World Health Organization

# Technical specifications series for submission to WHO prequalification – diagnostic assessment

# TSS-19

## In-vitro diagnostic medical devices for monitoring of blood glucose in capillary blood

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# Contents

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## List of contributors

A technical consultation on WHO prequalification requirements was held from 8 to 10 November 2022.

Meeting participants: M. Banerjee, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; E. English, Faculty of Medicine and Health, University of East Anglia, Norwich, and Department of Clinical Biochemistry, Norfolk and Norwich University Hospital, Norwich, United Kingdom of Great Britain and Northern Ireland; B. Fancke, Independent consultant, Rolle, Switzerland; G. Freckmann, Institut für Diabetes-Technologie, Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Germany; F. Ibrahim, Médecins Sans Frontières – Operation Center Amsterdam, Kenya; G. John, Norfolk and Norwich University Hospital and Norwich Medical School, Norwich, United Kingdom; L. Jafri, Department of Pathology and Laboratory Medicine, Aga Khan University, Pakistan; L. Landree, Division of Chemistry and Toxicology Devices, Office of In Vitro Diagnostics and Radiological Health, Office of Product Evaluation and Quality, Center for Devices and Radiological Health, U.S. Food and Drug Administration, United States Of America (USA)[1]; E. Lenters-Westra, Klinisch Chemisch Laboratorium, Isala, Zwolle, Netherlands (Kingdom of the); G. Omuse, The Aga Khan University Hospital, Nairobi, Kenya; T. Pillay, University of Pretoria & National Health Laboratory Service, South Africa; B. Pratumvinit, Department of Clinical Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand; D. Sacks, National Institutes of Health; Georgetown University; George Washington University; University of Cape Town; USA; P. Singh, FIND, Geneva, Switzerland; R.J. Slingerland, Departments of Diabetes, Isala, Zwolle, Netherlands (Kingdom of the); H. Storey, PATH, Seattle, USA; B. Vetter, FIND, Geneva, Switzerland; M. Wehbi, Department of Universal Health Coverage/Health Systems, World Health Organization Regional Office for Eastern Mediterranean, Cairo, Egypt.

WHO Secretariat: D. Healy; M. Lanigan; A.L. Page; U. Ströher, In Vitro Diagnostics Assessment Team, Regulation and Prequalification Department, WHO, Geneva.

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[1] Joined by teleconference

## Abbreviations

| | |
|---|---|
| BG | blood glucose |
| BGMS | blood glucose monitoring system (BG meter + reagent system) |
| IFU | instruction for use |
| IMDRF | The International Medical Device Regulators Forum |
| IMDRF ToC | IMDRF Table of contents |
| ISO | International Organization for Standardization |
| IVD | in vitro diagnostic |
| JCTLM | The Joint Committee for Traceability in Laboratory Medicine |
| NIST | National Institute of Standards and Technology |
| POC | point of care |
| TSS | Technical specifications series |
| WHO | World Health Organization |

## A. Introduction

The purpose of this document is to provide technical guidance to in vitro diagnostic (IVD) medical device manufacturers that intend to seek WHO prequalification of handheld finger-stick capillary blood glucose (BG) monitoring systems (BGMS) used for monitoring of diabetes by self-testers, lay providers and/or professional users at point of care (POC)[2]. It does not cover the requirements for devices which are intended for diagnosis of diabetes. Where a manufacturer includes a claim for diagnosis, please contact WHO for additional requirements.

For the purpose of this document, the verbal forms used follow the usage described below:

- "shall" indicates that the manufacturer is required to comply with the technical specifications.
- "should" indicates that the manufacturer is recommended to comply with the technical specifications, but it is not a requirement.
- "may" indicates that the technical specifications are suggested methods to undertake the testing, but not requirements.

A documented justification and rationale shall be provided by the manufacturer when the WHO prequalification submission does not comply with the required technical specifications outlined in this document.

Minimum performance requirements for WHO prequalification are summarized in this document, and where possible, are aligned with published guidance, standards such as ISO 15197:2013 (*1*) (and the European standard EN ISO 15197:2015); and/or regulatory documents. Studies which have been already conducted following ISO 15197:2013 may be submitted as part of the dossier for prequalification as a number of the requirements overlap. Note that in some cases WHO prequalification has additional requirements. Source documents are listed in the tables (including the specific clauses in the ISO 15197: 2013) which may assist the reader by providing additional explanatory information and details for each study.

WHO prequalification requirements summarized in this document do not extend to the demonstration of clinical utility, i.e., the effectiveness and/or benefits of a BGMS, relative to and/or in combination with other measures, as a tool to inform clinical intervention in a given population or healthcare setting. To demonstrate clinical utility, a separate set of studies is required. Clinical utility studies usually inform programmatic strategy and are thus the responsibility of program managers, ministries of health and other related bodies in individual WHO Member States. Such studies do not fall under the scope of WHO prequalification.

The manufacturers shall provide evidence in support of the clinical performance of an BGMS to demonstrate that reasonable steps have been taken to ensure that a properly

[2] Point-of-care in-vitro diagnostic testing (POC) refers to decentralized testing that is performed by a minimally trained healthcare professional near a patient and outside of central laboratory testing facilities. It does not refer just to specimen collection procedures. In some jurisdictions, the concept "near patient testing" is used instead of "point of care testing". Either term may be used in the intended use statement.

manufactured BGMS (designed to be easy to use), being correctly operated in the hands of the intended user in its own environment, will detect the target analyte consistently and fulfill its indications for use.

## B. Other guidance documents

This document should be read in conjunction with other WHO guidance documentation, including:

WHO prequalification documents:[3]

- Technical Guidance Series for WHO Prequalification – Diagnostic Assessment.
- Instructions for compilation of a product dossier – IMDRF ToC, WHO document PQDx_018 (*2*).

WHO Noncommunicable disease programme documents:

- Diagnosis and management of type 2 diabetes (HEARTS-D)(*3*).

## C. Performance principles for WHO prequalification

### C.1 Intended use

A BGMS submitted for WHO prequalification assessment shall be accompanied by a sufficiently detailed intended use statement. This should allow an understanding of at least the following:

- The analyte or measurand that is detected or measured: glucose.
- The clinical indication of the BGMS (e.g., monitoring diabetes, aid in monitoring blood glucose levels from finger-stick capillary blood in people with diabetes, or monitoring people with conditions that may result in hypo or hyperglycaemia).
- The target population: people with diabetes or people with expected high or low blood glucose concentrations.
- The intended use environment and user: home-use/self-testing (monitoring) by lay persons[4], by laboratory professionals[5], healthcare professionals or trained lay persons at POC healthcare settings.
- The intended specimen types: finger-stick capillary blood.
- The BGMS shall report calculated quantitative plasma-like glucose values.
- Limitations for use: where use of the device is not recommended (e.g., patients in intensive care units, neonates).
- Whether or not it includes algorithms (e.g., how to interpret measurand values).
- Whether it is intended to be used with or in combination with other instruments (e.g., mobile phones etc.).

[3] Available at: https://extranet.who.int/pqweb/vitro-diagnostics/guidance-documents
[4] Any person who performs functions related to healthcare delivery and has not received a formal professional or paraprofessional certification or tertiary education degree.
[5] Medical technologists, medical laboratory technicians or similar, who have received a formal professional or paraprofessional certification or tertiary education degree

## C.2 Diversity of specimen types, users and testing environments and impact on required studies

For WHO prequalification submission, all studies shall be conducted using finger-stick capillary whole blood specimens as claimed in the instructions for use (IFU) except where otherwise stated in the tables below. All results shall be reported as capillary plasma-like glucose values.

Prequalified BGMS in low- and middle income countries are likely to be used in a variety of geographical settings by

- lay persons in the home setting,
- lay persons trained in the use of the device, healthcare professionals or laboratory professionals in healthcare settings and POC.

Depending on the intended use of the BGMS, analytical and clinical performance studies shall be designed to consider not only the diversity of knowledge and skills across the population of BGMS users, but also the likely operational settings in which testing will occur. It is a manufacturer's responsibility to ensure that the risk assessment for an IVD device reflects the intended operational settings, including laboratory or service delivery complexity, user expertise, training received, testing population, environmental and storage conditions.

## C.3 Applicability of supporting evidence to BGMS under review

Analytical and clinical performance studies shall be undertaken using the specific, final (locked-down) version of the BGMS intended to be submitted for WHO prequalification. No changes in software, algorithms, measurement time, reagent systems used (including but not limited to e.g., enzyme concentration spotted on reagent system), volume of specimen needed for the assay, nor the design of the instrument shall be changed after the locked-down version has been submitted for WHO prequalification. For WHO prequalification, design lock-down is the date that final documentation, including quality control and quality assurance specifications, is signed off and the finalized method is stated in the IFU. Where this is not possible, a justification shall be provided, and additional supporting evidence may also be required. This may occur in the case of minor variations to design where no impact on performance has been demonstrated (see WHO document PQDx_121 Reportable changes to a WHO prequalified in vitro diagnostic medical device).(*4*) If the method  section of the IFU has been changed in any way, both the study protocol provided to the laboratory  and that in the final version of the IFU intended for users shall be provided with the submission for WHO prequalification assessment. The version of the IFU used in the verification and validation studies submitted for WHO prequalification assessment shall be stated. If the test procedure in the IFU is changed in any way after completing verification and validation studies, the change(s) shall be reported to WHO, including a rationale for the change, and an explanation of why the study results support the claimed performance.

Specific information is provided in this document for the minimum numbers of reagent system lots required for each study. Where more than one reagent system lot is required, each reagent system lot shall comprise different production (or manufacturing etc.) runs of critical reagents (such as enzymes), representative of routine manufacturing process. It is a manufacturer's responsibility to ensure, via risk analysis of its BGMS that the minimum numbers of reagent system lots chosen for estimating performance characteristics

considers the variability in performance likely to arise from the inter-lot diversity of critical components and their formulation or from changes that could occur during the assigned shelf life of the BGMS. Differences in analytical and clinical performance observed when using different reagent system lots shall be reported.

Estimation (and reporting) of IVD performance parameters should include confidence interval where appropriate. Evaluation of BGMS performance shall include the rate of non-numeric results. The cause of the non-numeric results should be reported if available. Data should be presented in clear and understandable format.

Clinical performance studies at POC in intended use settings shall be based on testing human finger-stick capillary blood specimens sourced from population cohorts reflective of the intended use and collected under the conditions of intended use (consider environmental conditions like temperature, humidity and altitude if relevant).

### C.4 Acceptable laboratory methods/comparator system for validation and verification studies

Trueness and precision of the laboratory method shall be provided and be verified during the evaluation of the BGMS.

#### Part 1 – Analytical performance and other evidence

For validation studies listed in part 1 the accurate quantitation of glucose shall be determined by the manufacturer using an established laboratory method. The laboratory method shall be traceable (as defined in ISO 17511:2020 (*5*)) and meet at a minimum the following criteria:

- All results of the laboratory method obtained with reference materials (e.g. NIST standard reference materials (*6*) or reference material listed in the JCTLM database (*7*)) shall be within desirable analytical performance specifications based on biological variation (*8*), (*9*);
  - Bias ≤2.4%.
  - Imprecision ≤2.5%.
  - Error ≤6.5%.

#### Part 2 - Device specific clinical studies

For clinical studies conducted at POC in intended use settings, the accurate quantitation of glucose shall be determined using a suitable comparator system (BGMS).

- The comparator system shall be traceable to reference materials for glucose and deviations shall declared and documented and included in the interpretation of the final results (*1*).
- The comparator system shall be qualified by a laboratory using an established laboratory method (see above) for glucose measurement that has been calibrated or controlled against reference materials for glucose. All results of the laboratory method obtained with reference materials shall be within desirable analytical performance specifications based on biological variation (see bias, imprecision and error specifications above).
- The validated comparator method shall meet at a minimum the criteria of:
  - Test results within ±10 mg/dL (0.56 mmol/L) for glucose concentrations <5.55 mmol/L, and

230 ○ Test results within ±10 % for glucose concentrations ≥5.55 mmol/L. (*1*)
231 • The comparator BGMS shall not be from the same manufacturer as the BGMS under
232 evaluation.

## D. Tables with requirements

WHO requires that a product dossier is submitted in the "Table of Contents" (ToC) format, described in the International Medical Device Regulators Forum (IMDRF) document IMDRF/RPS WG/N13 FINAL:2019 (Edition 3) (*10*). In the tables below, the chapters and subheadings are labelled and numbered according to IMDRF ToC format. As the IMDRF ToC is comprehensive in nature, not all subheadings are required for WHO prequalification and are excluded. As a result, the subheading numbering in the tables below is not always continuous (e.g., 3.1.1, 3.1.3, etc). This has been done to maintain consistency between sections required in a product dossier for WHO prequalification assessment and the corresponding numbering defined in the IMDRF ToC format.

| **Part 1** | |
|---|---|
| **IMDRF ToC Chapter 3** | **Analytical performance and other evidence** |
| **3.05.03** | **Metrological traceability of calibrators and control material values** |
| **3.05.04** | **Accuracy of Measurement** |
| 3.05.04.01 | **Trueness** |
| | System accuracy |
| 3.05.04.02 | **Precision** |
| 3.05.04.02 a | Repeatability |
| 3.05.04.02 b | Reproducibility |
| **3.05.06** | **Analytical specificity** |
| 3.05.06 a | General requirements |
| 3.05.06 b | Packed cell volume (haematocrit) evaluation |
| 3.05.06 c | Potentially interfering substances (exogenous and endogenous) |
| **3.05.08** | **Measuring range of the assay** |
| | Linearity |
| **3.05.10** | **Validation of the assay procedure** |
| | Validation of assay parameters |
| **3.06.01** | **Electrical systems: safety, mechanical and environmental protection, and electromagnetic compatibility** |
| **3.06.02.08** | **Software verification and validation** |
| **3.06.03** | **Cleaning and disinfection validation** |
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| 3.06.04 a | Flex studies/robustness |
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| 3.06.05.02 | In-use stability (open pack or open vial stability) |

| | | |
|---|---|---|
| 272 | **Part 2** | |
| 273 | **IMDRF ToC Chapter 4** | **Clinical evidence** |
| 274 | **4.02.03** | **Device specific clinical studies** |
| 275 | 4.02.03 a | General requirement for clinical performance and usability |
| 276 | | study conducted in intended use settings |
| 277 | 4.02.03 b | Trained user performance assessment |
| 278 | 4.02.03 c | Qualification of usability - Observed lay user performance |
| 279 | | assessment |
| 280 | 4.02.03 d | Qualification of usability - Label comprehension study |
| 281 | 4.02.03 e | Qualification of usability - Results interpretation study |

## Part 1: IMDRF ToC Chapter 3 Analytical performance and other evidence

| | IMDRF ToC Chapter heading and aspect | Testing requirements | Notes on testing requirement | Source documents and additional information |
|---|---|---|---|---|
| 283 | **3.05.03 Metrological traceability of calibrators and control material values** | | | |
| 284 | Metrological traceability of laboratory methods | 1. As applicable, the metrological traceability of reference measurement procedures and the provided control material(s) shall be provided.<br>2. Traceability to a validated reference material (e.g. from NIST) shall be determined as well as identification of applicable reference materials and/or reference measurement procedures. | 1. The requirements for metrological traceability specified in ISO 15197:2013 and ISO 17511:2020, respectively, shall be applied.<br>2. Minimum acceptance criteria for traceability should be described (i.e., when compared to a higher order material):<br>• Imprecision ≤2.5%<br>• Bias ≤2.4%<br>• Error ≤6.5%.<br>3. External control material shall be provided by the manufacturer to the user. Target value assigned to the control should be meaningful. Controls shall be available at more than 1 concentration. The manufacturer shall describe what failures are detected by the control material provided (in the risk analysis as appropriate). | ISO 15197:2013 (*1*)<br>ISO 17511:2020 (*5*)<br>NIST website (*6*)<br>EFLM biological variation database (*9*) |
| 285 | **3.05.04 Accuracy of Measurement** | | | |
| 286 | **3.05.04.01 Trueness** | | | |
| 287 | System accuracy | 1. At least 100 different subjects shall be tested at 1 site by trained users/healthcare professionals (see note 1 & 2).<br>2. Testing shall be conducted in finger-stick capillary whole blood.<br>3. Glucose concentrations of tested subjects shall be distributed as follows:<br>Bin # \| Percentage of samples % \| Glucose concentration mmol/L (mg/dL) | 1. Evaluation shall be performed by users trained in the use of the BGMS.<br>2. Subjects do not have to be diagnosed with diabetes prior to the study.<br>3. Data or specimens may be excluded if the difference of the two blood glucose comparator values (samples taken before and after measurements with BGMS) are outside predefined acceptance criteria as outlined in ISO 15197:2013, clause 6.1.3: e.g., >4% at glucose ≥5.55 mmol/L (≥100 mg/dL) | ISO 15197:2013, clause 6.1.3, clause 6.3 (*1*) |

<table>
<tr><th></th><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirement</th><th>Source documents and additional information</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>1</td><td>5</td><td>≤2.77 (≤50)</td></tr>
<tr><td>2</td><td>15</td><td>>2.77 to 4.44 (>50 to 80)</td></tr>
<tr><td>3</td><td>20</td><td>>4.44 to 6.66 (>80 to 120)</td></tr>
<tr><td>4</td><td>30</td><td>>6.66 to 11.10 (>120 to 200)</td></tr>
<tr><td>5</td><td>15</td><td>>11.10 to 16.65 (>200 to 300)</td></tr>
<tr><td>6</td><td>10</td><td>>16.65 to 22.20 (>300 to 400)</td></tr>
<tr><td>7</td><td>5</td><td>>22.20 (>400)</td></tr>
</table>
4. Testing of at least 3 reagent system lots, each in duplicate (resulting in 600 values).<br>5. Comparator testing with established laboratory methods (see note 4) shall be performed on capillary blood before and after the duplicate testing of 3 reagent system lots (see note 3).</td><td>or >0,22 mmol/L (>4 mg/dL) at glucose <5.55 mmol/L (<100 mg/dL).<br>4. Refer to section “C.4 Acceptable laboratory methods/comparator system for validation and verification studies” for criteria describing an established laboratory method.<br>5. System accuracy shall be visualized using a modified Bland-Altman plot (system accuracy plot) in which the difference between the BGMS results and the reference results are plotted against the mean reference results. The graph shall include predefined accuracy acceptance criteria.</td><td></td></tr>
<tr><td>288</td><td colspan="4">3.05.04.02 Precision</td></tr>
<tr><td>289</td><td>3.05.04.02 a Repeatability</td><td>1. Measurement repeatability shall be estimated by 1 user (note 5) using:<br>• A minimum of 10 meters.<br>• 3 reagent system lots.<br>2. A panel of 5 venous blood specimens within the following glucose concentration intervals shall be used:
<table>
<tr><th>Interval</th><th>Glucose concentration mmol/L (mg/dL)</th></tr>
<tr><td>1</td><td>1.7 to 2.8 (30 to 50)</td></tr>
<tr><td>2</td><td>2.9 to 6.1 (51 to 110)</td></tr>
<tr><td>3</td><td>6.2 to 8.3 (111 to 150)</td></tr>
</table></td><td>1. The preferred specimens for intermediate measurement precision are control materials provided by the manufacturer.<br>2. Lots shall be composed of different batches of critical components (see section C.3).<br>3. The operator of the devices shall not be an employee/representative of the IVD device manufacturer.<br>4. Results shall be statistically analysed (e.g., using ANOVA to identify and isolate the sources and extent of any variance).<br>5. At a minimum result shall be reported as mean, standard deviation, and coefficient of variation for each combination</td><td>ISO 15197:2013, clause 6.2.3 (1)</td></tr>
</table>

<table>
<tr><th></th><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirement</th><th>Source documents and additional information</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>4</td><td>8.4 to 13.9 (151 to 250)</td></tr>
<tr><td>5</td><td>to 22.2 (251 to 400)</td></tr>
</table>
3. Testing shall be conducted for the packed cell volumes (haematocrit) range 0.35 L/L to 0.50 L/L (35 – 50%).<br>
4. Ten measurements with each combination of meter, reagent system lot and specimens shall be conducted within a short interval of time.
</td><td rowspan="2">of glucose concentration and reagent system lot and as pooled standard deviation with 95% confidence interval.</td><td></td></tr>
<tr><td>290</td><td>3.05.04.02 b<br>Reproducibility</td><td>
1. Intermediate measurement precision (reproducibility) shall be evaluated in normal conditions of use, by an individual using the same meter and reagent system lot over multiple days.<br>
2. A panel representing the following glucose concentration intervals shall be used (representative of hyperglycaemic, euglycaemic and hypoglycaemic conditions) (see note 1):
<table>
<tr><th>Interval</th><th>Glucose concentration mmol/L (mg/dL)</th></tr>
<tr><td>1</td><td>1.7 to 2.8 (30 to 50)</td></tr>
<tr><td>2</td><td>5.3 to 8.0 (96 to 144)</td></tr>
<tr><td>3</td><td>15.5 to 23.3 (280 to 420)</td></tr>
</table>
3. Testing shall be conducted:<br>
• With multiple users (at least 2 users).<br>
• In a minimum of 10 meters.<br>
• Using 3 reagent system lots.<br>
• Over at least 10 days.
</td><td>ISO 15197:2013, clause 6.2.4 (1)</td></tr>
</table>

<table>
<tr><th></th><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirement</th><th>Source documents and additional information</th></tr>
<tr><td></td><td></td><td>4. One measurement of each specimen per day shall be conducted with each combination of meter, reagent system lot and specimen.</td><td></td><td></td></tr>
<tr><td>291</td><td colspan="3">3.05.06 Analytical specificity</td><td></td></tr>
<tr><td>292</td><td>3.05.06 a<br>General requirements</td><td>1. The effect of packed cell volume (haematocrit) and interfering substances in blood, shall be evaluated and addressed in the risk management process.<br>2. Venous blood shall be used.<br>3. Testing shall be conducted:<br>• In multiple meters (in rotation, if required).<br>• Using 3 reagent system lots.</td><td>1. Any observed interference (including those that are not listed in the testing requirements column) shall be investigated and performance limitations of the IVD reported in the IFU.<br>2. Results should be reported with respect to each condition.</td><td>ISO 15197:2013, clause 6.4 (1)</td></tr>
<tr><td>293</td><td>3.05.06 b<br>Evaluation of packed cell volume (haematocrit) effects</td><td>1. Evaluation of packed cell volume effects shall be conducted with a minimum of 5 packed cell volumes (see note 1, 2) at each of 3 glucose concentrations:
<table>
<tr><th>Interval</th><th>Glucose concentration mmol/L (mg/dL)</th></tr>
<tr><td>1</td><td>1.7 to 2.8 (30 to 50)</td></tr>
<tr><td>2</td><td>5.3 to 8.0 (96 to 144)</td></tr>
<tr><td>3</td><td>15.5 to 23.3 (280 to 420)</td></tr>
</table>
2. The mid-level packed cell volume sample shall be adjusted to 0.42 L/L ± 0.02 L/L (42 % ± 2 %).<br>3. At least 10 replicates per specimen with each reagent system lot shall be conducted.</td><td>1. The manufacturer shall evaluate the effect of packed cell volume (haematocrit) on the performance of the BGMS for the range stated in the IFU.<br>2. The BGMS shall at a minimum be able to adequately measure glucose across the range of 0.35 L/L to 0.50 L/L (35 - 50%) packed cell volume (haematocrit).</td><td>ISO 15197:2013, clause 6.4.3 (1)<br>U.S FDA (11)</td></tr>
</table>

<table>
<tr><th></th><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirement</th><th>Source documents and additional information</th></tr>
<tr><td>294</td><td>3.05.06 c<br>Potentially interfering substances (exogenous and endogenous)</td><td>1. Evaluation of interfering substances shall be conducted using a paired-sample experimental design at a minimum of 2 glucose concentrations for each test substance:<br><table><tr><td>Interval</td><td>Glucose concentration mmol/L (mg/L)</td></tr><tr><td>1</td><td>2.8 to 5.5 (50 to 100)</td></tr><tr><td>2</td><td>13.9 to 19.4 (250 to 350)</td></tr></table>2. For the paired-sample experimental design, measured glucose values from specimens with an added test substance shall be compared to a control sample without the added test sample (see note 2).<br>3. At least 10 replicates of each individual sample (control sample and sample with an added test substance) with each reagent system lot shall be conducted.<br>4. The following list shall be tested (see note 1, 2):<br>• Acetaminophen (paracetamol)<br>• Ascorbic acid<br>• Conjugated Bilirubin, Unconjugated Bilirubin, Cholesterol, Triglycerides<br>• Creatinine, Uric acid<br>• Dopamine<br>• EDTA, Heparin (see note 3)<br>• Galactose<br>• Gentisic acid<br>• Reduced Glutathione<br>• Haemoglobin<br>• Ibuprofen<br>• L-Dopa</td><td>1. The risk assessment conducted should identify substances at medically relevant levels for which the potential for interference can reasonably be expected for the BGMS, in the areas of intended use and not simply rely on published lists of such compounds and conditions which might be of limited relevance in resource limited settings.<br>• By conducting appropriate risk assessment, testing can be conducted on specimens spiked with the substances/conditions identified as likely to be significant and testing of potentially irrelevant substances/conditions avoided.<br>• Under some circumstances stringent risk evaluation may eliminate the requirement to test some of the items in the list. In addition, such stringent risk evaluation may also reveal the requirement to test substances that are not already included in the list. Any such decision shall be documented in any submissions to WHO and taken into account in the risk-benefit statements.<br>2. Substances shall be spiked at the highest clinically relevant level compared with healthy individuals.<br>3. The inclusion of EDTA and Heparin refers to their use as therapeutic substances and not as anticoagulants for sample preparation.<br>4. Patients with a broad range of blood oxygen levels shall be considered as intended users, therefore partial oxygen pressures (pO2) shall be chosen that allow the determination of the range of blood oxygen levels the BGMS can be used with.</td><td>ISO 15197:2013, clause 6.4.4 (1)<br>U.S FDA (11)<br>CLSI EP07 Ed3 (12)<br>CLSI EP37 Ed1 (13)<br>ISO 14971:2019 (14)</td></tr>
</table>

| | IMDRF ToC Chapter heading and aspect | Testing requirements | Notes on testing requirement | Source documents and additional information |
|---|---|---|---|---|
| | | • Maltose<br>• Mannitol<br>• Methyldopa<br>• Oxygen (see note 4)<br>• Salicylic acid<br>• Sodium<br>• Tolbutamide<br>• Tolazamide<br>• Xylose<br>• Sugar Alcohols: sorbitol, xylitol, lactitol, isomalt, maltitol | | |
| 295 | **3.05.08 Measuring range of the assay** | | | |
| 296 | Linearity | 1. The linearity of the BGMS across the claimed measuring range shall be determined using specimens with known glucose concentrations which have had values assigned using an established laboratory method (see note 2).<br>2. Testing shall be conducted using venous whole blood:<br>• Using 11 concentrations that span the measuring range.<br>• Using 2 reagent system lots.<br>• 2 to 4 replicates at each concentration shall be conducted with each reagent system lot. | 1. The test results shall be analysed using appropriate statistical tools to demonstrate correlation between the BGMS results and the nominal concentrations of the analyte.<br>2. Refer to section "C.4 Acceptable laboratory methods/comparator system for validation and verification studies" for criteria describing an established laboratory method. | CLSI EP06 Ed2 (*15*) |
| 297 | **3.05.10 Validation of the assay procedures** | | | |
| 298 | Validation of assay parameters | 1. Evidence shall be provided demonstrating how parameters (specified in the IFU) were determined, verified and validated (see note 2). | 1. The parameters may be investigated as part of 3.06.04 Usability/human factors studies. Provide a cross reference if the studies are submitted in other sections of the dossier. | U.S FDA (*11*) |

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| | | 2. A panel of 3 venous blood specimens with the following glucose concentration shall be used (see note 4):<br>• 2.8 mmol/L (50 mg/dL).<br>• 8.3 mmol/L (150 mg/dL).<br>• 16.7 mmol/L (300 mg/dL).<br>3. Validation shall be performed at each concentration using a minimum of 2 different reagent system lots:<br>• 1 freshly made reagent system lot.<br>• 1 reagent system lot towards the end of its assigned shelf life.<br>4. The following parameters shall be considered depending on the assay and IFU requirements (see note 1, 2, 3):<br>• Time between drawing specimen, handling and loading.<br>• Operating temperature, humidity (see note 5 and 6).<br>• Varying specimen volume ranging from reduced blood volume to too much specimen.<br>• Error codes for specimens outside the measuring range.<br>• Intermittent specimens (see note 7).<br>• Specimen perturbation (see note 8). | 2. The extent of the assay parameter validation shall be subject to a documented risk assessment.<br>3. The intent of assay parameter validation is to demonstrate that a combination of small but defined deviations of the parameters outlined in the IFU will not result in inaccurate results i.e., to demonstrate the assay is robust.<br>4. Control solution may be used for the high glucose concentration interval.<br>5. Performance studies shall be conducted at the extremes of the intended operational temperature range. The number of invalid results shall be recorded for each temperature investigated.<br>6. The ranges of humidity tested shall be risk-based, taking into consideration likely operational settings in resource limited settings.<br>7. The purpose of an intermittent specimen study is to evaluate the impact of running the assay with an incomplete specimen volume and adding additional specimen before the glucose measurement is completed.<br>8. The impact of specimen perturbation that results in an altered specimen volume during the glucose measurement should be evaluated. E.g., wicking of blood away from the test strip, flicking of the test strip, or flicking of the meter. | |
| 299 | **3.06.01 Electrical systems; safety, mechanical and environmental protection, and electromagnetic compatibility** | | | |
| 300 | Electromagnetic compatibility/ interference, protection against | 1. Evidence of conformity to recognised standards (such as IEC), conducted by an accredited organisation shall be provided. | | IEC 61010-1:2010 (*16*) |

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| | electric shock and mechanical hazards | • A copy of a valid conformity certificate and report shall be provided. | | |
| 301 | **3.06.02.08 Software verification and validation** | | | |
| 302 | Software validation | 1. Software validation reports shall be available for submission if requested (see note 1). | 1. Software validation to include as a minimum:<br>• Verification of built-in fail-safe.<br>• Verification of alert mechanisms.<br>• Verification of quantitative results detection.<br>• Verification of quantitative results calculation.<br>• Evidence to demonstrate that appropriate error codes are provided to the end user. | IEC 62304:2006/ Amd 1:2015 (*16*)<br>U.S FDA (*18*, *19*) |
| 303 | **3.06.03 Cleaning and disinfection validation** | | | |
| 304 | Cleaning and disinfection validation | 1. Disinfection efficacy studies shall be performed to demonstrate:<br>• Effectiveness of the chosen disinfectant against Hepatitis B virus.<br>• Effectiveness of the cleaning and disinfection procedure with external meter materials.<br>• That the analytical performance of the BGMS is not impacted (even after multiple cleaning and disinfection cycles).<br>• That the functionality of the BGMS's components and features, including reagent system port and any parts particularly susceptible to blood contamination, are not impacted (even after multiple cleaning and disinfection cycles).<br>2. Physical indicators of deterioration (to the screen, buttons, plastic housing) during the cleaning and disinfection phase | 1. The studies conducted shall be based on the design of the device and risk assessment.<br>• Infection control considerations and measures shall be documented in the risk analysis and risk assessment.<br>2. At a minimum, the disinfectant product shall be effective against HIV, Hepatitis C, and Hepatitis B viruses.<br>3. Products for cleaning and disinfection should be readily available to the home user. | U.S FDA (*11*)<br>ASTM E1053-20 (*20*) |

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| | | shall be evaluated and this information shall be included in the study.<br>3. Demonstrate that accuracy is not affected by repeated cleaning and disinfection. | | |
| 305 | **3.06.04 Usability/human factors** | | | |
| 306 | 3.06.04 a<br>Flex and robustness studies | 1. The influence of the following factors on expected results should be considered:<br>• Testing with used test strips.<br>• Handling contamination (e.g., from sweat, cleaning or inadequate cleaning of the sampling site, latex, powder, hand lotion, as appropriate).<br>• BGMS instrument sturdiness (including the effect of non-level work surface).<br>• Ruggedness such as mechanical vibration testing, shock testing (see note 2).<br>2. Testing shall be performed at each of 3 glucose concentrations in venous blood using a minimum of 2 different reagent system lots (see note 7):<br>• 2.8 mmol/L (50 mg/dL).<br>• 8.3 mmol/L (150 mg/dL).<br>• 16.7 mmol/L (300 mg/dL). | 1. The risk assessment conducted for an IVD shall identify factors which have potential to affect the performance of the assay.<br>2. For the purposes of this document, ruggedness means the ability to resist environmental shocks of a variety of kinds.<br>3. Refer to WHO document PQDx_018 "Instructions for compilation of a product dossier" (*2*) for other flex studies that may be relevant, taking into consideration the broad range of operational and environmental conditions consistent with intended use.<br>4. The factors should be investigated in ways that not only reflect, but also exceed, likely operating conditions in lower- and middle- income countries so that the limitations of the device can be understood.<br>5. Robustness testing generally takes the form of statistically designed experiments to evaluate the effect of simultaneous "small but deliberate changes" in method parameters.<br>6. The parameters may be investigated as part of 3.05.10 Validation of the assay procedure. Provide a cross reference if the studies are submitted in other sections of the dossier.<br>7. Control solution may be used for the high glucose concentration interval. | ISO 15197:2013, clause 4.4 (*1*)<br>WHO PQDx_018 (*2*)<br>U.S FDA (*11*)<br>IEC 62366-1:2015 (*21*) |

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| 307 | b) Qualification of usability for point of care testing by the intended user | 1. The qualification of usability study requirements are outlined in part two of the tables:<br>• **4.02.03 c** Observed lay user performance assessment.<br>• **4.02.03 d** Label comprehension.<br>• **4.02.03 e** Result interpretation.<br>2. The studies may be conducted as part of the clinical performance studies or as separate studies as long as all testing requirements are fulfilled. | | |
| 308 | **3.06.05 Stability of the IVD** | | | |
| 309 | 3.06.05.01<br>Claimed shelf-life (including transport stability) | For evaluation of the shelf life of the reagent system and control solution if applicable, stability studies shall be conducted in the environment of the intended use (note 1). The following conditions shall be investigated:<br>1. Transport stability: Conditions chosen shall mimic extremes of conditions (temperature, humidity, pressure, drop-shock, vibration) exposed to during transport. These conditions shall be applied to the kit firstly, before placing the kits into real time stability studies.<br>2. IVD in its final packaging shall be subjected to drop-shock testing.<br>3. Testing shall be performed in venous blood at each of 3 glucose concentrations using a minimum of 3 different reagent system lots (see note 2):<br>• 2.8 mmol/L (50 mg/dL).<br>• 8.3 mmol/L (150 mg/dL).<br>• 16.7 mmol/L (300 mg/dL). | 1. Expected storage temperature and humidity range shall be considered for real-time stability studies.<br>2. If control solutions are available from the manufacturer, and recommended for use, then stability shall be evaluated.<br>3. Lots shall comprise different batches of critical components (see section C.3).<br>4. Multiple instruments may be used to allow simultaneous testing at each time point.<br>5. Determination of transport (shipping) stability shall be performed using simulated extreme stress conditions, ensuring that application of those conditions is consistent and controlled.<br>6. Claims for stability shall be based on the second-last successful data point from the least stable reagent system lot. If reagent system lots are different, a statistical analysis will be expected, showing that the bulk of reagent system lots meet the claimed life. For example: if stability was still observed at 24 months, for testing conducted at 3, 6, 9, 12, | ISO 23640:2011 (*22*)<br>CLSI EP25 (*23*)<br>WHO TGS-2 (*24*)<br>ASTM D4169-22 (*25*) |

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| | | 4. Each specimen shall be tested in duplicate for each condition (see note 1). | 15, 18 and 24 months, the maximum stability claim can be set to 18 months.<br>7. The numbers of invalid results shall be reported.<br>8. Accelerated studies do not replace the need for real time studies. | |
| 310 | 3.06.05.02<br>In-use stability (open pack or open vial stability) | 1. In-use stability of labile components shall be conducted using components in their final configuration.<br>2. In-use stability of controls provided or recommended for use in the IFU shall be established.<br>3. The operating temperature and humidity ranges investigated as part of the in-use stability studies shall reflect the worst case use scenario (see note 1, 2).<br>3. Testing shall be performed in venous blood at each of 3 glucose concentrations:<br>• 2.8 mmol/L (50 mg/dL).<br>• 8.3 mmol/L (150 mg/dL).<br>• 16.7 mmol/L (300 mg/dL.<br>4. Each specimen shall be tested in duplicate at each of the glucose concentrations.<br>5. Testing shall be conducted in at least 1 lot. | 1. The testing shall reflect conditions that exceed the expected operating conditions (temperature and humidity range) in so intended use settings so that the limitations of the BGMS can be understood.<br>• For example, in addition to investigating deviations of temperature within those claimed in the IFU (lower and upper extremes of a claimed temperature range), temperature ranges should be investigated that exceed those of claimed operating conditions and which cause test failure (incorrect/invalid results).<br>2. The testing shall reflect the expected in-use conditions for opened containers in the user environment (e.g., opening the reagent system container multiple times per day over the in-use shelf life).<br>3. The number of invalid tests with each reagent system lot shall be recorded/reported, e.g., for each temperature investigated. | |

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284 **Part 2: IMDRF ToC Chapter 4 Clinical evidence**

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| 287. | **4.02.03 Device specific clinical studies** | | | |
| 288. | 4.02.03 a<br>General requirements for clinical performance and usability study conducted in intended use settings | The following clinical studies shall be performed in intended use settings (see note 1):<br>• **4.02.03 b** Trained user performance assessment.<br>• **4.02.03 c** Qualification of usability - Observed lay user performance assessment.<br>• **4.02.03 d** Qualification of usability - Label comprehension.<br>• **4.02.03 e** Qualification of usability - Result interpretation.<br>These 4 different evaluations may be combined in 1 study, as described below, however other study designs are acceptable if they meet the requirements outlined in this section.<br>1. Subjects taking part in the lay user performance assessment may serve as subjects in the trained user performance assessment; however lay user testing must be performed before professional user testing so as not to influence the lay user performance (see note 2).<br>2. A validated BGMS shall be used as comparator for performance evaluations (see note 3, 4).<br>3. Different geographical settings shall be covered (minimum 2 regions, see note 1).<br>4. At least 100 subjects or their caregivers shall be included per region. | 1. Geographical regions shall cover different settings, taking into consideration a range of environmental conditions (temperature/humidity/altitudes), users.<br>2. As specimens tested during lay user performance assessment are taken by the subjects themselves as part of the usability assessment, the subjects shall not have been exposed to the procedure of the BGMS under investigation (i.e. when used by a trained user/healthcare professional).<br>3. Refer to section "C.4 Acceptable laboratory methods/comparator system for validation and verification studies" for criteria describing an established laboratory method.<br>4. Comparator measurements shall be performed in duplicate. | ISO 15197:2013, clause 6.3, clause 8 (*1*)<br>IEC 62366-1:2015 (*21*)<br>WHO TGS-3 (*26*) |

<table>
<tr><th></th><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirement</th><th>Source documents and additional information</th></tr>
<tr><td></td><td></td><td>5. For the trained user and observed lay user performance assessment, packed cell volume (haematocrit) shall be assessed and recorded per subject.</td><td></td><td></td></tr>
<tr><td>289.</td><td>4.02.03 b<br>Trained user performance assessment</td><td>1. Performance of the BGMS with trained users shall be evaluated as per the requirements outlined in chapter 3.05.04.01 of this document.<br>2. Capillary blood specimens shall be taken by 3 to 5 trained users/healthcare professionals (see note 1):<br>• Using 1 lot of the BG meter.<br>• Using 3 different reagent system lots, each in duplicate.<br>3. Subjects shall fall into the following glucose ranges:
<table>
<tr><th>Percentage of subjects<br>%</th><th>Glucose concentration<br>mmol/L (mg/dL)</th></tr>
<tr><td>40</td><td><6.66 (<120)</td></tr>
<tr><td>30</td><td>>6.66 to 11.10 (>120 to 200)</td></tr>
<tr><td>15</td><td>>11.10 to 16.65 (>200 to 300)</td></tr>
<tr><td>10</td><td>>16.65 to 22.20 (>300 to 400)</td></tr>
<tr><td>5</td><td>>22.20 (>400)</td></tr>
</table>
4. Comparator testing shall be performed before and after (within 3 minutes) measurement with the BGMS under assessment (see note 2).</td><td>1. Laboratory professionals/healthcare professionals either in centralized testing laboratories or lay persons trained in the use of the device at POC.<br>2. If the trained user performance assessment is performed directly after the observed untrained user performance assessment, the comparator results obtained after the lay user measurements can also be used for the evaluation of the trained user performance assessment.</td><td>ISO 15197:2013, clause 6.3 (1)</td></tr>
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| 290. | 4.02.03 c<br>Qualification of usability - Observed lay user performance assessment | 1. Each subject shall receive (see note 1):<br>• IFU provided by the manufacturer with the test device.<br>• Blood glucose meter.<br>• Reagent system.<br>• Control solution.<br>2. 1 lot of reagent system and blood glucose meters shall be tested.<br>3. Subjects shall perform a measurement using capillary fingerstick blood with the BGMS under evaluation according to the IFU (see notes 2, 5 and 6):<br>4. Reading out results (glucose values) and interpretation of guiding symbols (see note 6).<br>5. The subjects' measurement technique and difficulties in operating the BGMS (≙ human factors) shall be observed and documented by trained users/healthcare professionals e.g.:<br>• Insertion of the reagent system into the meter.<br>• Application of blood to the reagent system.<br>• Reading out of the result.<br>• Correct reporting of the result.<br>6. The final BG measurements obtained by subjects shall be used as performance data for the lay user performance assessment.<br>7. Finger-stick capillary BG testing with the comparator BGMS shall be performed by a trained users/healthcare professional immediately after | 1. If the blood glucose meter is for single person use, all lay user subjects shall be provided with an individual meter. If the blood glucose meter is for multiple patient use, 10 devices shall be provided per 100 subjects.<br>2. Subjects may be allowed to practice testing with the BGMS after reviewing the materials/IFU. However, no further instructions, training, assistance and feedback shall be provided to the subjects.<br>• The number of practice tests shall be limited and defined in the study protocol.<br>3. Lay users:<br>• Adults living with diabetes or providing care for people living with diabetes.<br>• Minors (≥13 years) living with diabetes who are able to read and manage diabetes independently from a caregiver (at least 10% of total lay users).<br>• Different levels of literacy shall be considered.<br>• If a subject is illiterate, the witness or family member can assist in reviewing procedures. However, measurements shall be only performed by people living with diabetes.<br>4. Lay users shall be naïve to the BGMS under evaluation:<br>• At least 10% of all lay users should be naïve to any self-monitoring BGMS (defined of not having performed any self-monitoring BGMS in the past 12 months). These subjects may be non-diabetic.<br>5. Particular attention shall be paid to documenting the subjects' compliance with each of the factors raised during | ISO 15197:2013, clause 6.3, clause 8 (*1*)<br>IEC 62366-1:2015 (*21*) |

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| | | (within 5 minutes of) the subject's own glucose measurement:<br>• Blood specimens shall be collected in duplicate (as for trained user performance assessment, see chapter **4.02.03 b**). | risk assessment of the process. Factors likely to arise during risk evaluation could be for example:<br>• Paying attention to the IFU before starting.<br>• Correct use and disposal of the specimen collection accessories, e.g., lancet, swab.<br>• Application of correct volumes to the BGMS.<br>6. All occurred mistake(s) shall be documented in the case report form.<br>7. If a mistake has been made and reported by subjects in performing the test e.g., incorrect application of blood to the reagent system, or occurrence of a non-quantitative result, subjects shall be allowed to repeat self-testing up to (maximum) 3 times. | |
| 291. | 4.02.03 d Qualification of usability - Label comprehension study | Once testing is complete, the result interpretation and label comprehension evaluations shall be performed.<br>1. Questionnaire shall be administered to at least 200 subjects, representative of intended users, in order to demonstrate comprehension of key messages.<br>2. Subjects shall receive a questionnaire to:<br>• Provide feedback on usage of the self monitoring BGMS.<br>• Assess whether the subjects understood how to use the BGMS under evaluation correctly.<br>• Assess whether the subjects correctly understand key messages from packaging and labelling such as: | 1. Different geographical settings shall be covered (minimum of 2 regions.<br>2. Labelling shall be clear and easy to understand; instruction material shall include pictures, quick guides, or job aids.<br>3. Additional resources such as a QR code linking to a demonstration video in local language(s) is encouraged.<br>4. A caregiver can assist in label comprehension if the subject is illiterate. | |

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| | | ○ Proper self-selection (whether users understand if it is appropriate for them to undertake testing).<br>○ Understanding key warnings, limitations and/or restrictions.<br>○ Test result interpretation.<br>3. Subjects shall have the opportunity to provide unrestricted comments on their experience when using the BGMS under evaluation and the IFU. | | |
| 292. | 4.02.03 e Qualification of usability - Results interpretation study | 1. Questionnaire shall be administered to at least 200 subjects, representative of intended users (see note 1).<br>2. Results interpretation: Subjects to interpret key symbols of the BGMS that may be provided to guide interpretation of the results.<br>3. Interpretation of guiding symbols can be done based on stored glucose values that signal:<br>• Low.<br>• Within range.<br>• High BG measurements.<br>• Warnings that indicate the measurement is outside of the measuring range. | 1. Different geographical settings shall be covered (min. 2 regions. | |

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## E. Source documents


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