicitly mentioned in other technical documentation items, e.g., in design specifications, risk analysis or instructions for use,
2. description of variants including information about size, colour, weight, model number, etc.,

Assessment score concerning general description of any variants planned

Not applicable
Absent
Insufficient: item 1 present
Good: items 1+2 or item 2 present

C Design specifications

Availability options:

Absent: the technical documentation does not contain information concerning design specifications.

Present: the technical design is univocally laid down, e.g., in a drawing, description or list of parts.

Contents (items absent/present):

1. (design) drawing(s) (e.g., essential device sizes specified; design drawing present only if relevant),
2. specification of the materials used, biomaterials or components,
3. description /explanation necessary to understand the drawings

Assessment score concerning design specifications

Absent
Insufficient: only one of the items present
Moderate: any combination with two items present
Good: all items present

D Information on tissue of human origin or substances derived from such tissue

Availability options:

Not applicable: manufacturer states that no tissue of human origin or substances derived from such tissue are used.

Absent: the technical documentation does not contain information concerning tissue of human origin or substances derived from such tissue.

Present: the technical documentation contains information concerning tissue of human origin or substances derived from such tissue.

Contents (items absent/present/not applicable):

1. information on the origin of such material
2. information on the conditions in which it was collected is given
3. quality and consistency of product/reagent

Assessment score concerning information on tissue of human origin or substances derived from such tissue

Not applicable
Absent
Insufficient: only one of the items present
Moderate: items 2 or 3 present
Good: all items present

E Explanations necessary to understand the function of the device

Availability options:

Absent: the technical documentation does not contain explanations to understand the function of the device.

Present: the technical documentation contains explanations to understand the function of the device (e.g., characteristics, drawings/pictures and the operation of the product).

F Results of the risk analysis

Availability options:

Absent: the technical documentation does not contain the results of the risk analysis.

Present: the document contains the results of the risk analysis. Check and note date and standard used (ISO 14971 (4), EN 1441 (18)) for performing the risk analysis.

Contents (items absent/present):

Results of the risk analyses items 1-4

1. are all applicable category foreseeable hazards addressed (see Appendix 3A: Hazards and contributing factors (a-n)),
2. risks arising from the identified hazards are estimated,
3. actions taken to reduce or eliminate the risks are adequate, i.e., control measures are consistently described in line with essential requirement article 3 (IVDD 98/79/EC, Annex I (1)):
 - eliminate or reduce risks as far as possible (inherently safe design and construction),
 - where appropriate take adequate protection measures in relation to risks that cannot be eliminated,
 - inform users of residual risks / hazards due to any shortcomings of any protection measures adopted,
4. residual risks / hazards are justified in relation to anticipated benefits (IVDD, Annex I (1)),

Results of the risk analyses items 5-6 (a, b, c, d)

5. coherence: warnings / precautions/symbols on label are mentioned in risk analysis as residual risks / hazards (Note: warnings / precautions/ symbols on the label must be marked distinguishably from the text on the label, e.g., bold, italics, underlined, an exclamation mark, etc.):
 - a. *not applicable*
 - b. *<20%*
 - c. *20-80%*
 - d. *>80%,*
6. coherence: warnings / precautions / contraindications in instructions for use are mentioned in risk analysis as residual risks / hazards (Note: warnings / precautions/ symbols in the instruction for use must be marked distinguishably from the text in the instructions for use, e.g., bold, italics, underlined, an exclamation mark, etc.):
 - a. *not applicable*
 - b. *<20%*
 - c. *20-80%*
 - d. *>80%,*

Assessment score concerning results of the risk analysis (items 1-4)

Absent_1-4
 Insufficient_1-4: <three items present
 Moderate_1-4: three items present
 Good_1-4: all items present

Assessment score concerning warnings / precautions and residual risks-b (item 5-6)

Absent_5-6
 Insufficient_5-6: (item 5b + item 6a or 6b or 6c or 6d) or (item 5a or 5b or 5c or 5d + item 6b)
 Moderate_5-6: (item 5c + item 6a or 6c or 6d) or (item 5a or 5c or 5d + item 6c)
 Good_5-6: item 5a or 5d + item 6a or 6d

Assessment score concerning results of the risk analysis 1-6 (all items)

Absent-1-6
 Insufficient: (insufficient (1-4 + 5-6)) **or** (insufficient-1-4 + moderate-5-6) **or** (insufficient-1-4 + good-5-6) **or** (moderate-1-4 + insufficient-5-6) **or** (good-1-4 + insufficient-5-6)
 Moderate: (moderate (1-4 + 5-6)) or (moderate-1-4 + good-5-6) or (good-1-4 + moderate-5-6)
 Good: good (1-4 + 5-6)

G Hazards from the circular letter of the Netherlands Health Care Inspectorate (9)

Availability options (items absent/present) (IFU):

1. clear instructions for use
2. hygienic safety addressed (e.g., chemical hygiene)
3. warnings of hazards associated with the use of device (e.g., sampling – measurement – assessment of measurement – further action)
4. use of medicinal products, diet, etc., which can influence the outcome of the results

H List of essential requirements and/or applied standards

Availability options:

Absent: the technical documentation does not contain a document with (harmonised product) standards.

Present: a separate list of applied standards or checklist of essential requirements with applied standards is present.

I Sterilisation

Availability options:

Not applicable: manufacturer states that the medical device is a non-sterile product.

Absent: the technical documentation does not contain information with regard to sterilisation.

Present: information on sterilisation is present in one of the documents.

J Performance evaluation (inventory of performance characteristics)

Note: this part of study is an inventory not an assessment.

Availability options:

Absent: the technical documentation does not contain specific analytical adequate performance characteristics.

Present: the technical documentation does contain specific analytical adequate performance characteristics.

Contents (EN 375 (6), EN 13612, IVDD (1) and CTS (5)) (items absent/present):

1. analytical sensitivity (may be expressed as the limit of detection, i.e., the smallest amount of the target marker that can be precisely detected (5)).
2. analytical specificity (means the ability of the method to determine solely the target marker (5)).
3. trueness (closeness of agreement between the average value obtained from a large series of test results and an accepted reference value (6))⁴
4. repeatability (condition of measurement in a set of conditions including the same measurement procedure, same operator, same measurement system, same operating conditions and same location and replicated measurements over a short period of time (19))
5. reproducibility (condition of measurement in a set of conditions including different locations, operators and measuring systems (19))
6. limits of detection and measurement interval
7. interfering substances
8. diagnostic sensitivity (the probability that the device gives a positive result in the presence of the target marker (5)).
9. diagnostic specificity (the probability that the device gives a negative result in the absence of the target marker (5)).
10. other, if applicable (e.g., precision)
11. patient groups, if applicable
12. intended users, if applicable (e.g., doctors or their assistants, pharmacists, etc.)
13. reference to standard, if applicable (e.g., EN 13612 (7), National Committee for Clinical Laboratory Standards (CCLS) documents or European Committee for Clinical Laboratory Standards (ECCLS) documents, etc.).

The accuracy of the examination results of an IVD medical device depends on the performance characteristics of the device. There are three types of IVD medical devices; quantitative, semi-quantitative and qualitative tests. According to ISO14971:2009(4) :

- *The main analytical performance characteristics of quantitative examination procedures are: precision (imprecision), trueness (bias), analytical specificity and detection limit. Performance requirements depend on the medical application. A falsely high or falsely low result can lead to an incorrect diagnosis or delayed treatment and harm to the patient.*

⁴ Note: IVDD uses "accuracy" synonymously with "trueness", whereas the term "accuracy" includes both "trueness" and "precision", according to ISO 3534-1 and ISO 5725-1.(EN 375).

- *Performance of qualitative examination procedures is generally expressed in terms of diagnostic sensitivity and specificity. A positive result when the analyte is absent or a negative result when the analyte is present can lead to incorrect diagnosis or delayed treatment and to harm to the patient.*

K Connecting to / combination with other medical device

Availability options:

Not applicable: manufacturer states that the medical device cannot be connected to other medical device(s). Devices with a measuring function used in combination with test strips or test cassettes or accessories (and the other way round) are considered as one device for this assessment.

Absent: the technical documentation does not contain information concerning characteristics to identify the correct devices or equipment to use in order to obtain a safe and proper combination.

Present: the technical documentation contains information concerning characteristics to identify the correct devices or equipment to use in order to obtain a safe and proper combination.

L Test reports

Availability options:

Absent: the technical documentation does not contain a document concerning test reports.

Present: the technical documentation contains a document concerning test reports

M Label

Availability options:

Absent: the technical documentation does not contain a label.

Present: an original label or a copy thereof is present.

Contents (items absent/present/not applicable):

1. label in Dutch/English/language independent label.
2. Standardised symbols (EN 980:2008 (20)) (Not applicable if the label does not contain any symbols)
3. label complies with the applicable essential requirements concerning information supplied by the manufacturer, i.e., 8.4 a – 8.4 j; 8.4 f is not applicable for this assessment (IVDD, Annex I (1)),
 - a. the name or trade name and address of the manufacturer.
For devices imported into the Community with a view to their distribution in the Community, the label, the outer packaging, or the instructions for use shall contain in addition the name and address of the authorised representative of the manufacturer;
 - b. the details strictly necessary for the user to uniquely identify the device and the contents of the packaging;
 - c. where appropriate, the word 'STERILE' or a statement indicating any special microbiological state or state of cleanliness;
 - d. the batch code, preceded by the word 'LOT', or the serial number (if a design drawing of the label is submitted, a space for lot number must be specified/marked);

- e. if necessary, an indication of the date by which the device or part of it should be used, in safety, without degradation of performance, expressed as the year, the month and, where relevant, the day, in that order (if a design drawing of the label is submitted, a space for expiry date must be specified/marked);
 - f. where appropriate, a statement indicating the in vitro use of the device;
 - g. any particular storage and/or handling conditions;
 - h. where applicable, any particular operating instructions;
 - i. appropriate warnings and/or precautions to take;
 - zz. CE mark (IVDD, article 16 (1))
 - xx. CE number (IVDD, article 16(1))
4. coherence: label-related residual risks / hazards in risk analysis are mentioned on label (in the form of symbols, where appropriate):
- a. *not applicable*
 - b. <20%
 - c. 20-80%
 - d. >80%,

| Assessment score concerning label | |
|--|------------------------------------|
| Absent | |
| Insufficient: | <three items present |
| Moderate: | three items present |
| Good: | items 1 + 2 + 3 + 4a or 4d present |

N Instructions for useAvailability options:

Absent: the technical documentation does not contain instructions for use.

Present: the original instructions for use or a copy thereof is present.

Contents (items absent/present/not applicable):

1. complete instructions for use in Dutch and/ or English.
2. instructions for use complies with the applicable essential requirements concerning information supplied by the manufacturer, i.e., 8.7.a – 8.7.u (8.7 t excluded, this is for self-tests) (IVDD (1)):
 - a. the details referred to in section 8.4 a - 8.4 j with the exception of points (d) and (e);
 - b. composition of the reagent product by nature and amount or concentration of the active ingredient(s) of the reagent(s) or kit as well as a statement, where appropriate, that the device contains other ingredients, which might influence the measurement;
 - c. the storage conditions and shelf life following the first opening of the primary container, together with the storage conditions and stability of working reagents;
 - d. the performances referred to in section 3 of part A of the IVDD (1);
 - e. an indication of any special equipment required including information necessary for the identification of that special equipment for proper use;
 - f. the type of specimen to be used, any special conditions of collection, pre-treatment and, if necessary, storage conditions and instructions for the preparation of the patient;

- g. a detailed description of the procedure to be followed in using the device;
- h. the measurement procedure to be followed with the device including as appropriate:
 - the principle of the method,
 - the specific analytical performance characteristics (e.g., sensitivity, specificity, accuracy, repeatability, reproducibility, limits of detection and measurement range, including information needed for the control of known relevant interferences), limitations of the method and information about the use of available reference measurement procedures and materials by the user,
 - the details of any further procedure or handling needed before the device can be used (for example, reconstitution, incubation, dilution, instrument checks, etc.),
 - the indication whether any particular training is required;
- i. the mathematical approach upon which the calculation of the analytical result is made;
- j. measures to be taken in the event of changes in the analytical performance of the device;
- k. information appropriate to users on: internal quality control including specific validation procedures, the traceability of the calibration of the device;
- l. the reference intervals for the quantities being determined, including a description of the appropriate reference population;
- m. if the device must be used in combination with or installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe and proper combination;
- n. all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the device operates properly and safely; information about safe waste disposal;
- o. details of any further treatment or handling needed before the device can be used (for example, sterilisation, final assembly, etc.);
- p. the necessary instructions in the event of damage to the protective packaging and details of appropriate methods of re-sterilisation or decontamination (for this assessment, sterile and non-sterile products are included);
- q. if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and re-sterilisation or decontamination and any restriction on the number of reuses;
- r. precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources (for this assessment aspects as temperature, humidity, etc., are included;

- s. precautions to be taken against any special, unusual risks related to the use or disposal of the device, including special protective measures; where the device includes substances of human or animal origin, attention must be drawn to their potentially infectious nature;
- u. date of issue or latest revision of the instructions for use.
- zz. CE mark (IVDD, article 16 (1))
- xx. CE number (IVDD, article 16 (1))
- 3. coherence: instructions for use-related residual risks / hazards in risk analysis are mentioned in instructions for use (as warnings, precautions, contraindications, adverse / side effects, complications, etc.):
 - a. *not applicable*
 - b. <20%
 - c. 20-80%
 - d. >80%,

| Assessment score concerning instructions for use | |
|---|--|
| Absent | |
| Insufficient: | only items 2 + 3a or 3d present only items 1 + 3b or 3c present only item 3a or 3b or 3c or 3d present |
| Moderate: | items 1 + 3a or 3d present items 1 + 2 + 3b or 3c present |
| Good: | items 1 + 2 + 3a or 3d present |

O Results of stability studies

Availability options:

Absent: the technical documentation does not contain results of the stability studies.

Present: the technical documentation contains results of the stability studies

P Post-market surveillance procedure

Availability options:

Absent: the technical documentation does not contain information with regard to a post-market surveillance procedures or not even a non-systematic approach.

Present: the technical documentation contains information with regard to a post market surveillance procedure or a non-systematic approach.

Contents (items absent/present):

1. customer or user complaints procedure,

2. a principle or procedure for the *proactive* collection and review of experiences (e.g., customer satisfaction questionnaire / surveys), to collect experiences other than (customer / user) complaints⁵
3. corrective and preventive actions will be taken: a principle or procedure for corrective and preventive actions is mentioned, i.e., procedure is referenced in post-market surveillance procedure,
4. risk management activities will be taken, e.g., update of the results of risk analysis is mentioned (post-market surveillance should be part of the risk management plan).

Assessment score concerning post-market surveillance procedure

| | |
|---------------|-----------------------------------|
| Absent | |
| Insufficient: | only item 1 or 1+3 or 1+4 present |
| Moderate: | other combinations |
| Good: | all items present |

Q Vigilance procedure

Availability options:

Absent: the technical documentation does not contain information with regard to vigilance.

Present: the technical documentation contains information with regard to vigilance

Contents (items absent/present):

1. principle or procedure for incident reporting and the notification duty to competent authorities of any malfunction or shortcoming of the medical device,
2. principle or procedure for field safety corrective action (formerly known as recall) is mentioned or described,
3. (internal) corrective actions will be taken: a principle or procedure for corrective (and preventive) actions (field safety corrective action) is mentioned, i.e., procedure is referenced in the vigilance procedure,
4. risk management activities will be taken, e.g., update of the risk analysis is mentioned.

Assessment score concerning vigilance procedure

| | |
|---------------|------------------------|
| Absent | |
| Insufficient: | only two items present |
| Moderate: | three items present |
| Good: | all items present |

⁵ Note: Sources of information for post market surveillance are (proactive / reactive) are for instance expert users groups, customer complaints and warranty claims, post CE market clinical studies, literature reviews, user feedback other than complaints: surveys, customer satisfaction, device tracking / implant registries, user reactions during training programs, competent authorities, the media (including internet and email), experience with similar devices made by the same or different manufacturer, maintenance / service reports, retrieval studies on explants, in-house testing, failure analysis (analysis of complaints), fieldworkers, retailers, buyers satisfaction forms, panel sessions, meeting with users, feedback from marketing data.

R Questionnaire

Availability options:

Absent/Present

1. Do you offer training to users of your point-of-care device? (No/Yes)

If yes:

- To hospital users (yes/no)
- To non-hospital users (yes/no)

2. Is the training given by:

- Personal instruction or training and/or (yes/no)
- Written or digital (e.g., CD, web-based) instruction or training and/or (yes/no)
- Hands-on training (yes/no)

3. Is training given:

- As part of the purchase and/or (yes/no)
- Upon request?
 - o Free (yes/no)
 - o At a charge (yes/no)

Appendix 3A. Hazards and contributing factors

This appendix provides a selection of categories of risks for the use of in vitro diagnostics point-of-care tests and is based on hazards described in the standard EN ISO 14971:2009 (4) Medical devices – Application of risk management to medical devices

a. Energy hazards (examples)

Electromagnetic energy:

- Line voltage
- Leakage current (e.g., enclosure leakage current, earth leakage current, patient leakage current)
- Electric fields
- Magnetic fields
- Electric shock
- Component drift
- Dielectric strength

Radiation energy

- Ionising radiation
- Non-ionising radiation
- Visible light
- UV light
- Infrared light
- Microwaves

Thermal energy

- High temperature
- Low temperature

Mechanical energy

- Gravity (e.g., falling, suspended masses)
- Vibration (e.g., resonance)
- Release of stored energy
- Inertia
- Moving parts (e.g., squeezing, crushing, shearing, cutting or severing, entanglement, trapping, stabbing or puncturing, friction or abrasion, expelled parts, instability, impact, moving and positioning of patients)
- Acoustic energy (e.g., ultrasonic energy, infrasound energy, sound)
- High pressure fluid injection due to leakage

b. Biological hazards (examples)

- Bio-contamination (e.g., by bacteria or by viruses or inability to maintain hygienic safety)
- Contact with organic material skin/airway
- Contact with organic material invasive
- Contact with non-organic material (skin/airway/invasive)
- Bio-incompatibility (e.g., toxicity, allergenicity, mutagenicity, oncogenicity, teratogenicity, carcinogenicity, re- and/or cross-infection, pyrogenicity, substances that produce adverse physiological effects)
- Animal tissue

c. Chemical hazards (examples)

- release/leakage/impurity (substances that should be incorporated) (e.g., contacts with acids or alkalis, leakage of gases or liquids, gas, liquid, impurity, leakage of reagents)

d. Hazards related to the environment of the IVD (examples)

- Medical gases
- Emission of electromagnetic fields
- Substances that produce adverse physiological effects

e. Hazards related to the information (examples)

- Inadequate labelling
- Inadequate operating instructions (e.g., inadequate specifications of accessories to be used with the medical device, inadequate specifications of pre-use checks, overcomplicated operating instructions)
- Inadequate specification of service and maintenance
- Insufficient warnings of side effects
- Inadequate warnings of hazards likely with re-use of single use devices
- Incorrect measurements and other metrological aspects

f. Design (examples)

- Material degradation
- Incompatibility with other devices with which the device is intended to be used

g. Manufacturing processes (examples)

- Change in manufacturing process
- Insufficient material compatibility information
- Insufficient control of manufacturing processes
- Insufficient control of subcontractors

h. Transport and storage (examples)

- Inadequate packaging
- Storage conditions
- Transportation

i. Environmental effects to the IVD (examples)

- Corrosion
- Degradation
- Biodegradation
- Electromagnetic fields
- Susceptibility to electromagnetic interference
- Temperature, sunlight, humidity, radiation, high-altitude

j. Installation, maintenance and service (examples)

- Assembly
- [Preparation prior to use
- Use requires specific training/skills (covered by use error?)]

k. Cleaning, disinfection and sterilisation (examples)

- Re-sterilisation

l. Disposal and scrapping

m. Normal operation (examples)

- Ageing
- Shelf-life
- Inadequate supply of power
- Inadequate supply of coolant

n. Use errors (examples)

- Reasonably foreseeable misuse
- Potential for intentional misuse
- Insufficient warning of side effects
- Inadequate warnings of hazards associated with re-use of single-use medical devices
- Incorrect measurement and other metrological aspects
- Incompatibility with consumables/accessories/other medical devices
- Incorrect formulation
- Operation outside prescribed environmental conditions
- Human factors (e.g., mistakes and judgment errors, lapses and cognitive recall errors, slips and blunders, violation or abbreviation of instructions, procedures, etc., complex or confusing control system, ambiguous or unclear device state, ambiguous or unclear presentation of settings, measurements or other information, misrepresentation of results, insufficient visibility, audibility or tactility, poor mapping of controls to action, or of displayed information to actual state, controversial modes or mappings as compared to existing equipment)
- Failure modes (e.g., erroneous data transfer, lack of or inadequate specification for maintenance, including inadequate specification of post-maintenance functional checks, inadequate maintenance, lack of adequate determination of the end of life of the medical device, loss of electrical/mechanical integrity, deterioration in function as a result of repeated use, failure to perform to essential performance requirements)

Appendix 4. Assessment score

Table A1. Availability of the technical documentation per product (ID)

| ID | Device description | Variant description | Design specification | Human tissue origin | Explanations | Risk analysis | ER / standards | Sterilisation | Performance evaluation | Combination | Test reports | Label(s) | Instructions for use | Stability studies | PMS procedure | Vigilance procedure | Questionnaire |
|----|--------------------|---------------------|----------------------|---------------------|--------------|---------------|----------------|---------------|------------------------|-------------|--------------|----------|----------------------|-------------------|---------------|---------------------|---------------|
| 10 | pres. | abs. | pres. | pres. | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 11 | pres. | pres. | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | abs. | pres. | pres. | pres. | pres. | pres. | pres. |
| 12 | pres. | pres. | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | abs. | pres. | pres. | pres. | pres. | pres. | pres. |
| 13 | pres. | abs. | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 14 | pres. | NA | abs. | pres. | pres. | pres. | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 15 | pres. | NA | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 16 | pres. | pres. | pres. | pres. | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | abs. | pres. | pres. |
| 27 | pres. | pres. | pres. | NA | pres. | pres. | pres. | NA | pres. | pres. | abs. | pres. | pres. | pres. | abs. | abs. | pres. |
| 28 | pres. | NA | pres. | NA | pres. | pres. | pres. | NA | abs. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 29 | pres. | abs. | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 30 | pres. | abs. | pres. | NA | pres. | pres. | pres. | NA | abs. | NA | pres. | pres. | pres. | NA | pres. | pres. | pres. |
| 25 | pres. | abs. | abs. | NA | pres. | pres. | pres. | NA | pres. | NA | abs. | pres. | pres. | abs. | pres. | pres. | pres. |
| 26 | pres. | pres. | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | abs. | pres. | pres. | abs. | pres. | pres. | pres. |
| 31 | pres. | abs. | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | abs. | pres. | pres. | pres. |
| 32 | pres. | pres. | abs. | pres. | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 33 | pres. | abs. | pres. | pres. | pres. | pres. | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 23 | pres. | pres. | pres. | NA | pres. | pres. | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 17 | pres. | abs. | pres. | pres. | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | abs. | abs. | pres. |
| 18 | pres. | pres. | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |
| 19 | pres. | NA | pres. | pres. | pres. | pres. | pres. | NA | pres. | NA | abs. | pres. | pres. | abs. | pres. | pres. | pres. |
| 22 | pres. | abs. | pres. | NA | pres. | pres. | pres. | NA | pres. | NA | pres. | pres. | pres. | pres. | pres. | pres. | pres. |

pres. - present; abs. - absent; NA - Not applicable

Table A2. Assessment of the quality of the technical documentation per product (ID)

| ID | Device description | Variant description | Design specification | Human tissue origin | Risk analysis | Label(s) | Instructions for use | PMS procedure | Vigilance procedure |
|----|--------------------|---------------------|----------------------|---------------------|---------------|--------------|----------------------|---------------|---------------------|
| 10 | good | abs. | good | good | good | good | good | moderate | moderate |
| 11 | good | good | good | NA | moderate | good | moderate | insufficient | moderate |
| 12 | good | good | good | NA | moderate | moderate | insufficient | moderate | moderate |
| 13 | good | abs. | moderate | NA | moderate | moderate | moderate | moderate | Good |
| 14 | good | NA | abs. | insufficient | moderate | good | moderate | good | moderate |
| 15 | moderate | NA | insufficient | NA | moderate | good | moderate | good | moderate |
| 16 | good | insufficient | good | moderate | moderate | moderate | moderate | abs. | Good |
| 27 | good | insufficient | good | NA | moderate | good | moderate | abs. | abs. |
| 28 | good | NA | moderate | NA | moderate | good | moderate | insufficient | moderate |
| 29 | good | abs. | good | NA | moderate | good | good | moderate | moderate |
| 30 | moderate | abs. | good | NA | moderate | good | moderate | moderate | moderate |
| 25 | moderate | abs. | abs. | NA | insufficient | moderate | insufficient | moderate | Good |
| 26 | good | good | abs. | NA | insufficient | moderate | moderate | insufficient | insufficient |
| 31 | moderate | abs. | good | NA | insufficient | moderate | moderate | insufficient | moderate |
| 32 | good | insufficient | abs. | insufficient | insufficient | good | good | good | Good |
| 33 | good | abs. | good | good | moderate | good | moderate | good | moderate |
| 23 | good | good | good | NA | insufficient | good | moderate | moderate | moderate |
| 17 | good | abs. | good | insufficient | insufficient | good | moderate | abs. | abs. |
| 18 | good | good | good | NA | moderate | insufficient | moderate | insufficient | moderate |
| 19 | good | NA | moderate | insufficient | moderate | good | moderate | insufficient | moderate |
| 22 | moderate | abs. | good | NA | insufficient | moderate | moderate | good | insufficient |

abs. – absent; NA - Not applicable

Table A3 Other performance characteristics, test population and intended users

| ID | Type of measurement | Test population | Intended users | Reference documents as mentioned by the manufacturer |
|----|---------------------|--|--|--|
| 10 | Qualitative | According to CTS for IVDs | According to CTS for IVDs | CTS |
| 11 | Qualitative | Sensitivity: specimen from patient with colorectal cancer, adenomas (<1 cm), all adenomas. Specificity: specimen from asymptomatic individuals. | Laboratory professionals. Sample collection can be performed by patients. | Nss |
| 12 | Qualitative | Clinical sensitivity, specificity and accuracy: specimen from women attending sexually transmitted disease clinics, family planning and OB/GYN clinics | Users with various levels of work experience and educational background | NCCLS, EN375 |
| 17 | Qualitative | Specimens from patients with allergy and patients without allergy | Medical personnel who have been trained in the use of the IVD | DIN/ISO13485 |
| 18 | Qualitative | - | - | Nss |
| 19 | Qualitative | - | - | Nss |
| 22 | Qualitative | - | - | Nss |
| 25 | Qualitative | Specimen from patients suspected of having influenza and paediatric | - | EN375 |
| 13 | Quantitative | Not specified (multi-centre study at three sites) | Professionals and lay users | ISO 15197 |
| 14 | Quantitative | Specimens from non-diabetics, type I and type II diabetics | trained operators, untrained operators, lay persons | IFCC standard |
| 15 | Quantitative | - | - | NCCLS docs, ISO 15197 |
| 16 | Quantitative | Specimens from healthy volunteers and hospitalised patients | Doctors' offices | Internal SOP |
| 23 | quantitative | Specimen from a clinic and a study under consumers was performed (self-test) | Health care professionals | EN13612, EN375 |
| 26 | quantitative | - | - | Nss |
| 27 | quantitative | - | - | NCCL protocol EP5 |
| 29 | quantitative | - | - | Nss |
| 31 | quantitative | - | - | NCCL protocol EP5 and EP9 |
| 32 | quantitative | Specimen from potentially pregnant women | - | NCCLS |
| 33 | quantitative | - | - | Nss |
| 28 | semi-quantitative | Description of the origin of the specimen is not available. | Tests are performed by students. | Nss |

Nss- No standard specified, SOP –Standard Operating Procedure.

CTS-Common technical specification for in vitro-diagnostic medical devices (5)

NCCLS – The National Committee for Clinical Laboratory Standards (EP5: Evaluation of Precision Performance of Quantitative Measurement, EP9: Method Comparison and Bias Estimation Using Patient Samples)

EN 375- Information supplied by the manufacturer with in vitro diagnostic reagents for professional use (6)

ISO13485- Medical devices –quality management systems –Requirements for regulatory purposes (10)

ISO 15197- In vitro diagnostic test systems -- Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus (11)

IFCC –International Federation of Clinical Chemistry and Laboratory Medicine

EN 13612- Performance evaluation of in vitro diagnostic medical devices (7)

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