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

Blood glucose meters

Performance of devices on the Dutch market

RIVM Letter report 2016-0087
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Synopsis

Blood glucose meters
Performance of devices on the Dutch market

In 2015, the performance of blood glucose meters available on the Dutch market has been questioned. Blood glucose meters are used by part of the patients with diabetes to monitor their blood glucose levels. Therefore, RIVM assessed technical documentation of these medical devices, the reliability of measurements in practice and possible consequences for patients with diabetes. Manufactures are obliged to have technical documentation available, but the documentation showed shortcomings. Data from clinical chemistry laboratories showed that blood glucose measurements fail the tests according to the laboratories criteria in 21% (range 0-44%), dependent on the meter used by the patient.

Experts claim that inaccurate blood glucose measurements do not necessarily lead to hazardous situations because of the regular checks built into the system for diabetes management in the Netherlands. Patients should receive all the information necessary about these checks. For example, health care providers regularly test blood of patients with diabetes, in order to prevent the patient from using too high or too low doses of insulin for a longer period of time.

Shortcomings in the technical documentation often concerned information about the quality of the meter, and the gathering of information about the meter after it has been granted market authorization (*post marketing surveillance)*. Complete and correct documentation is important to warrant quality and safety of the device for patients and needs to be complete and correct. The technical documentation is relevant for the market authorization of the product. However, shortcomings in the documentation do not necessarily mean that the quality and safety of the meter is insufficient. Among the meters that showed shortcomings or that performed worse than others in laboratory tests were meters from both established manufacturers and from new players on the Dutch market.

Besides possible inaccuracies of the meter, several additional factors may influence the quality of a blood glucose measurement. These may be ambient conditions such as temperature, and not complying with the instructions for use, such as hand washing before using the meter. European legislation allows meters to deviate a maximum of 15% from the actual blood glucose level. However, it is important to reduce all potential sources of deviation as much as possible as the potential deviation may be larger when these sources add up. Moreover, it is important patients receive appropriate guidance when they are required to switch to another meter.

Keywords: diabetes, blood glucose meters, blood glucose measurement, performance, technical documentation, assessment, clinical laboratories

Publiekssamenvatting

Bloedglucosemeters
De situatie op de Nederlandse markt

In 2015 is de meetnauwkeurigheid van bloedglucosemeters voor patiënten met diabetes ter discussie gesteld. Bloedglucosemeters worden door een deel van de patiënten met diabetes gebruikt om de hoeveelheid suiker (glucose) in het bloed in de gaten te houden. Het RIVM onderzocht daarom de technische dossiers over deze medische hulpmiddelen, de betrouwbaarheid van de meting van bloedglucose in de praktijk en eventuele gevolgen voor de gezondheid van patiënten. De technische dossiers, die fabrikanten verplicht moeten aanleggen, bleken tekortkomingen te vertonen. In onafhankelijke laboratoria voldeed, afhankelijk van de gebruikte meter, 21 procent (met een spreiding tussen de meters van 0 tot 44 procent) van de metingen niet aan de nauwkeurigheidseisen die het laboratorium stelde.

Volgens experts hoeven er geen gevaarlijke situaties te ontstaan door onnauwkeurige bloedglucosemetingen doordat de Nederlandse diabeteszorg verschillende vangnetten biedt. Patiënten moeten goed geïnformeerd worden over deze vangnetten in de diabeteszorg. Zo wordt het bloed van patiënten periodiek gemeten door de zorgverlener, waardoor de kans klein is dat lange tijd verkeerde hoeveelheden insuline worden ingespoten.

Tekortkomingen in technische dossiers betroffen vooral de informatie over de kwaliteit van de meter en over de informatievergaring over het product nadat het op de markt is gekomen (*post market surveillance*). Volledige en correcte dossiers zijn essentieel om de kwaliteit en veiligheid van het hulpmiddel voor de patiënt te waarborgen. Deze informatie is belangrijk bij de toelatingsprocedure van het product op de markt en moet correct en volledig zijn. Onvolledigheden betekenen overigens niet per definitie dat een product onveilig of onnauwkeurig is. Zowel de meters van nieuwe spelers op de Nederlandse markt als meters van gevestigde marktpartijen vertoonden tekortkomingen in de dossiers of scoorden slechter in de laboratoria.

Verder blijkt dat buiten de kwaliteit van het meetinstrument ook andere factoren van invloed zijn op de resultaten van bloedglucosemetingen. Dat kunnen omgevingsfactoren zijn zoals de temperatuur, maar ook het niet naleven van de gebruiksaanwijzing, bijvoorbeeld handen wassen voor gebruik. Europese regelgeving staat toe dat bloedglucosemeters maximaal 15 procent afwijken van de feitelijke waarde in het bloed. Het is wel van belang om alle mogelijke verstorende factoren zo klein mogelijk te houden omdat deze opgeteld tot een grotere afwijking kunnen leiden. Daarnaast is het belangrijk om patiënten die van meter wisselen hier goed bij te begeleiden.

Kernwoorden: diabetes, bloedglucosemeter, bloedglucosemeting, prestaties, technische documentatie, beoordeling, klinische laboratoria

Contents

1 Introduction

1.1 Diabetes mellitus

Diabetes mellitus is a metabolic disorder that involves a disturbed glucose metabolism. The disease is caused by defects in secretion or action of insulin: a hormone produced in the pancreas that promotes absorption of blood glucose into fat, liver and skeletal muscle cells. A distinction is made between type 1 diabetes in which insulin is depleted due to an auto-immune reaction in the pancreas, and type 2 diabetes, involving a combination of insulin resistance and insufficient insulin production (1). Worldwide, 415 million adults have diabetes, and by 2040 this will rise to 642 million (2). In the Netherlands, almost 1.1 million people with diabetes are known by the general practitioner, about ten percent has type 1 diabetes (3). All patients with type 1 diabetes are dependent on daily insulin administration. About 18% of patients with type 2 diabetes need insulin injections because the disease cannot be managed with oral medication, diet and exercise only.

People with diabetes are at higher risk of developing disabling health problems. Administering too much insulin results in low blood glucose (hypoglycemia). This manifests itself in symptoms like shakiness, sweating, nervousness, rapid heartbeat and blurred vision. If left untreated, hypoglycemia may lead to a seizure or unconsciousness. The opposite, under dosing of insulin, leads to high blood glucose (hyperglycemia). Early signs include frequent urination, thirst, headache and fatigue. If left untreated, ketones build up in blood and urine, resulting in a fruity-smelled breath, nausea and vomiting, shortness of breath and eventually coma. Complications resulting from consistently high blood glucose levels may include macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) (4). The risk of developing these complications depends on both duration and magnitude of the high blood glucose. Although complications may begin to develop years before the diabetes is diagnosed, they may be recognized much later (5).

1.2 Monitoring blood glucose

The discovery of the blood glucose test strip and the first meters for home glucose monitoring in the 1980s enabled self-monitoring of blood glucose (SMBG) for insulin dependent patients. From then on, patients could independently monitor their blood glucose concentrations, and adjust insulin doses accordingly in order to improve glycemic control. It is now generally acknowledged that improving glycemic control decreases the risk of especially the above mentioned microvascular complications and macrovascular complications (6, 7).
The goal of SMBG is to achieve blood glucose levels as near to normal as possible in order to prevent long-term complications. Nowadays, SMBG is an important therapy component for insulin-treated patients with diabetes (8). For many patients with diabetes, SMBG is every day practice, but the frequency of measuring blood glucose varies. For example, for patients with an intensive insulin program, taking three or

more injections per day, targeted SMBG of four to five times a day is recommended (8). A positive correlation between frequency of SMBG and glycemic control among patients with insulin-treated type 1 or type 2 diabetes has been demonstrated (9). SMBG not only comprises self-measurement of the capillary glucose concentration, but also self-regulation: interpreting the readings and responding adequately. In the Netherlands, several health care providers are involved in the supervision of patients performing SMGB, such as the general practitioner, the diabetes specialized nurse and the pharmacist. Self-measurements of blood glucose are performed with a blood glucose meter (BGM). In the Netherlands, an estimated 260.000 patients with diabetes are dependent on insulin administration and thus use a BGM. The patient applies a small drop of blood, obtained by means of a finger prick, onto a disposable reagent test strip. Enzymatic reagents on the test strip such as glucose oxidase, glucose dehydrogenase or hexokinase react with the blood glucose. Subsequently, the meter detects the products of the enzymatic reaction and calculates and displays the blood glucose level in units of mmol/l. People with diabetes are taught to use their SMBG results to correct deviations from their blood glucose target range by either changing intake of carbohydrates, by exercising, or by using more or less insulin. Effective and reliable monitoring of blood glucose may depend on several factors. For example, the correct use of the BGM and strips, and the quality of the device may play a role (10).

1.3 Market authorization of BGMs in the Netherlands

The market for in-vitro diagnostic medical devices is a European market, governed by European legislation. BGMs have to comply with Directive 98/79/EC on In-Vitro Diagnostics Medical Devices (11), which is transposed in the Dutch legislation as the Decree on In-Vitro Diagnostic Devices (12). The market access of a BGM to the European market requires a third party, a so-called notified body[1], to be involved. Basically, two procedures can be followed. In the first procedure, manufacturers have a full quality system, which is to be checked and approved by the notified body. The devices manufactured under this quality system are granted market access, without further assessment by the notified body. For devices used for self-testing, the Decree additionally requires the Notified Body to check aspects of the device specifically related to the use of these devices by untrained users, e.g. instructions for use and test reports related to the use by untrained users. The second procedure requires the notified body to examine both the documentation and a representative sample of a specific BGM, including the aspects of the device specifically related to self-testing. The common method for BGMs to show compliance with the device-related requirements in the Directive is to comply with the harmonized EN ISO 15197 standard for BGMs. The standard requires tests on both the analytical performance as well as the technical and safety aspects. The first edition of the standard was published in 2003 and was revised in 2013 (13, 14). The 2013 version superseded the 2003 version in June 2016.

[1] A notified body is an independent, government-approved testing and certification organization, which verifies whether medical devices meet all quality requirements and the specifications laid down by law. A manufacturer may choose which of the European notified bodies is to inspect and assess its products. [Source: http://www.igz.nl/english/medical_devices/]

The 2013 version of the standard requires that bloodglucose monitoring systems meet with both of the following minimum criteria for acceptable system accuracy (15):

a) **95%** of the measured glucose values shall fall within either ±**0,83** mmol/l (±15 mg/dl)[2] of the average measured values of the reference measurement procedure at glucose concentrations <5,55 mmol/l (<100 mg/dl) or within **±15 %** at glucose concentrations >5,55 mmol/l (>100 mg/dl).
b) **99%** of individual glucose measured values shall fall **within zones A and B** of the Consensus Error Grid (CEG) for type 1 diabetes (16).

At present, there is no requirement to engage an independent laboratory for testing the BGMs against the ISO standard as part of the market authorization procedure.

1.4 Aims and scope of the study

From January 2015, health insurance companies changed their reimbursement policies and decided to reimburse only a limited number of BGMs, e.g. only those supplied by a contracted supplier. As a result of these changes, patients could be required to switch to another BGM, as their previous BGM and associated strips were no longer reimbursed (17).
The Dutch Diabetes Association (DVN) raised their concerns about patient safety which was also addressed in a television broadcast (18). The changes highlighted above resulted in commotion amongst patients with diabetes and a discussion on BGMs and their accuracy (19). For example it was claimed in the media that, differences were observed between blood glucose measurements using different BGMs and that BGMs introduced by new market players in the Netherlands are not accurate enough.
This study aims to address the performance of BGMs from both established manufacturers and new players on the Dutch market and the potential clinical consequences of inaccurate blood glucose measurements. The following research questions will be addressed:

1. Is the performance of BGMs sufficiently warranted?
   - Do BGMs fulfil the regulatory requirements (IVDD) according to technical documentation provided by the BGMs manufacturers?
   - What information on post marketing surveillance (PMS) is available with the manufacturers of BGMs?
   - What is the performance of BGMs in tests performed by independent clinical chemistry laboratories?
2. What could be the impact of inaccurate blood glucose measurements on patient safety?
   - What factors may influence accuracy of blood glucose self-measurements?
   - What are potential clinical consequences of inaccurate blood glucose measurements?

[2] Besides the standard unit of mmol/l in the Netherlands, blood glucose can also be expressed in mg/dl.

2 Methods

2.1 General approach

To investigate the quality of BGMs on the Dutch market, data from the technical documentation provided by BGMs' manufacturers, and data from independent clinical chemistry laboratories were analyzed. In addition, data gathered from interviews with stakeholders and from literature search were combined to provide a comprehensive overview of Dutch health care pathways in diabetes care, factors that may influence blood glucose measurements, and potential impact of inaccurate measurements on patient safety. Testing analytical performance of BGMs, according to the tests described in the EN ISO 15197 standard, was beyond the scope of this first explorative study primarily aimed at obtaining insight in the extent of a potential problem with BGM's on the Dutch market

The combination of data acquired from interviews and literature and from assessment of technical documentation enables the assessment of quality of medical devices (20, 21).

2.2 Literature search and interviews

2.2.1 Literature search

A literature and internet search was performed to provide context on diabetes care and blood glucose measurements. The search aimed to obtain information on:

- Health care institutions in the Netherlands involved in monitoring blood glucose monitoring
- Factors that may impact accuracy of blood glucose measurements
- Clinical consequences of inaccurate blood glucose measurements
- Analytical performance of BGMs and test strips.

2.2.2 Interviews

Interviews with experts in the field and relevant stakeholders were performed to obtain information on perceived problems with BGMs and possible clinical consequences. Interviews were semi-structured, had open-ended questions and addressed the following topics:

- Interviewees' position in the field of diabetes care
- Perceived problems with BGMs
- Opinion on the consequences of inaccurate BGM measurements.

As a varying group of stakeholders was interviewed, the interview further focused on the points brought up by that stakeholder. Results of each interview were summarized in reports, which were sent to the interviewees for approval.

Interviewed stakeholders (1-3 representatives) and experts:

- Netherlands Society for Clinical Chemistry and Laboratory Medicine (NVKC)
- TÜV Rheinland the Netherlands
- Dutch association of manufacturers and importers of in vitro diagnostics (Diagned)

- The Royal Dutch Pharmacists Association: the umbrella organization for both professional pharmacists and the pharmacy in general (KNMP)
- Dutch professional organization for diabetes care providers (EADV)
- Netherlands Diabetes Federation (NDF)
- Experts in diabetes care and research.

2.3 Assessment of technical documentation of BGMs

2.3.1 Selecting BGMs for inclusion in the study

A list was created of BGMs available on the Dutch market. This list was based on BGMs that were reimbursed by health insurance companies in the Netherlands in the period 2014-2015. In addition, an internet search was performed in order to add BGMs to the list that were supplied by Dutch websites or stores but are not reimbursed by health insurance companies. When available, the list also contained information on a number of relevant parameters for the selection of meters such as the TÜV quality mark[3], and outcome of performance tests in literature.

Two BGMs were selected for each manufacturer/distributor that is well represented on the Dutch market and from two other manufacturers/distributers that had a relative large number of BGMs on the market, that were also reimbursed. One BGM was selected from the remaining manufacturers/distributers on the list. Information obtained from literature concerning analytical performance of BGMs, the TÜV quality mark, as well as information provided during the interviews was used to select individual BGMs, when the manufacturer/distributor marketed several BGMs.

2.3.2 Requesting technical documentation

The Dutch Health Care Inspectorate (IGZ) contacted the manufacturers of the selected BGMs. Manufacturers were requested to provide the following information to be processed and reported on anonymously in an RIVM letter report (see Annex 1 for full list of required documentation set and description):

1. Device description
2. Label and instructions for use
3. Risk analysis
4. Product verification and validation – relevant parts for this investigation:
   - General
   - Analytical performance testing
   - Mechanical testing
   - Studies carried out with lay persons
5. Procedures and reports:
   - PMS procedure
   - Summary and analysis of PMS data
   - Information on vigilance actions.

[3] TÜV Rheinland performs measurements on a yearly basis on BGMs to show that a particular type of BGM (still) complies with the requirements in the EN ISO 15197:2013 standard for BGMs (see 3.2.2). A BGM that fulfils the requirements obtains a TÜV quality mark. Despite the presence of a CE mark that indicates a BGM conforms to the IVD Directive, a number of health insurance companies, as a prerequisite for reimbursement, require this additional quality mark.

Following receipt, the documentation was checked for completeness and any missing documentation was requested. BGMs with incomplete documentation sets or BGMs for which no information was received, were excluded from this study. The IGZ will follow up with the manufacturers/distributors that did not submit the information in time for this investigation.

2.3.3 Assessment method

To facilitate consistent assessment, the documentation was assessed independently by two assessors, after which assessments were compared, and any discrepancies were discussed and resolved. The assessment form (see Annex 3) was developed in order to enable a structured and uniform assessment of the documentation sets. Several sub-items (e.g. device description) were used as background information for the assessment. For most sub-items requested, presence of adequate information was scored with 'yes', 'no', or 'partial' if applicable. For certain sub-items, a similar scoring was used, but using dedicated terminology for that sub-item, e.g. 'no', 'limited', 'clear' for PMS procedure, and summary and analysis of PMS data. Using a scoring system that discerned sub-items of normal and major importance in relation to risk and safety aspects, eventually an item was classified as 'good', 'moderate' or 'insufficient'. Failing one major sub-item led to an insufficient score. For the analytical performance, the PMS procedure and the summary and analysis of PMS-data, all sub-items were considered to be of similar importance. As all sub-items were considered essential, a score was insufficient when one sub-item was missing.

2.4 Results from clinical chemistry laboratories

Several clinical chemistry laboratories in the Netherlands offer patients the opportunity to annually check the performance of their BGM. During this check, the value measured using the patient's BGM is compared to the blood glucose measurement of the laboratory using their standard method. An electronic survey among clinical chemistry laboratories was conducted in collaboration with the Netherlands Society for Clinical Chemistry and Laboratory Medicine (NVKC). Laboratories that were contacted by the NVKC (n=82) were asked about the annual performance checks of BGMs recommended by the NVKC (22), about the number of tests performed since January 1st, 2014 until the date of response, about the number of times a BGM or the strips failed the tests, and about the criteria that were used for a BGM to fail or pass the tests. Last, laboratories that were willing to share data with the RIVM were requested to send their data.

Data supplied by the laboratories were categorized according to types of BGMs and manufacturers. Incomplete BGM names or types (i.e. it was unclear what type of BGM was tested) were removed from the list. Subsequently, the number of times a specific BGM was tested and passed or failed the tests according to the criteria used by the specific laboratory was assessed. The percentage of BGMs that passed or failed the tests according to the criteria specified by the laboratories was calculated per specific BGM, per laboratory and overall. Data were analyzed anonymously.

3 Results

3.1 Literature search and interviews

Representatives of stakeholders and experts were interviewed and their views, combined with findings from scientific literature, are summarized in the paragraphs 3.1.1-3.1.3. The text refers specifically to literature when this was available or to the whole set of interviews indicated by the reference number (23).

3.1.1 Blood glucose management for patients with diabetes in the Netherlands

In the Netherlands, the chain of blood glucose management starts when either the general practitioner or a medical specialist (internist or endocrinologist) diagnose a patient with diabetes (Figure 3.1) (23). Patients with diabetes who are insulin dependent – all patients with diabetes type 1, and part of patients with diabetes type 2 - will be required to perform self-monitoring of blood glucose (SMBG) (24). Subsequently, the patient visits a physician assistant of the general practitioner (PA) or a diabetes specialized nurse (DSN). This health care provider educates the patient about management of the disease and measuring blood glucose. Together with the patient, the PA/DSN decides on a specific type of BGM. This decision is based on experiences of the healthcare provider, on the contracts with the patient's health insurance company, and additional factors such as the patient's age, lifestyle, visual and hearing ability, hand function, type of diabetes, comorbidities (e.g. renal failure) and required frequency of blood glucose measurements. Most health insurance companies categorize sub-selections of meters for groups of patients with specific requirements such as meters to be used for patients with impaired vision or hand function (23).

The patient may be able to take the BGM home when the particular meter is in stock with the PA/DSN. Otherwise, the patient collects his/her BGM at the pharmacy or it may be sent to the home address by the supplier contracted by the health insurance company. After having received the BGM, the correct use, control, and maintenance of the BGM and the strips will be explained to the patient. This can be done by either the PA/DSN, by a pharmacist or, by the supplier of the BGM. The patient is regularly checked by the PA/DSN in the management of blood glucose levels (23). Every three months, a clinical chemistry laboratory tests the patient's HbA1c level, which is an index of the average glucose level over the preceding weeks to months. This HbA1c level provides information about whether a patient is in good glycemic control (23, 25).

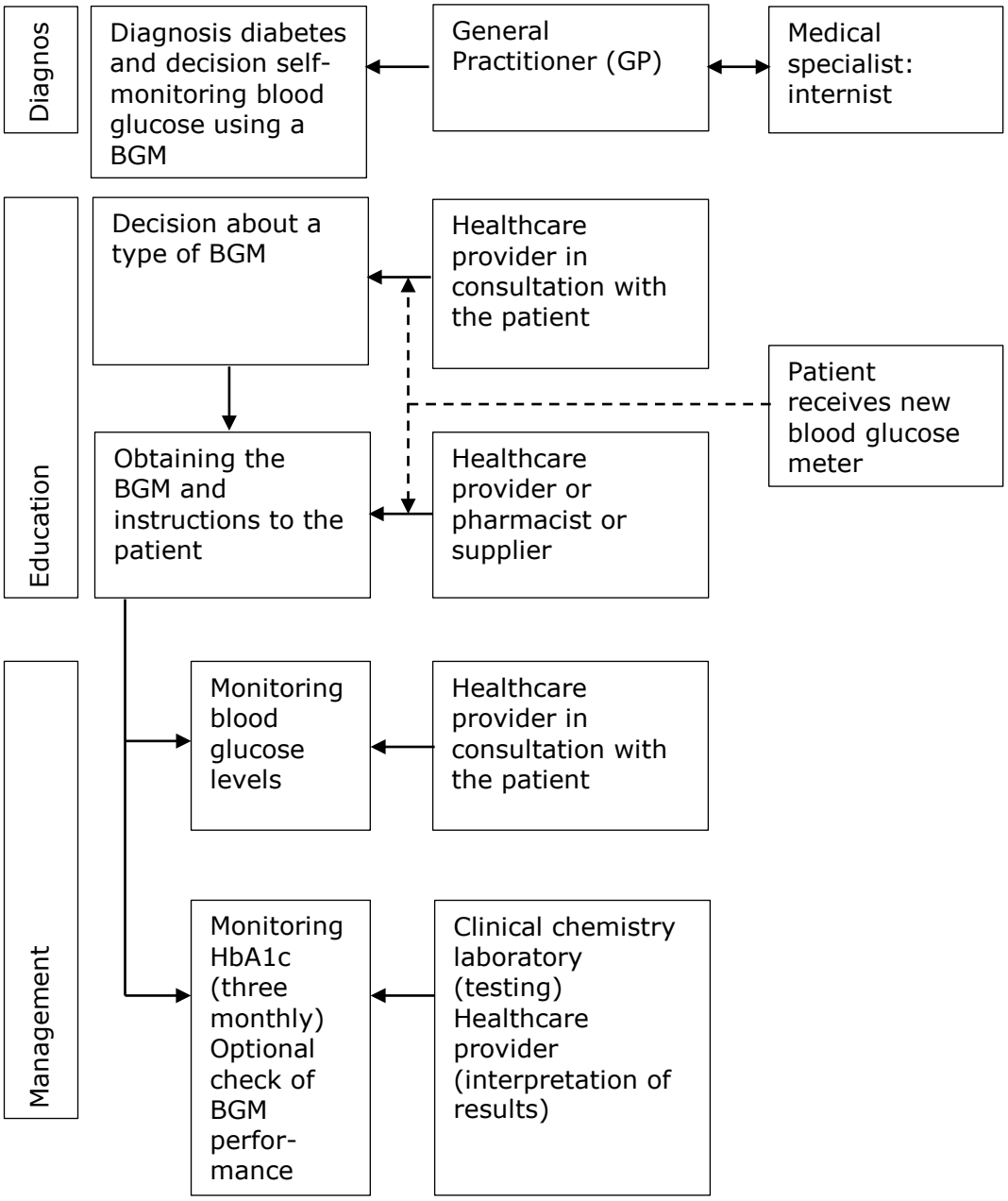


Figure 3.1: Chain of blood glucose measurements in the Netherlands.

3.1.2 *Expert views on diabetes care and switching to other BGMs*

Experts in diabetes care and research, and the various stakeholders indicated that diabetes care in the Netherlands is generally good, especially when compared to other countries (23). According to stakeholders, the patient should be made aware of the possible measurement deviation between devices and the fact that a new balance must be created between the measurement of the BGM and the action to be taken, to remain in good glycemic control. This process must be controlled and supervised by the healthcare provider. In the beginning of 2015, patients were required to switch to other BGMs due to the changes in reimbursement introduced by health insurance companies. In interviews it was addressed that communication about

this issue by the pharmacists and the PA/DSN may initially have been insufficient, resulting in inadequate supervision of patients and questions among patients (23). In the months following this change, these problems in communication were mostly solved. In response to the commotion, a consensus document is being developed by the NDF, EADV, DVN, NVKC, KNMP, the Diabetes General Practitioners Advisory Group (DiHAG), Dutch Association of Dietitians (NVD), Dutch association internal medicine (NIV), Scientific association of Dutch Pediatricians (NVK), Federation of technology branches (FHI), Diagned, and health insurers the Netherlands (ZN), in collaboration with BGM manufacturers, suppliers and health insurance companies that includes information about instructions and education to patients who are required to switch to another BGM (23).

Several stakeholders noted that the switch to other BGMs has induced commotion, although according to their knowledge, no acutely dangerous situations for patients or their health have occurred (23). Additionally, experts in diabetes care and research indicate it is unlikely – especially for an experienced patient with diabetes – not to recognize the symptoms of a hypoglycemia or even a considerably different blood glucose concentration. Initial symptoms of a hyperglycemia may be more difficult to recognize compared to those of low blood glucose levels. Therefore, patients using too low doses of insulin for a longer period – which could be the result of deviations in blood glucose measurements – may be at increased risk for long-term complications (23). In exceptional cases, a patient could have injected incorrect doses of insulin for up to six months, considering the regular checks built into the system for diabetes management in the Netherlands. In most cases, the patient would contact the PA/DSN after having recognized an unusual difference between their old and the new BGM, thus solving potential problems (23).

The diabetes mellitus type 2 guideline of the Dutch College of General Practitioners (NHG) mentions that general practitioners must point out the importance of annual checks of the BGM by an accredited laboratory to the patient. However, health care providers do not routinely monitor the regular performance of this annual check (23).

3.1.3 Accuracy of blood glucose measurements and insulin dosing

During normal use, besides possible inaccuracies of the BGM itself, several additional factors may influence the quality of a capillary blood glucose measurement performed at home by a patient with diabetes (17). These may be categorized into factors regarding ambient conditions, interfering substances, physiological factors, and issues during use.

In general, BGM and strips are tested under stable temperature, humidity and at sea level. However, measurements of BGMs have shown to deviate at high altitudes, in practice as well as under standardized conditions in the lab (26). Moreover, variations in O_2 pressure in blood samples may cause deviations – especially for systems using the enzyme glucose oxidase – and most of the test strips on the market are temperature dependent. Despite manufacturers testing devices over a certain temperature range (often between 10 and 40 °C), some BGMs

showed deviations in blood glucose measurement results of more than 5% within this temperature range (27). Temperature shifts may also cause deviations, e.g. when the BGM or strips are transported from conditions outside to room temperature (27).

Certain substances interfere with the enzymatic reaction that takes place on the test strip. An important example is the widely used analgesic agent acetaminophen (in Dutch: paracetamol). Above a certain concentration of acetaminophen, which varies between patients, it may impact blood glucose measurements causing inaccurately high values (28). According to experts in diabetes care and research, in extreme situations this may lead to variations of up to 20% (23). With regard to physiological factors, a low hematocrit value in the blood may result in extremely high blood glucose values (29). Low blood hematocrit values may occur when a patient suffers from anemia, certain types of cancer, renal disease, malnutrition of specific diet deficiencies, rheumatoid arthritis or other conditions.

Issues arising during use may be the most important source of deviations (23). First, compliance to SMBG varies considerably between patient groups, e.g. adolescents are known to often not comply with directives (23). Inappropriate handling of the BGM or the test strips may substantially impact the results of blood glucose measurements. For example, it is important for patients to obtain an adequate drop of blood, since a low volume or incorrect application on the strip can affect the measurements (10). However, many BGMs have a system that should detect underfilling of the test strip. Patients may also use test strips that are deteriorated, which may be caused by expiration or due to inappropriate storage of the strips. Analytical stability of a blood glucose measurement system decreases when strips are stored in open vials, at high humidity, at high temperature, or in direct sunlight (30).

A major and well-known source of inaccurate blood glucose values are unwashed hands. Sugar containing products such as fruits leave considerable amounts of glucose on the skin which has shown to result in false high blood glucose measurements (31).

The administration of insulin is not subject to considerable variation (23). Nowadays, insulin concentration in syringes is fairly accurate as insulin pens contain 100 units/ml with a maximum of 10% deviation, but often much less (23, 32). However, the resorption of insulin may vary substantially. This depends on using short-acting or long-acting insulin, but also on temperature, physical activity and stress. Patients must take these considerations into account when using insulin (23).

3.2 Technical documentation of BGMs

3.2.1 BGMs on the Dutch market and selection for the study

Health insurance companies together provide reimbursement for up to eighty different BGMs. Market leaders such as Roche, Abbott, LifeScan and Bayer have dominated most of the market for years. However, since a few years, new players on the market are emerging, and these have changed market shares for BGMs. Although headquarters are located in western countries, the vast majority of BGMs are manufactured in Asian

countries. Based on the criteria described in paragraph 2.3.1, 27 BGMs marketed by 21 manufacturers were selected for further evaluation (see Annex 2). The results presented in this report are anonymized.

3.3 Assessment of documentation

Of the 27 BGMs for which the technical documentation was requested by IGZ, the documentation of seven BGMs was not assessed. Four BGM documentation sets were incomplete and therefore could not be included in the assessment process. Three BGMs were excluded because the BGMs were not delivered to patients in the Netherlands or the manufacturer or distributor could not be contacted due to uncertainties about the contact details obtained from the internet. Overall, the documentation of 20 BGM was assessed (Annex 2). Among these 20, eight were from manufacturers that have been on the Dutch market for a considerable time.

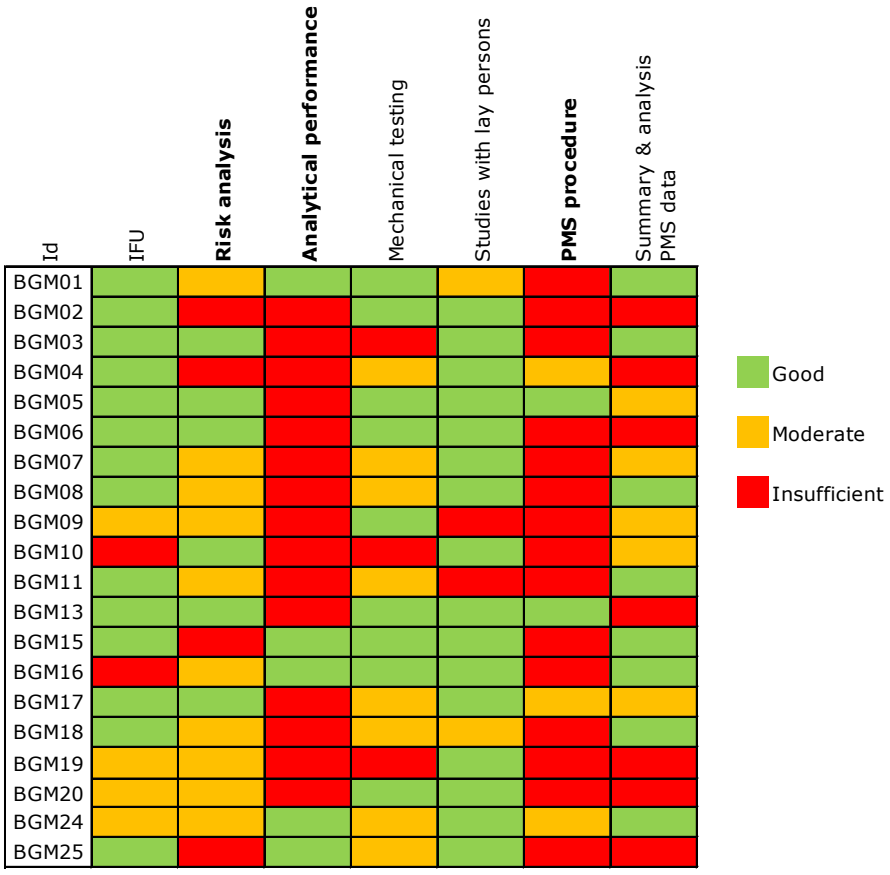
The following paragraphs summarize the results of the technical documentation assessment, starting with an overview of the overall quality per BGM. The subsequent paragraphs describe the findings in more detail for what were considered the most critical items: risk analysis, analytical performance and PMS. Details of the results of the technical documentation assessment are presented in Annex 4.

3.3.1 Overall quality of the documentation

The assessment scores varied considerably per BGM documentation set (Figure 3.2), but none of the documentation sets was entirely 'good', 'moderate', or 'insufficient'. Only one documentation set had no 'insufficient' items. For all of the documentation items, shortcomings were found in part of the files (Figure 3.2). Analytical performance and PMS procedure items often scored 'insufficient'. The items IFU and studies with lay persons most often scored 'good'.

3.3.2 Risk analysis

The risk analyses for half of the BGMs addressed all required general risk categories based on hazards as derived from the standard for risk management of medical devices (33) (see Table A4.3). Examples of categories that were missing in some cases are: incomplete design requirements, hazards related to the manufacturing process, cleaning/disinfection, and disposal/scrapping. BGM-related risks, including contra-indications, as identified in the literature were not fully addressed in five of the cases. Physiological interferences, e.g. endogenous/exogenous substances, dehydration, were not analyzed and evaluated. Risk control/mitigation was described partially in three of the cases. Acceptability of residual risks was not addressed once. Overall, risk analyses for four BGMs scored 'insufficient', ten scored 'moderate', and six scored 'good'.



Abbreviations:

BGM	Blood glucose meter
Id	Identification code
IFU	Instructions for use
PMS	Post-market surveillance

Figure 3.2: Results of the assessment of technical documentation

3.3.3 *Analytical performance*

The analytical performance frequently scored 'insufficient', mainly due to non-compliance to requirements with regard to interfering substances (Table A4.4). For five BGMs, manufacturers indicated that the BGM complied to EN ISO 15197:2003, whereas the other manufacturers claimed compliance to the 2013-version of the standard (Table A4.5). Nine BGMs did not fulfill the system accuracy requirements. For one BGM (BGM08) the system accuracy for the low blood glucose levels was below the minimum acceptance criteria of 95% (94.4%), although this deficiency was not acknowledged by the manufacturer (Table A4.5). Three other cases referred to acceptance criteria with a cut-off of 6.5 mmol/l (instead of 5.55 mmol/l), see paragraph 1.3. One manufacturer did not submit the documentation on analytical performance, but merely a TÜV Report (BGM09). As TÜV Reports do not contain all the testing as is required in the standard, these cannot be used to claim compliance to the standard. For one BGM (BGM01), a TÜV report was submitted additionally, which indicated that the analytical performance was not in accordance with the requirements in the standard.

3.3.4 PMS procedure

The concept of the continuous cycle of improvement of medical devices requires the manufacturer to use results from PMS activities as feedback in the risk management process and to consider the need for corrective and preventive actions (CAPA), including changes in design and/or IFU.

Most of the submitted documentation about PMS procedures contained a description for the collection, and review of experiences concerning BGMs in an active manner, using at least two methods such as literature review and/or customer surveys (Table A4.6). Four PMS procedures did not use two or more active PMS sources. Complaints as a passive source for PMS data were always used. A specific approach for receiving user feedback was absent in more than half of the PMS procedures. Manufacturers should be aware that collecting user experiences of self-test in vitro diagnostic medical devices such as BGMs requires more direct contact with the end-user.

Only four PMS procedures noted criteria for the necessity to take actions as a consequence of PMS outcomes, indicating inadequacies/problems were well-defined. Eight manufacturers (12 BGMs) indicated that a periodic review of PMS data is conducted. Risk management activities were only briefly mentioned as stand-alone reference in five cases, while in four cases such activities were not mentioned at all. In the other cases, risk management activities were integrated in the PMS activities. CAPA was only briefly mentioned as stand-alone reference in four cases, while it was not at all mentioned in one case. In the other cases, CAPA was integrated in the PMS activities. In summary, only two PMS procedures scored ‘good’, and eighteen procedures showed shortcomings.

3.3.5 Summary and analysis of PMS data

All manufacturers submitted a summary and analysis of PMS data or a statement that no complaints had been received and thus no PMS report was submitted. Apart from complaints, other sources of PMS data were customer surveys, in-house testing, social media, and literature review (Table A4.7). Six manufacturers did not describe actions to be taken based on the PMS findings. In two cases, PMS sources were not identified. The analysis of PMS data varied considerably. In one case, only complaint rate was given and complaints were not categorized. The number of vigilance actions also varied considerably, ranging from none to 320, although most manufacturers indicated that there were actions. Due to the fact that most manufacturers indicated that there were no vigilance actions, no link could be established between the number of vigilance actions and the market share of products (Table A4.7). One BGM (BGM15) was taken off the Dutch market by the manufacturer based on PMS data. Overall, the summary and analysis of PMS data was assessed as ‘good’ in eight cases and as ‘moderate’ or ‘insufficient’ in six cases.

3.4 Results of clinical chemistry laboratories

The NVKC sent the survey to 82 laboratories. Fourteen laboratories of the 44 that completed the survey indicated to regularly perform annual performance tests of BGMs and to be willing to share the data. During

these tests, laboratories compare the value measured by the patients with their own BGM to the blood glucose measurement of the laboratory using their standard method. Of these laboratories, four did not respond to the request to send the data and three laboratories indicated to have no or only incomplete data for the suggested period (January 1st, 2014 until the date of response). The data of the seven remaining laboratories were used for the study.

Together, laboratories provided data about performance tests of 57 different BGMs from 19 manufacturers. The number of tests in the data provided by the laboratories ranged from 9 to 2079 tests per laboratory. Some BGMs were more common than others as the number of tests per specific BGM ranged from 1 to 385. In total, 2671 tests were performed (Table 3.1).

Table 3.1: number of tests performed, and tests failed per laboratory.

Laboratory	**Number of tests performed**	**Number of tests did not meet criteria**	**Percentage of tests did not meet criteria**
1	159	10	6%
2	43	4	9%
3	224	13	6%
4	9	2	22%
5	26	7	27%
6	2079	513	25%
7	131	4	3%
Total	**2671**	**553**	**21%**

The criteria that were used for a BGM to pass or fail the tests differed between the laboratories. Although the applicability of the ISO 15197 standard is currently in transition from the 2003 to the 2013 version, the BGMs on the market can still comply to the 2003 standard instead of the 2013 version, which allows deviations of up to 20% above glucose levels of 5.55 mmol/l. Nevertheless, most of the laboratories used criteria that were in some way based on the ISO 15197:2013 standard (3.2.2). Since this can be considered state of the art, this choice can be justified. Some laboratories used criteria that were even stricter. For example, one laboratory only allowed the meter to deviate a maximum of 12.2% over the whole range from the applied reference measurement. Other laboratories permitted a deviation of 15% for blood glucose levels ≥5.5, 6 or 6.5 mmol/l; at levels below that threshold the deviation was not allowed to exceed 1.0 mmol/l.

Overall, in 21% (553/2671) of the tests, the BGMs did not meet the laboratories' criteria. The percentage of BMGs that failed the test ranged from 3% to 27% between the laboratories (see also Table 3.1). There appears to be no correlation between the laboratories using more or less stringent criteria and the proportion of BGMs that passed or failed the tests. However, due to the small number of tests performed for some of the laboratories, a possible correlation may not have been picked up.

When patients use the test facility, the value measured using their own BGM is compared to the blood glucose measurement of the laboratory

using their standard method. Therefore, blood glucose measurements by the patients in the laboratory are not necessarily performed under conditions that are similar to other laboratories and may not be controlled by e.g. a technician or a nurse. Besides the quality of the BGM itself other factors may influence the measurement result such as the use expired strips or patients' refraining from hand washing (see paragraph 3.1.3). Only part of the laboratories supervise this process or this is done only in part of the cases. In some cases a patient's BGM was tested more than once, e.g. when the BGM initially failed the test, and both measurements were then included in the analysis. Overall, laboratories respond to user-induced variations in different ways.

Even though these results must be interpreted with caution, differences were observed between types of BGMs and the proportion of measurements that failed or passed the tests. Twenty-eight of the BGMs were tested for performance more than ten times, which was regarded a minimum number to interpret results of the measurements. Among these 28 BGMs 21% (range 0-44%, dependent on the BGM used by the patient) of the measurements failed the tests according to the laboratories criteria. Five BGMs failed the tests in more than 30% of the cases (Figure 3.4). Among these five BGMs were three BGMs from established manufacturers and two from manufacturers that are relatively new to the Dutch market.

Among the 28 BGMs that were tested more than ten times, for nine BGMs also the documentation was assessed and these are numbered BGM 04 – BGM 24 in figure 3.4. The other BGMs are addressed as BGM 30 – BGM 48. With regard to analytical performance, the assessment scores of the documentation appears not to be related to performance of the BGM in the data from the clinical chemistry laboratories. For example, BGM 13 and BGM 15 score worst in the laboratory tests (failed in 43% and 44% of tests respectively) but their analytical performance score 'insufficient' and 'good' respectively in the technical documentation assessment.

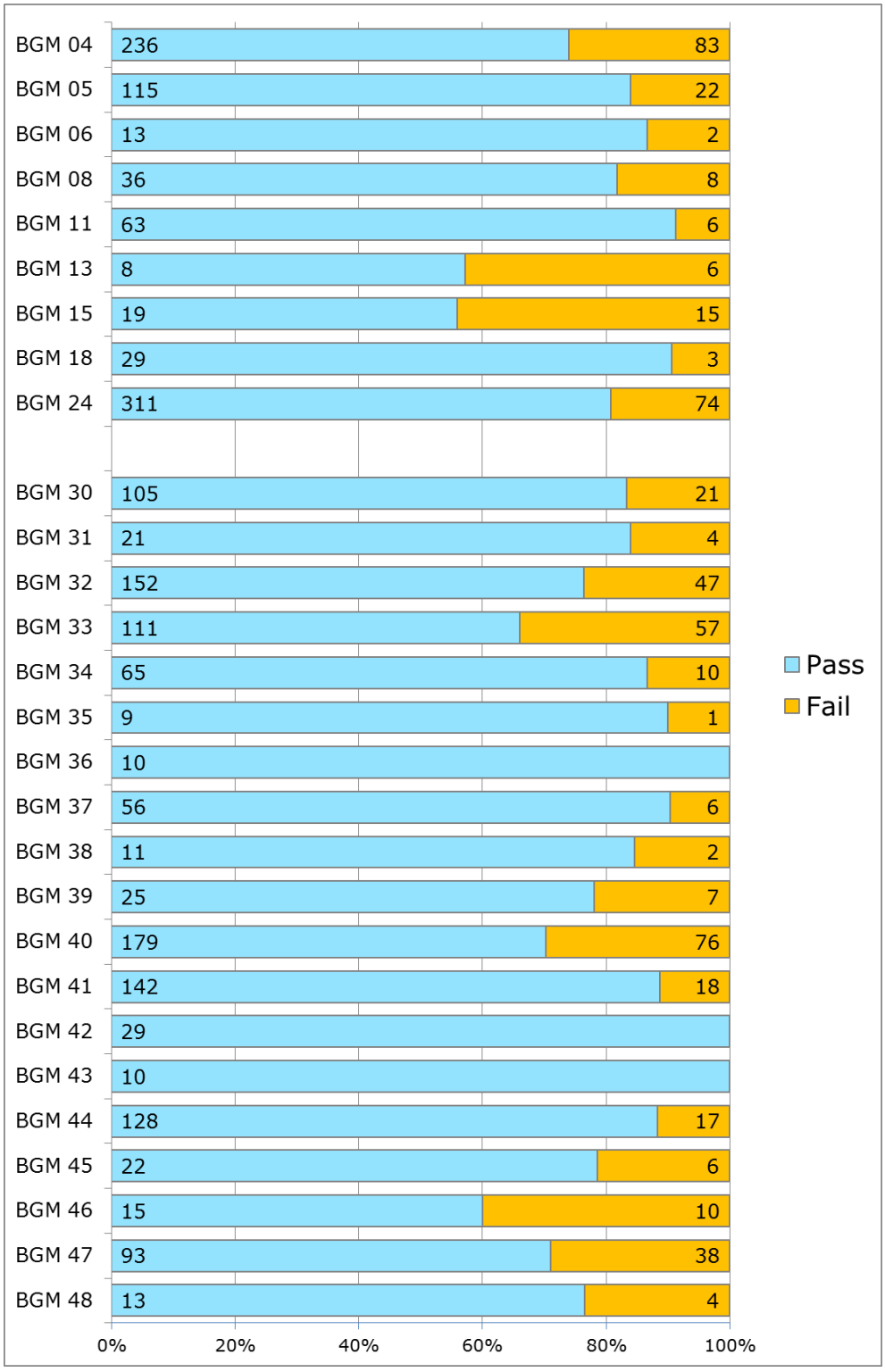


Figure 3.4: Results of seven clinical chemistry laboratories; only BGMs that were tested more than ten times were included. Patient's initial tests that may not have been monitored by a technician or nurse.

4 Discussion and conclusions

4.1 In general

This study addresses the performance of BGMs used by patients with diabetes in the Netherlands. BGMs from both established manufactures and new players on the Dutch market were included in the study. Technical documentation provided by manufacturers as well as data from annual tests of BGMs by clinical chemistry laboratories were used to assess accuracy of the BGMs. Accuracy was described in the context of the health care system for blood glucose management for patients with diabetes. In addition, other factors that may influence blood glucose measurements were described using information obtained from literature and interviews with relevant stakeholders.

Main conclusions

1. The technical documentation provided by the manufactures showed considerable shortcomings, particularly on the items analytical performance and PMS.
2. Data from clinical chemistry laboratories showed that blood glucose measurements fail the tests according to the laboratories' criteria in 21% (range 0-44%, dependent on the BGM used by the patient) of the cases, which indicates there were large differences between BGMs.
3. Among the BGMs that failed more frequently in laboratory tests or that showed shortcomings in the technical documentation, were BGMs from both established manufacturers and from new players on the Dutch market.
4. Besides possible inaccuracies of the BGM, several additional factors, including issues during use, may influence the quality of a blood glucose measurement.
5. Inaccurate blood glucose measurements may impact patient safety in some cases, but experts consider the risk of long-term complications to be low because of the regular checks built into the system for diabetes management the Netherlands.

4.2 Is the performance of BGMs sufficiently warranted?

4.2.1 Implications of shortcomings in technical documentation

Particularly the items analytical performance and PMS-procedures show shortcomings in technical documentation provided by the BGM manufacturers. Shortcomings in the submitted documentation do not necessarily mean that the quality and safety of the BGMs is insufficient. However, the regulatory system of in-vitro diagnostic medical devices depends for a large extent on the quality of the technical documentation which should demonstrate compliance to the applicable requirements. Therefore, shortcomings in that documentation could imply that product safety and safe use of the device are insufficiently warranted.

Reason for concern are the shortcomings found for the items IFU, PMS procedure, summary and analysis of PMS data, risk analysis and analytical performance. Patient safety could be impacted by several factors, such as the ability to understand the provided information in the

IFU, and/or the adequacy of the information provided. Shortcomings in the PMS activities may lead to late or no discovery of, or inadequate reaction to signals about product safety and performance. When risk management activities or corrective and preventive actions (CAPA) are not integrated in the PMS procedure, structural analysis and, if required, elimination of problems may be omitted. If the concept of continuous cycle of improvement of medical devices (20) (i.e. feeding back PMS results into the risk analysis and taking appropriate action where necessary), is not applied adequately, opportunities to improve product performance and safety might be missed. The importance of an adequate PMS system was illustrated by one BGM, that was taken off the market, due to complaints about the performance. When not all relevant risks are analyzed in the risk analysis or adequate risk control is not demonstrated, important measures to mitigate these risks may be missed. If analytical performance is insufficiently addressed this may imply that a BGM does not meet the criteria for analytical performance, such as system accuracy, resulting in measurements that may deviate too much from actual blood glucose values.

TÜV Rheinland performs measurements on BGMs to verify that a particular type of BGM (still) complies with requirements comparable to the EN ISO 15197:2013 standard. The fact that for one meter the TÜV report indicates shortcomings in the analytical performance illustrates that regular checks on the quality of the BGM and the applicable test strips after being CE-marked may be essential. Independently of the RIVM study described in this report, data of TÜV Rheinland about performance of BGMs were recently presented at the European Association for the Study of Diabetes (EASD) annual meeting on September 9th, 2016. These data indicate that 8% of 59 BGMs fail the requirements on system accuracy in TÜV tests (34). Criteria on system accuracy used by TÜV Rheinland are slightly less strict compared to the ISO 15791:2013 standard (13). Taking into account the additional criteria applied by TÜV Rheinland, e.g. with regard to reproducibility of a measurement and haematocrit and temperature range, 45% of the BGMs failed the tests (33).

In the future European in-vitro diagnostic medical device regulation, requirements for important elements of the regulatory system like PMS activities and the conformity assessment procedure will be considerably strengthened, which should aid in ensuring compliance to the legislative requirements (35). Complete as well as correct documentation is essential to warrant quality of the BGM. Therefore, it is important that shortcomings as observed in our study are adequately addressed.

4.2.2 Accuracy of BGMs on the Dutch market

Inaccuracy of specific BGMs has been described in literature, and was addressed in the media (18, 36, 37). There appears to be no link between specific BGMs that fail the tests often in the clinical chemistry laboratories compared to international reports on comparisons of BGMs (37). In clinical chemistry laboratories, BGMs failed the tests in 21% (range 0-44%) of the cases, dependent on the BGM used by the patient. There were large differences in procedures, percentages of tests that failed, and criteria used among the laboratories. There appears to be no relation between BGMs that failed in the laboratory tests, BGMs that

showed poor analytical performance in literature or BGMs that had shortcomings in the technical documentation. Nevertheless, these results suggest that BGMs may be underperforming in part of the tests, which is strengthened by the findings of the assessment of technical documentation that show shortcomings particularly with regard to the topic of analytical performance.

Data of an Dutch expert in blood glucose measurements presented at the European Association for the Study of Diabetes (EASD) annual meeting 2016 and confirmed by personal communication also showed that some of the BGMs deviate more often from the laboratory reference than others (34). In addition, this data showed that the percentage of measurements that deviates decreased considerably (0.5-4%) in a repeated measurement performed under optimized conditions, e.g. patient received education and a fresh strip was used. This illustrates that the performance of the BGM is only one factor among others that impact a blood glucose measurement. Therefore, harmonization of test procedures in the laboratories, would allow for a better comparison and consequent improvement of patients' self-monitoring of blood glucose. Reducing other factors that can influence the measurements as far as possible (as part of e.g. education) is also a major contributor to minimizing measurement deviations and consequent improvement of patients' self-monitoring of blood glucose.

With regard to the technical documentation, there appears to be room for improvement. It is expected that adequate PMS procedures help to identify technical problems with BGMs earlier. When not properly acted upon, this could lead to larger deviations than necessary. Potential added value may lie in improved communication between field parties and manufacturers about BGMs, their performance and user experiences.

4.3 Possible impact of inaccurate BGMs on patient safety

4.3.1 Clinical consequences of inaccurate measurements

In daily life, glucose measurements may deviate substantially from those performed under standardized conditions, irrespective of the BGM used (10, 38). The percentage of BGM measurements that deviate from the actual blood glucose must be evaluated in the light of other factors that potentially influence the accuracy of measurements such as ambient factors and issues during use (as discussed in 3.1.3) (23). Large deviations in the measurements (i.e. ≥30%) may result in a patient administering an under- or overdose of insulin which could in specific cases lead to hyperglycemia or hypoglycemia (23). Although the accuracy requirement is ± 15%, the manufacturer is also required to calculate the measurement imprecision, and thereby large deviations should be avoided (15). Due to the regular built in checks of HbA1c to assess whether a patient is in good glycemic control, it is, according to clinical experts, unlikely a patient consistently either uses too much, or not enough insulin over a prolonged period of time (23).
In general, although BGMs offer considerable help for patients to manage their diabetes, patients must continue to be vigilant for aberrations and symptoms. It is important for patients to be aware of the possible interfering factors, and to be able to act accordingly. In

order to keep the total deviation of a blood glucose measurement low, all potential sources of deviation should be reduced as much as possible (23).

4.3.2 Switching to another BGM

A potential risk for patients occurs when a patient switches to another BGM without adjusting insulin dosing in response to measurements. Namely, other blood glucose meters will have different systematic measurement deviations. As both the former BGM and the alternate BGM are allowed to deviate 15%, or even 20% if the BGM that was replaced was a few years old, the theoretical difference between two meters complying to the applicable standard(s) can be as high as 35%. In practice, switching meters will be necessary when the patient's health insurance company no longer reimburses a specific BGM, which can be prompted by changes in the reimbursement of BGMs as seen in the beginning of 2015 in the Netherlands.

In general, the Dutch chain of diabetes care is well equipped to respond to perceived problems with regard to SMBG (23). If the process of blood glucose management is closely supervised by the health care provider, systematic measurement deviations of the BGM of up to 15% from the actual blood glucose are not problematic. Stakeholders confirmed that to their knowledge, the policy changes and patients' switching to other BGMs have not led to significant health hazards (23).

Appropriate guidance by either the supplier, the physician assistant of the general practitioner or a diabetes specialized nurse is paramount when a patient starts using another BGM. However, the current change in the reimbursement of BGMs resulted in patients being required to switch to another meter by their insurance companies, in some cases without proper communication or education about this change to and with the healthcare provider (23).

The NDF, EADV, DVN, NVKC and KNMP, in collaboration with BGM manufacturers, suppliers and health insurance companies are developing a consensus document with quality criteria for blood glucose measurements with BGMs. The consensus document shall be made public in the near future and includes information about instructions and education for patients and recommendations about annual checks of BGMs (23).

4.4 Methodological considerations

4.4.1 Assessment methodology of technical documentation

A rather strict assessment methodology was used, in which missing one essential sub-item or an equivalent number of points led to an 'insufficient' score for a documentation item. This methodology is considered justified based on the principle that all essential elements (i.e. essential sub-items) are needed to show compliance with the requirements that a particular documentation item is covering (20, 21). It should be noted that manufactures were requested to provide technical documentation on BGMs at one moment in time. Between the assessment of the data and the publishing of this report, manufactures may already have implemented changes.

4.4.2 Analysis of data from clinical chemistry laboratories

A number of limitations must be taken into account while interpreting the laboratory results. Data supplied by the laboratories included initial measurements performed by the patients themselves, and were not necessarily monitored by a technician or nurse. Two laboratories indicated that a large extent of the deviations in measurements may be attributed to issues during use. The criteria used for BGMs to fail or pass the tests differed between the laboratories, but were mostly derived from the ISO 15197:2013 standard that states that BGMs may deviate up to 15% from the actual blood glucose level. However, the majority of the BGMs tested were likely released to the market before the introduction of the ISO 15197:2013 standard and only had to comply to the 2003 standard which allows a deviation of 20%. Therefore, the results may have been different when the same criteria had been used. There were large differences between the number of tests that were performed for the different types of BGMs and manufacturers. As the popularity of BGM types may be region specific, these numbers are not related to relative market shares of the different BGMs. In addition, two clinical chemistry laboratories stated that a large proportion of the measurements that failed their criteria was attributable to issues during use.

4.5 Conclusions

This report addressed the performance of BGMs and the potential clinical consequences of inaccurate blood glucose measurements. Both BGMs from established manufacturers and from new players on the Dutch market were assessed. Findings indicate that technical documentation provided by the manufacturers showed considerable shortcomings, particularly on the items analytical performance and PMS. Data from clinical chemistry laboratories showed that blood glucose measurements fail the tests according to the laboratories' criteria in 21% (range 0-44%), dependent on the BGM used by the patient. Among the BGMs that failed more frequently in laboratory tests or that showed shortcomings in the technical documentation, were BGMs from both established manufacturers and from new players on the Dutch market. The performance of the BGM is only one factor among others that may impact a blood glucose measurement. Therefore, correct use of the BGM is of high importance for an accurate blood glucose measurement. Inaccurate blood glucose measurements may impact patient safety in some cases. However, according to experts, the risk of long-term complications is considered low because of the regular checks built into the system for diabetes management in the Netherlands, and because patients themselves may notice when their blood glucose is too low or too high and will take required action. Patients should receive all the information necessary, about these regular checks. Finally, it is important that all shortcomings observed in this study are adequately addressed.

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Annex 1: Checklist for Dutch request study blood glucose monitoring systems for self-testing

Device description

- CE certificate
- product history/time line, including the first introduction of the device and strips, date of initial CE certification, revisions to the design of the device or strips, and, if applicable, dates of recertification;
- a general description including its intended use/purpose;
- the intended patient population and medical condition to be diagnosed and/or treated and other considerations such as patient selection criteria;
- principles of operation;
- an explanation of any novel features;
- a description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it;
- a description or complete list of the various configurations/ variants of the device that will be made available;
- a general description of the key functional elements:
    - its parts/components (including software if appropriate),
    - its formulation,
    - its composition,
    - its functionality.

  where appropriate, this will include:
    - labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts/components, including sufficient explanation to understand the drawings and diagrams;
    - a description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body, e.g. during extracorporeal circulation of body fluids.
- manufacturing site and name of the company, if this is an OEM, of the BGM
- manufacturing site and name of the company, if this is an OEM, of the strips to be used for the BGM

Label and instructions for use

The label(s) and instructions for use[†] of the device as described in essential requirement 8, including requirement 3.1 of the IVDD.

[†]For the purpose of the investigation, the labels on the device and its packaging and the instructions for use should be the ones associated with the device as marketed in the Netherlands.

Risk analysis

This documentation should contain a full report (NOT a summary) of the risks identified during the risk analysis process and how these risks have been controlled to an acceptable level. Preferably, this risk analysis should be based on recognised standards, be consistent with the manufacturer's risk management plan, and be in English. It available,

the risk management plan should be included. The information to be submitted to include/address at least:

- date/version number of risk analysis;
- reference to any standards used, e.g. EN ISO 14971;
- all hazard categories (for example: Table Annex E of the current standard EN ISO 14971) identified or declared not applicable with a rationale;
- estimates of associated risk;
- risk control, i.e. control measures that are consistently described in line with essential requirement 2 (IVDD, Annex I);
- (overall) justification/acceptability of residual risks in relation to anticipated benefits;

Product verification and validation – relevant parts for this investigation

General

The documentation should summarise the results of verification and validation studies undertaken to demonstrate conformity of the device with the essential requirements that apply to it. For this investigation, the information should cover only the following items:

- an evaluation of any published literature regarding the device or substantially similar devices;
- analytical performance testing (see 4.2);
- mechanical testing (see 4.3);
- studies carried out with lay persons (see 4.4);
- where no new testing has been undertaken, the documentation should incorporate a rationale for that decision.

Analytical performance testing

- the organization performing the testing;
- the tests conducted;
- standards applied;
- protocols of the tests conducted;
- analysis of data;
- summary of results;
- conclusion.

If other testing has been performed for your BGM (e.g. by TÜV Rheinland in the Netherlands), the test report of that analytical performance testing.

Mechanical testing

Where mechanical testing has been undertaken, detailed information should be included on:

- the tests conducted;
- standards applied;
- protocols of the tests conducted;
- analysis of data;
- summary of results;
- conclusion.

If other testing has been performed for your BGM (e.g. by TÜV Rheinland in the Netherlands), the test report of that mechanical testing (see also 4.2).

Studies carried out with lay persons
Where studies with lay persons have been undertaken, detailed information should be included on:

- the tests conducted;
- standards applied;
- protocols of the tests conducted;
- analysis of data;
- summary of results;
- conclusion.

Post-market surveillance (PMS) procedure
The submitted documentation should contain the PMS procedure, as laid down in the European IVDD, plus any directly related procedures, preferably in English. This should include:

- customer or user complaints procedure;
- a principle or procedure for the active collection and review of experiences (e.g., customer satisfaction questionnaire/surveys), to collect experiences other than (customer/user) complaints#;
- corrective and preventive actions will be taken: a principle or procedure for corrective and preventive actions is mentioned, i.e., procedure is referenced in PMS procedure;
- criteria for the necessity to take actions;
- risk management activities will be taken, e.g., update of the results of risk analysis is mentioned (PMS should be part of the risk management plan).

#Note: Sources of information for PMS are (active/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.

Summary and analysis of PMS data
In relation to the device concerned, the submitted documentation should contain a PMS report of the last three years containing the following elements:

- summary of the PMS data, including the sources used;
- analysis of PMS data;
- actions taken based on the analysis of the PMS data;

Information on vigilance actions
Description of vigilance actions undertaken since the introduction of the medical device, including reports to any European Competent Authority and (corrective) actions taken.

Annex 2: BGM's for which files were requested

Manufacturer/distributor	**BGM**
File complete and within deadline	
A. Menarini	Glucomen LX Plus+
Abbott Diabetes Care*	FreeStyle InsuLinx
Abbott Diabetes Care*	FreeStyle Freedom Lite
Arkray	Glucocard Σ Sigma
Bayer*	Breeze 2
Bayer*	Contour TS
Diabetes Checkpoint	Diabetes Checkpoint Blue-meter
Flynther	Glucosafe/gluco dr auto
GD Medical Pharma	HT One TD-GLUCO TD-4277
GD Medical Pharma / Philosys	HT One Gmate Wheel
DiME	GlucoRX Nexus mini
LifeScan*	OneTouch Select Plus
LifeScan*	OneTouch Verio IQ
Med Trust	Wellion Calla Classic
Med Trust	Wellion Luna Duo
Roche*	Accu-Chek Mobile
Roche*	Accu-Chek Performa
Ypsomed	Mylife Pura
Zkope	Dario
Isens	Isense Care Sense N
File to late or incomplete or BGM excluded	
Andon/iHealthLabs	iHealth
BodyTel Europe	Glucotel
Dicomed	SensoLite Nova Plus
Infopia	GluNeo Lite
Isotech	IsoCheck BGM-501S
Medisana	Meditouch
Vitility (Boeren)	BM Diamond Mini

* The manufacturers indicated with an asterisk are manufacturers that have been on the Dutch market for a considerable time. Together they provided the majority of the BGMs on the Dutch market.

Annex 3: Assessment form

				BGMxx
			Score	
1	**Device description**	**Options**	**options**	**Score**
1.1.a	EC Certificate Directive 98/79/EC Annex IV	No, yes	0, 2	
1.1.b	Original/first date of EC Certificate Directive 98/79/EC Annex IV	dd-mm-yyyy	-	
1.1.c	Notified body involved	Description	-	
1.2.a	Product history/time line	No, yes	0, 2	
1.2.b	Lifetime company has been manufacturing BGMs	≤5 yrs (after 2010), >5yrs (before 2011)	-	
1.2.c	Lifetime product system (under the current name)	≤2 yrs (after 2013), >2yrs (before 2014)	-	
1.2.d	Remarks concerning product history/time line	If so, describe	-	
1.3	Any special intended patient population	If so, describe	-	
1.4	Principle of chemical analysis (glucose oxidase, glucose dehydrogenase, hexokinase)	Description	-	
	EU manufacturer or authorised representative	Description	-	
	Manufacturing site and name of the company of the BGM	Description	-	
	Manufacturing site and name of the company of the strips to be used for the BGM	Description	-	
		Total		
		Good	*4*	
		Moderate	*2*	
		Insufficient	*0*	
	Remark			

				BGMxx
			Score	
2	**IFU**	**Options**	**options**	**Score**
2.1	IFU are in Dutch	No, yes	0, 2	
2.2	Risks and contra-indications BGMs clearly mentioned in IFU (see attachment I)	No, partially, yes	0, 2, 4	
2.3	IFU are clearly written and well structured	No, partially, yes	0, 1, 2	
		Total		
		Good	*8*	
		Moderate	*5-7*	
		Insufficient	*≤4*	
	Remark			

BGMxx

			Score	
3	**Risk analysis**	**Options**	**options**	**Score**
3.1	All hazard categories addressed (see attachment II)	No, partially, yes	0, 2, 4	
3.2	BGM-related risks addressed (see attachment I)	No, partially, yes	0, 2, 4	
3.3	Risks estimated	No, yes	0, 2	
3.4	Risk control/mitigation adequately described	No, partially, yes	0, 2, 4	
3.5	Acceptability of residual risks addressed	No, yes	0, 2	
		Total		
		Good	*16*	
		Moderate	*14*	
		Insufficient	*≤12*	
	Remark			

				BGMxx
			Score	
4	**Analytical performance**	**Options**	**options**	**Score**
4.1	The organization performing the testing	Description	-	
	Is this organization the manufacturer	No, yes	-	
4.2	Compliance claimed to EN ISO 15197:2003	No, yes	-	
4.2.a	Repeatability cf. EN ISO 15197:2003	No, yes	0, 2	
4.2.b	Results: Intermediate precision cf. EN ISO 15197:2003	No, yes	0, 2	
4.2.c	Results: System accuracy cf. EN ISO 15197:2003	No, yes	0, 2	
4.2.d	Results: Interference testing cf. EN ISO 15197:2003	No, yes	0, 2	
4.3	Compliance claimed to ISO 15197:2013	No, yes	-	
4.3.a	Repeatability cf. ISO 15197:2013	No, yes	0, 2	
4.3.b	Intermediate precision cf. ISO 15197:2013	No, yes	0, 2	
4.3.c	System accuracy cf. ISO 15197:2013	No, yes	0, 2	
4.3.d	Interference testing cf. ISO 15197:2013	No, yes	0, 2	
4.4	Additional testing performed (eg TÜV)	No, yes	-	
	Results of additional testing	Describe	-	
		Total		
		Good	*8*	
		Moderate	*NA*	
		Insufficient	*≤6*	
	Remark			

BGMxx

			Score	
5	**Mechanical testing**	**Options**	**options**	**Score**
5.1	Tests specified in ISO 15197:2003/13 performed (see attachment III)	No, partially, yes	0, 1, 2	
		Total		
		Good	*2*	
		Moderate	*1*	
		Insufficient	*0*	
	Remark			

BGMxx

			Score	
6	**Lay person studies**	**Options**	**options**	**Score**
6.1	Conformity to ISO 15197:2003	No, yes, NA	0, 2, 2	
6.2	Conformity to ISO 15197:2013	No, yes, NA	0, 2, 2	
6.3	Summary of results	No, yes	0, 2	
		Total		
		Good	*6*	
		Moderate	*4*	
		Insufficient	≤2	
	Remark			

BGMxx

			Score	
7	**PMS procedure**	**Options**	**options**	**Score**
7.1	Customer or user complaints procedure (passive collection procedure)	No, yes	0, 2	
7.2	Principle / procedure for active collection & review of experiences (explicitly mentioned)	No, yes	0, 2	
7.3	Sources to actively collect experiences other than (customer/user) complaints ≥2	No, yes	0, 2	
7.4	Is special approach for receiving feedback for self-tests included?	No, yes	0, 2	
7.5	Principle or procedure for corrective and preventive actions to be taken	No, only stand-alone reference, yes	0, 1, 2	
7.6	Criteria for the necessity to take actions	No, not clearly defined (decided ad-hoc), yes	0, 1, 2	
7.7	Risk management activities will be taken	No, only stand-alone reference, yes	0, 1, 2	

7.8	Periodic review of PMS data	No, yes	0, 2	
		Total		
		Good	*16*	
		Moderate	*15*	
		Insufficient	*≤14*	
	Remark			

				BGMxx
			Score	
8	**Summary & analysis of PMS data**	**Options**	**options**	**Score**
8.1	PMS sources identified	No, yes, and describe	0, 2	
8.2	Analysis of PMS data	No, limited, yes, and describe	0, 1, 2	
8.3	Actions taken based on the analysis of PMS data	No, yes, and describe	0, 2	
8.4	Number of vigilance actions taken	Describe	-	
		Total		
		Good	*6*	
		Moderate	*5*	
		Insufficient	*≤4*	
	Remark			

Attachment I

Risks and contra-indications based on literature for BGM. It should be checked whether the headings (bold) given are addressed, not whether all items are addressed. Tick boxes: first column for instructions for use (IFU), second column for risk analysis (RA).

1. Use errors

	BGMxx	
	IFU	RA
Use errors		
(Blood) contamination		
Use of strips from another meter/manufacturer		
Incorrect storage/handling conditions of strips or meter		
Incorrect user conditions, e.g. unwashed hands before testing		
Failure to understand IFU and perform required steps		
Incorrect specimen collection, e.g. poor lancing technique or incorrect volume		
Use of expired strips		
Incorrect strip insertion		
Application of an insufficient amount of blood to the strip		
Test site location: side of fingertip versus alternative site		
Meter not calibrated properly		
Failure to adjust the meter properly, e.g. coding		

2. Product errors

System failures		
Incorrect calibration/adjustment (between lots of strips)		
Altitude, temperature, and humidity		
Incorrect data transfer		
Influence of moving BGM or touching buttons during measurement		
Readability of display for visually impaired users		
Results out of range		
Misreading the value due to missing segment on display		
Loss of data due to battery removal		

Software failures		
Confusing user prompts and feedback		
Incorrect algorithm		
Undetected or unrecognized signal errors		
Timing failure		
Incorrect storage of test results in memory		
Undetected failure		

Hardware failures		
Electronic failures		
Damage to the device from incorrect strip use		
Damage to the device from drop or vibration		
Battery reliability		
Component(s) failure		
Incorrectly manufactured		
Electromagnetic incompatibility		

3. Physiological interferences

Physiological interferences (see strip IFU if applicable)		
Interfering from endogenous substances (vitamin C, acetaminophen, uric acid)		
Interference of packed cell volume		
Severe physiological conditions, e.g. dehydration or anemia		
Interference from sugars, e.g. maltose intravenous solutions		
Interference from other exogenous substances (drugs), e.g. paracetamol		

Attachment II

This appendix provides a selection of categories of risks and subsequent examples, and is based on hazards described in the standard EN ISO 14971:2007, corrected 2012 Medical devices – Application of risk management to medical devices.

	BGMxx
Biological	
- Contamination with micro-organisms	
Functional hazards	
- Loss or deterioration of function	
Use error	
- Routine violation	
Labelling	
- Incomplete instructions for use - Inadequate description of performance characteristics - Inadequate specification of intended use - Inadequate disclosure of limitations	
Operating instructions	
- Inadequate specification of accessories to be used with the medical device - Inadequate specification of pre-use checks - Over-complicated operating instructions	
Warnings	
- Of side effects - Of hazards likely with re-use - Of single-use medical devices	
Incomplete requirements	
- Inadequate specification of: design parameters operating parameters performance requirements in-service requirements, e.g. maintenance, reprocessing end of life	
Manufacturing processes	
- Insufficient control of changes to manufacturing processes - Insufficient control of materials/materials compatibility information - Insufficient control of manufacturing processes - Insufficient control of subcontractors	
Transport and storage	
- Inadequate packaging - Contamination or deterioration - Inappropriate environmental conditions	
Environmental factors	
- Physical, e.g. heat, pressure, time - Chemical, e.g. corrosions, degradation, contamination - Electromagnetic fields, e.g. susceptibility to electromagnetic disturbance - Inadequate supply of power - Inadequate supply of coolant	
Cleaning, disinfection and sterilization	
- Lack of, or inadequate specification for, validated procedures for cleaning, disinfection and sterilization - Inadequate conduct of cleaning, disinfection and sterilization	

Disposal and scrapping	
- No or inadequate information provided	

Potential for use errors triggered by design flaws, such as	
- Confusing or missing instructions for use - Ambiguous or unclear device state - Ambiguous or unclear presentation of settings, measurements or other information - Misrepresentation of results - Poor mapping of controls to actions, or of displayed information to actual state - Use by unskilled/untrained personnel - Insufficient warning of side effects - Inadequate warning of hazards associated with re-use of single-use medical devices - Incompatibility with consumables/accessories/other medical devices	
Failure modes	
- Unexpected loss of mechanical integrity - Deterioration in function as result of ageing, wear and repeated use	

Attachment III

	BGMxx
Aspects for the assessment of mechanical testing	
Protection against electrical shock	
Protection against mechanical hazard, e.g. shock, vibration, impact	
Electromagnetic compatibility (EMC)	
Resistance to heat, i.e. low and high temperature testing	
Resistance to moisture and liquids	
Acceptance criteria IEC 61010-1	

Annex 4: Tables and figures

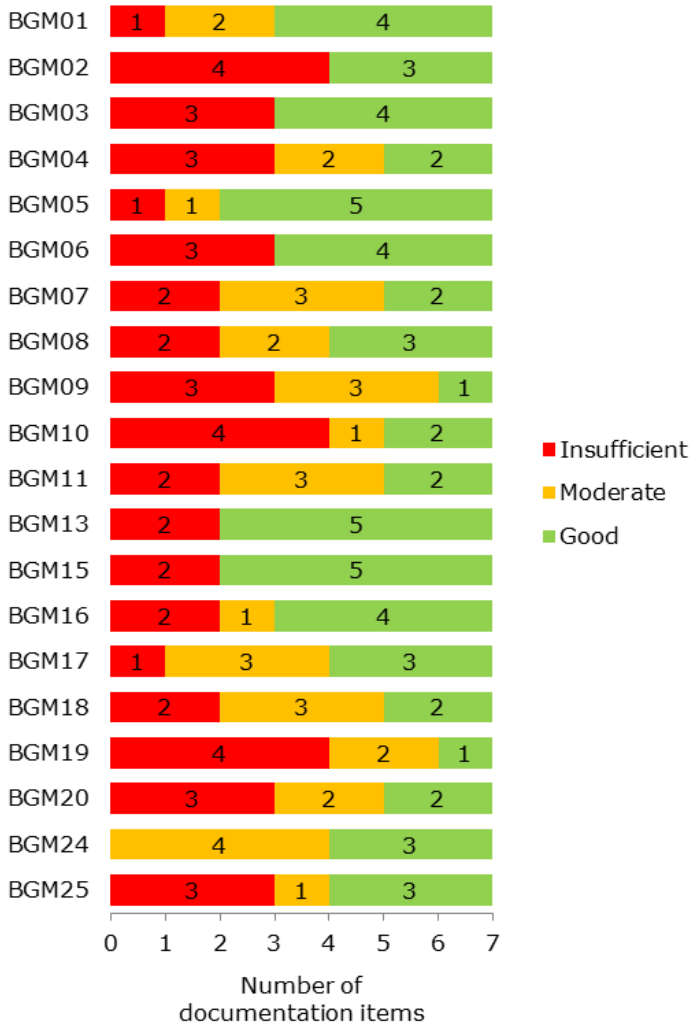

Figure A4.1a: Assessment score of documentation items for each BGM.

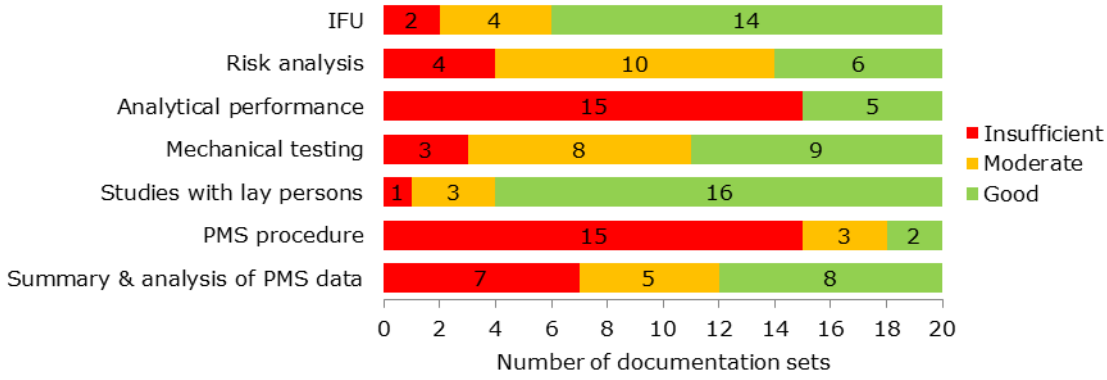

Figure A4.1b: Assessment score for each documentation item.

Table A4.2 Assessment of the IFU

Id	Dutch IFU	Risks and warnings mentioned	Clearly written, well-structured	Score
BGM01	Y	Y	Y	G
BGM02	Y	Y	Y	G
BGM03	Y	Y	Y	G
BGM04	Y	Y	Y	G
BGM05	Y	Y	Y	G
BGM06	Y	Y	Y	G
BGM07	Y	Y	Y	G
BGM08	Y	Y	Y	G
BGM09	N	Y	Y	M
BGM10	N	P	P	I
BGM11	Y	Y	Y	G
BGM13	Y	Y	Y	G
BGM15	Y	Y	Y	G
BGM16	N	P	P	I
BGM17	Y	Y	Y	G
BGM18	Y	Y	Y	G
BGM19	Y	P	P	M
BGM20	N	Y	Y	M
BGM24	Y	P	Y	M
BGM25	Y	Y	Y	G

Sub-item scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

Table A4.3 Assessment of the risk analysis

Id	Hazard categories	BGM-related risks	Risks estimated	Risk control/ mitigation	Acceptability residual risks	Score
BGM01	P	Y	Y	Y	Y	M
BGM02	Y	P	Y	Y	N	I
BGM03	Y	Y	Y	Y	Y	G
BGM04	P	Y	Y	P	Y	I
BGM05	Y	Y	Y	Y	Y	G
BGM06	Y	Y	Y	Y	Y	G
BGM07	P	Y	Y	Y	Y	M
BGM08	Y	Y	Y	P	Y	M
BGM09	P	Y	Y	Y	Y	M
BGM10	Y	Y	Y	Y	Y	G
BGM11	Y	P	Y	Y	Y	M
BGM13	Y	Y	Y	Y	Y	G
BGM15	P	P	Y	Y	Y	I
BGM16	P	Y	Y	Y	Y	M
BGM17	Y	Y	Y	Y	Y	G
BGM18	Y	P	Y	Y	Y	M
BGM19	P	Y	Y	Y	Y	M
BGM20	P	Y	Y	Y	Y	M
BGM24	P	Y	Y	Y	Y	M
BGM25	P	P	Y	Y	Y	I

Sub-item scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

Table A4.4 Assessment of the analytical performance

Id	Repeatability	Intermediate precision	System accuracy	Interference	ISO 15197 version†	Score
BGM01	Y	Y	Y	Y	2013	G
BGM02	Y	N	N	Y	2003	I
BGM03	Y	Y	Y	N	2003	I
BGM04	N	N	N	N	2013	I
BGM05	N	N	N	N	2003	I
BGM06	Y	Y	N	Y	2013	I
BGM07	N	N	Y	N	2013	I
BGM08	Y	Y	N	Y	2013	I
BGM09	Y	Y	N	N	2013	I
BGM10	Y	Y	Y	N	2013	I
BGM11	N	N	N	N	2013	I
BGM13	N	N	Y	N	2013	I
BGM15	Y	Y	Y	Y	2003	G
BGM16	Y	Y	Y	Y	2013	G
BGM17	Y	Y	N	N	2003/2013	I
BGM18	N	N	N	N	2013	I
BGM19	Y	Y	Y	N	2003/2013	I
BGM20	N	N	Y	N	2013	I
BGM24	Y	Y	Y	Y	2013	G
BGM25	Y	Y	Y	Y	2003	G

† Not taken into account for the assessment score.

Grey-shaded cells: Compliance claimed to EN ISO 15197:2003.

Sub-item scores: N – no, Y – yes.

Assessment scores: I – insufficient, G – good.

Table A4.5 Assessment of system accuracy

Id	ISO 15197 2003	100 subjects	100 fresh capillary blood samples	7 [blood samples]	1 lot of test strips	<4.2 mmol/l: 95% within ±0.83 mmol/l	±20% for ≥4.2 mmol/l	
	ISO 15197 2013	100 different subjects	100 fresh capillary blood samples	600 measure-ments	3 lots of test strips	<5.55 mmol/l: 95% within ±0.83 mmol/l	±15% for ≥5.55 mmol/l	CGE
BGM01	2013	x	x	x	x	x	x	x
BGM02	2003	x	x	x	0	x	x	
BGM03	2003	x	x	x	x	x	x	
BGM04	2013	0	0	x	x	x	x	x
BGM05	2003	0	0	0	0	0	0	
BGM06	2013	x	0	x	x	x	x	x
BGM07	2013	x	x	x	x	x	x	x
BGM08	2013	x	x	x	x	0	x	x
BGM09	2013	0	0	0	0	0	0	0
BGM10	2013	x	x	x	x	x	x	x
BGM11	2013	0	0	0	x	0	0	0
BGM13	2013	x	x	x	x	x	x	x
BGM15	2003	x	x	x	x	x	x	
BGM16	2013	x	x	x	x	x	x	x
BGM17	2003	x	x	x	x	x	x	
BGM18	2013	0	0	0	x	0	0	0
BGM19	2013	x	x	x	x	x	x	x
BGM20	2013	x	x	x	x	x	x	x
BGM24	2013	x	x	x	x	x	x	x
BGM25	2003	x	x	x	x	x	x	

Abbreviation: CGE – Consensus Grid Error
x – covered
0 – not covered

Table A4.6 Assessement of the PMS procedure

Id	Complaint procedure	Active PMS	Sources other than complaints	Special approach feedback	CAPA	Criteria for actions	Risk management activities	Periodic review PMS data	Score
BGM01	Y	Y	Y	Y	Y	N	N	N	I
BGM02	Y	N	N	N	P	P	N	N	I
BGM03	Y	N	N	N	Y	N	P	Y	I
BGM04	Y	Y	Y	Y	Y	P	Y	Y	I
BGM05	Y	Y	Y	Y	Y	Y	Y	Y	G
BGM06	Y	Y	Y	N	Y	Y	Y	Y	I
BGM07	Y	Y	Y	Y	N	N	P	Y	I
BGM08	Y	N	N	N	Y	N	P	Y	I
BGM09	Y	Y	Y	Y	Y	N	N	N	I
BGM10	Y	Y	Y	N	Y	P	Y	N	I
BGM11	Y	Y	Y	N	Y	P	Y	Y	I
BGM13	Y	Y	Y	Y	Y	Y	Y	Y	G
BGM15	Y	Y	Y	N	P	N	P	N	I
BGM16	Y	Y	Y	Y	Y	P	Y	N	I
BGM17	Y	Y	Y	Y	Y	P	Y	Y	M
BGM18	Y	Y	Y	N	Y	P	Y	Y	I
BGM19	Y	Y	Y	Y	Y	N	Y	N	I
BGM20	Y	Y	Y	N	P	P	N	N	I
BGM24	Y	Y	Y	Y	Y	P	Y	Y	M
BGM25	Y	N	N	N	P	Y	P	Y	I

Sub-item scores: N – no, P – partial, Y – yes.
Assessment scores: I – insufficient, M – moderate, G – good.

Table A4.7 Assessment of the summary and analysis of PMS data, vigilance actions

Id	PMS sources identified	Analysis PMS data	Actions taken	Vigilance actions†	Score
BGM01	Y	Y	Y	1	G
BGM02	Y	P	N	none	I
BGM03	Y	Y	Y	8	G
BGM04	Y	Y	N	none	I
BGM05	Y	P	Y	1	M
BGM06	Y	N	N	none	I
BGM07	Y	P	Y	none	M
BGM08	Y	Y	Y	25	G
BGM09	Y	P	Y	1	M
BGM10	Y	P	Y	none	M
BGM11	Y	Y	Y	1	G
BGM13	Y	P	N	none	I
BGM15	Y	Y	Y	none	G
BGM16	Y	Y	Y	none	G
BGM17	Y	P	Y	none	M
BGM18	Y	Y	Y	none	G
BGM19	Y	P	N	none	I
BGM20	N	N	Y	1	I
BGM24	Y	Y	Y	320	G
BGM25	N	N	N	none	I

† Not taken into account for the assessment score.

Sub-item scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

RIVM
Committed to *health and sustainability*