TSS-18

Haemoglobin A1c point of care analysers for professional use

Technical specifications series for submission to WHO prequalification – diagnostic assessment

World Health Organization

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Haemoglobin A1c point-of-care analysers for professional use

(Technical specifications series for submission to WHO prequalification – diagnostic assessment, TSS18)

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Declarations of interest

All external experts and meeting participants submitted to WHO a declaration of interest disclosing potential conflicts of interest that might affect, or might reasonably be perceived to affect, their objectivity and independence in relation to the subject matter of the guidance. WHO reviewed each of those and had concluded that none could give rise to a potential or reasonably perceived conflict of interest related to the subjects discussed covered by the guidance.
All the declarations were made known to all participants at the beginning of the meeting.
All the experts participated in their individual capacities and not as representatives of their countries, governments or organizations.

Abbreviations

CAP	College of American Pathologists
CLSI	Clinical and Laboratory Standards Institute
DCM	designated comparator method
DM	diabetes mellitus
EDTA	ethylenediaminetetraacetic acid
EMC	electromagnetic compatibility
EQA	external quality assessment
GHWP	Global Harmonization Working Party
HbA1c	haemoglobin A1c (also commonly referred to as glycated haemoglobin)
Hb	haemoglobin
HbF	foetal haemoglobin
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFU	instructions for use
IMDRF ToC	International Medical Device Regulators Forum “Table of Contents”
ISO	International Standards Organization
IVD	in vitro diagnostic
MFDS	Ministry of Food and Drug Safety, Republic of Korea
MHRA	Medicines and Healthcare products Regulatory Agency, United Kingdom of Great Britain and Northern Ireland
NORAD	Norwegian Agency for Development Cooperation
POC	point-of-care
PRMP	primary reference measurement procedure
NGSP	National Glycohemoglobin Standardization Program
TSS	technical specifications series
USA	United States of America
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 for point of care (POC)[2] IVDs for the quantitative detection of Haemoglobin A1c (HbA1c) in venous or capillary whole blood used:

- To monitor response to therapy in people who have been diagnosed with diabetes mellitus.
- As an aid to diagnosis of type 2 diabetes mellitus.

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 and/or regulatory documents. Although references to source documents are provided, in some cases WHO prequalification has additional requirements.

For WHO prequalification purposes, manufacturers shall provide evidence in support of the clinical performance of an IVD to demonstrate that reasonable steps have been taken to ensure that a properly manufactured IVD, being correctly operated in the hands of the intended user, will detect the target analyte accurately and consistently and fulfil its indications for use. The clinical study described in part 2 is intended to validate the performance of the IVD in the intended user and use setting. It is not intended to set diagnostic or treatment thresholds.

The requirements summarized in this document do not extend to the demonstration of clinical utility, i.e., the effectiveness and/or benefits of an IVD, 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

[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 sample 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.

studies is required. Clinical utility studies usually inform programmatic strategy and are thus the responsibility of programme managers, ministries of health and other related bodies in individual WHO Member States. Such studies do not fall under the scope of WHO prequalification.

B. Other WHO guidance documents

This document should be read in conjunction with other relevant WHO guidance documentation, including the WHO prequalification documents and diabetes publications:

- Technical guidance series documents for WHO prequalification - diagnostic assessment (*1*)
- Instructions for compilation of a product dossier, WHO document PQDx_018 (*2*)
- Use of glycated haemoglobin (HbA1c) in diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. (*3*)

C. Performance principles for WHO prequalification

C.1 Intended use

An IVD intended for prequalification must be accompanied by a sufficiently detailed intended use statement. This should allow an understanding of at least the following:

- The type of assay and what is detected or measured (e.g., POC assay to quantify HbA1c levels in whole blood);
- The clinical indication and function of the IVD (e.g., monitoring of people known to have diabetes mellitus; as an aid to diagnosis of type 2 diabetes mellitus);
- What the IVD reports (e.g., total haemoglobin A1c in blood in mmol/mol and derived % units);
- Whether or not it includes automated components or is intended to be used with automated instruments;
- The target population (e.g., patients at risk of type 2 diabetes mellitus and patients at risk of complications from diabetes);
- The intended use environment (e.g., for professional use in a laboratory setting, and/or POC settings);
- The intended user (e.g., laboratory professionals[3], trained healthcare professional, trained healthcare worker);
- The intended specimen type (e.g., capillary, or venous whole blood);
- Any limitations to the intended use or conditions that might affect the practical use in the intended population (e.g., presence of haemoglobin (Hb) variants, environmental conditions, age, ethnicity, etc. that affect test results).

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

Prequalified HbA1c POC IVDs in low- and middle-income countries are likely to be used by a range of users in different geographical settings:

- laboratory professionals either in centralised testing laboratories or at POC,

[3] Medical technologists, medical laboratory technicians or similar, who have received a formal professional or paraprofessional certification or tertiary education degree

- health care professionals in health care settings or at POC who are not experienced in biochemical testing,
- healthcare workers trained in the use of the test at the POC

Depending on the intended use of the IVD, analytical and clinical performance studies shall be designed to take into account not only the diversity of knowledge and skills across the population of individuals using the IVD, 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 reflects the intended operational settings, including laboratory or service delivery complexity, user expertise, training received and test population.

For studies investigating the effect of potentially interfering substances and medical conditions in part 1 of the tables below, the manufacturer is required to conduct a risk assessment to identify the substances that may interfere with the detection and appropriate interpretation of HbA1c, taking the device technology, specimen type and patient population into account. In some cases, an observed discordance may be due to the physiological condition. Any interference observed or known to exist from literature is required to be addressed the performance limitations section of the IFU.

For WHO prequalification submission, device specific clinical studies in part 2 of the tables below shall be conducted using capillary whole blood as a minimum.

C.3 Applicability of supporting evidence to IVD under review

Minimum performance requirements for WHO prequalification outlined in this document are applicable to quantitative HbA1c POC IVDs for use in human blood.

When establishing performance, the accurate HbA1c concentration of a specimen shall be determined using a suitable quantitative designated comparison method (DCM) test, with selection justification provided. The corresponding quantitative values of HbA1c concentration (mmol/mol or derived NGSP units (%)), and how these were calculated shall be reported. Determination of HbA1c levels using a DCM must take into account the imprecision and bias inherent in that test. Note that a different DCM can be used in the analytical and clinical performance studies, as long as the selected DCM meets the appropriate criteria described in part 1 and part 2 of this document.

Analytical and clinical performance studies shall be undertaken using the specific, final (locked-down) version of the assay intended to be 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)*

The version of the IFU used for verification and validation studies submitted to WHO prequalification shall be stated. If the test procedure in the IFU is changed in any way

after completing performance 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 lots required for each study. Where more than one lot is required, each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents, representative of routine manufacture. It is a manufacturer's responsibility to ensure, via risk analysis of its IVD that the minimum numbers of lots chosen for estimating performance characteristics considers the variability in performance likely to arise from the interlot diversity of critical components and their formulation or from changes that could occur during the commercial life of the IVD. Differences found between lots during the analytical and clinical performance studies shall be reported.

Estimation (and reporting) of IVD performance shall include the 2-sided 95% confidence interval around the estimated values for key performance metrics. The total percentage error shall be reported, and an explanation provided on how it was calculated. The cause of invalid results/errors should be reported if available. Data shall be presented in a clear and understandable format. Discrepant results should be resolved as much as possible, however performance characteristics shall be based on the original result.

For analytical performance studies described in part 1 below it may be also possible to carefully design protocols that will generate useful data for more than one of the required studies, provided the specific criteria for each requirement are met by the study (e.g., number of replicates, concentration of analyte etc.). Studies which may fall in this category are indicated in the appropriate chapters in the tables. In some analytical performance studies (where indicated) it is acceptable to use one specimen type, providing that equivalence between specimen types has been demonstrated by the manufacturer.

Studies that comprise the testing of left-over specimens by research and development staff at a manufacturer's facility shall not, on their own, be considered sufficient to meet many of the clinical performance study requirements summarized in part 2.

D. Table of 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) (*5*). 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.

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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
3.05 Analytical performance			
3.05.01 Stability of specimen(s)			
Specimen collection, storage, and transport	1. Real time studies shall be determined for each specimen type (e.g., venous, capillary whole blood) taking into account: • Storage conditions (e.g., duration at different temperatures and variation in humidity, temperature limits, where appropriate) • Transport conditions, where applicable (see note 1) • Intended use (see note 2) • Specimen collection and/or transfer devices, whether these contain anticoagulants and whether they can be sealed 2. Testing shall be conducted in 1 lot 3. The specimen panel shall contain a minimum of 10 specimens across the measuring range of the assay	1. Evidence shall be provided which verifies the maximum allowable time between specimen collection, and its processing or addition to the IVD or storage in the setting where testing takes place 2. Acceptance criteria shall confirm that claimed specimen types transported, processed, and stored under recommended conditions will give expected results unless all specimens are expected to be processed as fresh specimens within a specified time frame 3. The IVD performance shall be established for each storage condition at the beginning and end of the time period of stability stated in the IFU	
3.05.02 Validation of specimens			
3.05.02 a Demonstration of validity of all specimen types	1. The relationship between IVD performance in claimed specimen types shall be established • The specimen panel shall contain 40 specimens across the measuring range of the assay for each specimen type • Testing shall be conducted in 1 lot	1. All claimed specimen types (capillary and venous whole blood) shall be validated and taken through the entire process from the recommended specimen preparation/handling through to the assay protocol 2. The established relationship between IVD performance in claimed specimen types shall be considered in the design of subsequent studies. For example, if the studies show that 1 or more of the claimed specimen types are equivalent, then not all specimen	WHO TGS-3 (*6*) Lenters-Westra E, English E. (*7*) CLSI EP35 (*8*)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
		types need to be tested in some of the subsequent studies (where indicated)	
3.05.02 b Demonstration of equivalence of claimed anticoagulants	1. For each claimed anticoagulant, testing shall be conducted to demonstrate equivalent performance in at least 40 specimens across the measuring range of the assay 2. Testing shall be conducted in 1 lot 3. Testing shall be conducted in 1 specimen type only (capillary or venous whole blood)		CLSI EP35 (*8*)
3.05.02 c Demonstration of equivalence of frozen specimens	1. When frozen specimens are used for the analytical or clinical performance analysis, then equivalence to fresh specimens shall be demonstrated (see note 1): • Testing shall be conducted using 40 fresh and paired frozen specimens across the measuring range of the IVD (i.e., 40 specimens measured when fresh and the same 40 specimens measured after a freeze thaw cycle) 2. Testing shall be conducted in 1 lot 3. Testing shall be conducted in 1 specimen type only (capillary or venous whole blood)	1. It is known that some assays do not perform well with frozen specimens therefore demonstration of equivalence of paired fresh and frozen specimens is required on at least 1 specimen type – if frozen specimens are used for any analytical or clinical studies	CLSI EP35 (*8*)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
3.05.03 Metrological traceability of calibrators and control material values			
Metrological traceability of calibrators and assignment of control material values	1. As applicable; the metrological traceability of the provided control and calibration material(s) shall be provided 2. Traceability to IFCC primary reference measurement procedure (PRMP) shall be demonstrated as well as identification of applicable reference materials and/or reference measurement procedures (see notes 2 and 3)	1. The secondary reference materials used shall be stated and traceability to the IFCC PRMP demonstrated 2. Where the manufacturers controls are to be used with the IVD medical device then the value assignment process of the control material shall be described 3. If third party control material is used for any analytical studies, then the manufacturer of the IVD shall provide relevant information from the manufacturer of the specified control materials where applicable	Jeppsson et al (*9*) NGSP (*10*)
3.05.04 Accuracy of measurement			
3.05.04.01 Trueness	The trueness of the IVD shall be demonstrated by comparison of the performance of the IVD with an established quantitative method for HbA1c concentration determination (designated comparator method (DCM)) 1. The specimen panel described below shall be tested by the IVD and the reference method (see note 1-4): • A total of at least 100 specimens with HbA1c concentration covering the entire measuring range of the IVD (see note 2):	1. The DCM shall be authorized for use by a recognized stringent regulatory authority[4] and acknowledged in the literature as representing state of the art. In addition: • The DCM shall have passed IFCC certification and NGSP certification prior to use in any performance assessment • The DCM shall be externally validated through an EQA process (national EQA programme with accuracy-based values, EurA1c study or CAP survey in USA) 2. The range shall include 30 to ≥120 mmol/mol HbA1c. If the upper limit of the IVD device measurement range is less than 120 mmol/mol then justification of specimen concentrations chosen shall be provided	CLSI EP09 (*11*) WHO PQDx_173 (*12*) EurA1c Trial Group (*13*) NGSP CAP survey (*14*)

[4] The document PQDx_173 Abridged prequalification assessment contains a list of recognized stringent regulatory authorities

<table>
<tr><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirement</th><th>Source documents</th></tr>
<tr><td></td><td>
<table>
<tr><th>Distribution of subjects</th><th>HbA1c concentration range</th></tr>
<tr><td>10%</td><td>30-36 mmol/mol</td></tr>
<tr><td>60%</td><td>37-65 mmol/mol</td></tr>
<tr><td>30%</td><td>>65 (including specimens ≥120) mmol/mol</td></tr>
</table>
2. 100 specimens shall be tested on each of 2 IVD reagent lots (see note 3)
3. Testing in 1 specimen type, unless equivalence has not been demonstrated (see section 3.05.02)</td><td>3. If the risk analysis/file demonstrates that calibrator lots impact accuracy, then multiple calibrator lots shall be included in the study design as appropriate
4. Correlation of results between the IVD and the DCM shall be demonstrated statistically</td><td></td></tr>
<tr><td>3.05.04.02 Precision repeatability & reproducibility</td><td>1. Both repeatability and reproducibility shall be estimated using panels with defined analyte levels
2. Repeatability and reproducibility specimen panels shall at least include:
• 4 different HbA1c levels at appropriate clinically relevant concentrations: approx. 30, 50, 75, 110 mmol/mol
3. Testing in 1 whole blood specimen type unless no equivalence demonstrated (see section 3.05.02)
4. Each HbA1c level shall be tested:
• in duplicate
• using 2 different lots of reagents and instruments (note 3)
• over 20 days (not necessarily consecutive) with two runs/day at each of 2 different testing sites</td><td>1. E.g., within- or between-run, -lot, -day, -site, -operator etc.
Note: a run will be defined depending on the IVD's throughput; if the platform can accommodate all specimens in a single run, i.e., in the same test plate, the replicates will be run together. If the assay can only accommodate a smaller set or a single specimen(s), a run will be defined as a testing session carried out on the same instrument/module
2. Lots shall be composed of different batches of critical components
3. To understand irregularities in results obtained, at least 2 lots shall be tested at each of the testing sites
4. The operator of the devices shall not be an employee/representative of the IVD device manufacturer
5. Results must be statistically analysed (e.g., using ANOVA to identify and isolate the sources and extent of any variance)</td><td>WHO TGS-3 (6)
CLSI EP15-A3 (15)
CLSI EP05-A3 (16)</td></tr>
</table>

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	5. If it is not possible to use frozen specimens on the device or the stability of fresh specimens is not proven for 20 days, then an alternative protocol may be used: • Measure 5 times per day for at least 5 days (25 replicates) (the days do not necessarily need to be consecutive) • Using at least 3 lots of reagents and instruments (see note 2) • At 3 different sites (also see note 3) 6. If the effect of operator-to-operator variation on IVD performance is considered to be of significance (see note 7) then it shall be included as part of the precision studies. Testing shall be performed: • by 1 operator/site (see notes 4 and 7) • by operator's representative of expected end users • unassisted • using only the instruction material provided with the IVD (e.g., instructions for use, labels, and other instructional materials)	6. The numbers of invalid tests must be reported 7. The effect of operator-to-operator variation on IVD performance is also to be considered as a human factor when designing robustness (flex) studies (see section 3.06.04 Usability/human factors – Flex studies). The results of estimating operator-to-operator variation on IVD performance may be used in conjunction with studies to qualify the usability of the IVD 8. The repeatability and reproducibility studies may be investigated separately with appropriate study design to facilitate robust statistical analysis (refer to source document CLSI EP-05)	
3.05.06 Analytical specificity			
3.05.06 a Potentially interfering substances and medical conditions	1. The potential for false results (under or over quantification) arising from interference by the substances/conditions listed below shall be investigated in specificity studies 2. Testing is required in 1 claimed specimen type only	1. The risk assessment conducted for an IVD should identify substances at medically relevant levels that may interfere with the detection and appropriate interpretation of HbA1c, taking the device technology, specimen type and patient population into account	EU IVDR (*17*) CLSI EP07 (*18*) CLSI EP37 (*19*)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	3. A minimum of 5 replicates of the specimen with interferent added, and 5 replicates of the control specimen (no interferent) 4. Interference shall be investigated at 2 HbA1c levels (approx. 50mmol/mol and 75mmol/mol)	• Under some circumstances stringent risk evaluation may eliminate the requirement to test some of the items in the lists but any such decision shall be documented in any submissions to WHO and considered in the risk-benefit statements 2. 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 3. Results shall be reported with respect to each condition or substance and not be reported as an aggregate of the total number of specimens tested in the study 4. If specimens for high carbamylation cannot be obtained at the required HbA1c concentrations, then alternative HbA1c concentrations can be used with a justification provided 5. Exogenous substances shall be spiked at the highest medically relevant concentrations	
3.05.06 b Endogenous substances	1. Triglycerides, unconjugated bilirubin, glucose, rheumatoid factor, urea (2 high concentration specimens) 2. Haemolysis (2 high concentration specimens) 3. Carbamylated HbA1c (2 high concentration specimens) (see note 4) 4. Labile HbA1c (2 high concentration specimens) 5. Abnormally high and abnormally low haematocrit concentrations (10 high haematocrit and 10 low haematocrit specimens) 6. The impact of haemoglobinopathies and synthesis disorders such as sickle cell trait, thalassemia (elevated A2) shall be investigated across the full measuring HbA1c range of the device: • 20 specimens of each heterozygous haemoglobin variant (D, E, S, C) • 10 specimens of different (or varying) HbA2 and HbF concentrations		
3.05.06 c Exogenous substances	1. The interference of exogenous substances on the performance of the device shall be investigated as per manufacturer's risk assessment. (See also section C.2 of this document)		

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	2. The following substance should be considered (see note 5): • Acetaminophen, ibuprofen, aspirin • Anti-diabetic medicines (metformin, glibenclamide) • Ascorbic acid • Biotin		
3.05.08 Measuring range of the assay			
Linearity	The linear range shall be established: 1. Using a dilution series with 10 concentrations that span the measurement range (see note 1) 2. 2 to 4 replicates shall be tested at each concentration 3. Using 1 lot 4. Testing in EDTA venous blood specimens only	1. Hb concentration shall be uniform across the dilution series (the Hb concentration of the parent material shall be the same prior to creating the dilution series) 2. The test results shall be analysed using appropriate statistical tools (e.g., Deming Regression Analysis) to demonstrate correlation between the IVD results and the nominal concentrations of the analyte 3. Depending on the technology, the impact of a potential prozone effect shall be investigated if the upper limit of detection is > 120mmol/mol	CLSI EP06-A (*20*)
3.05.10 Validation of the assay procedures			
3.05.10 a Validation of assay parameters	1. Evidence shall be provided on how parameters (specified in the IFU) were determined, verified, and validated 2. The extent of the assay parameter validation shall be subject of a documented risk assessment. The actual requirement is dependent on the assay and shall be ascertained for each device (note 2) 3. The parameters specified in the IFU commonly include:	1. These parameters may be investigated as part of 3.06.04 Usability/human factors studies 2. The intent of parameter validation is to demonstrate that no combination of small but defined variations in the parameters of the protocol will result in the IVD failing to meet any of the manufacturer's claims i.e., the assay is robust 3. Performance studies shall be conducted at the extremes of the intended operational temperature range; the effect of humidity, and of reading times shall also be investigated. The impact of	IMDRF TOC (*4*) WHO PQDx_018 (*2*)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	• time between drawing specimen, handling, and loading • volumes (specimen and reagent) • temperature • humidity • shaking (where applicable) 4. Validation of parameters shall be documented as required in 1 specimen type 5. Validation shall be performed using a minimum of 2 reagent lots: • Freshly made reagents • Reagents towards the end of their assigned shelf lives 4. At least 2 specimens shall be tested at different HbA1c levels (approx. 50mmol/mol and 75mmol/mol)	extremes of temperature and humidity in the setting of use on the collection of specimens should be considered • For example, in addition to investigating deviations of temperature within those claimed in the IFU (in the middle and at both 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) 6. The extent of validation shall be subject to documented risk assessment 7. The range of humidity tested shall be risk-based, taking into consideration likely operational conditions in resource limited settings	
3.05.10 b Carry over	Carry over is not an issue with devices that have single use cartridges where the measurement takes place in the cartridge. However, where cuvettes or columns are used more than once a carryover study shall be undertaken 1. Using 3 specimens low (L), medium (M), high (H) and analyse in the following order: MHLMMLLHHM (see note 1)	1. Lowest possible concentration specimen for low and highest possible concentration specimen for high; medium should be approximately the mean of the high and low values	CLSI EP10 (*21*)
3.06 Other studies			
3.06.01 Electrical systems; safety, mechanical and environmental protection, and electromagnetic compatibility			
Electrical safety, mechanical and	1. Evidence supporting electrical safety, mechanical and environmental protection, and electromagnetic	1. Electromagnetic compatibility (EMC) testing 2. Electrostatic discharge/Electromagnetic interference testing	IEC 61326-1 (*23*)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
environmental protection, and electromagnetic compatibility	compatibility shall be provided (see note 1-3 for the categories of testing) 2. If recognised standards have been used (such as IEC), provide information regarding the type of testing performed, the reference standard followed, the acceptance criteria, and whether the device met these acceptance criteria	3. Protection against electric shock and mechanical hazards (IEC 61010-1) 4. This information may be provided as part of the flex studies outlined below in chapter 3.06.04.	IEC 61326-2-6 (*24*) IEC 61010-1 (*25*)
3.06.02 Software/Firmware			
3.06.02.08 Software verification and validation			
3.06.02.08 a Software validation	1. Software validation shall include: • Verification of built-in fail-safe and alert mechanisms • Verification of quantitative results detection • Verification of quantitative results calculation	1. Software validation procedures shall be conducted according to IEC 62304.	IEC 62304 (*26*)
3.06.02.08 b Error codes	1. Provide evidence to demonstrate that appropriate error codes are provided		US FDA (*22*) IEC 62304 (*26*)
3.06.03 Cleaning and disinfection validation			
Cleaning and disinfection validation	Disinfection efficacy studies shall be performed to 1. Demonstrate efficacy of the chosen disinfectant against blood borne viruses of concern (see note 1, 2) 2. Demonstrate that the procedure is effective with external analyser materials (note 4) 3. Demonstrate that the analytical performance is not impacted and that it is robust to cleaning and disinfection procedures after multiple cleaning and disinfection cycles (see note 3)	1. The studies conducted shall be based on the design of the device and risk assessment 2. The disinfectant product shall be effective against HIV, Hepatitis C, and Hepatitis B viruses 3. For the purpose of the cleaning and disinfection studies, the typical life of a device is 3 to 5 years, or the life span validated for warranty 4. Instructions shall be clear as to what are appropriate to the device and supported by evidence	US FDA (*27*) ASTM E1053-20 (*28*)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	4. Evaluate physical indicators of deterioration (to the screen, buttons, plastic housing) 5. Evaluate the functionality of the HbA1c features and any parts particularly susceptible to blood contamination, are not impacted (even after multiple cleaning and disinfection cycles)		
3.06.04 Usability/human factors			
3.06.04 a Flex studies/robustness	The influence of the following factors on expected results, when appropriate: 1. Handling contamination (e.g., from latex, powder, hand lotion, sweat, and/or soap, as appropriate) • Testing to be performed in 1 lot • At least 2 specimens shall be tested at different HbA1c levels (approx. 50mmol/mol and 75mmol/mol) 2. IVD instrument sturdiness (including the effect of non-level work surface) 3. Ruggedness such as mechanical vibration testing, shock testing (see note 4)	1. The risk assessment conducted for an IVD shall identify factors which have potential to affect the performance of the assay 2. Refer to WHO document PQDx_018 "Instructions for compilation of a product dossier" for other flex studies that may be relevant, taking into consideration the broad range of operational and environmental conditions consistent with intended use 3. The factors shall 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 4. For the purposes of this document, ruggedness means the ability to resist environmental shocks of a variety of kinds 5. Robustness testing generally takes the form of statistically designed experiments to evaluate the effect of simultaneous "small but deliberate changes" in method parameters	WHO PQDx_018 (*2*)
3.06.04 b Qualification of usability: label comprehension	1. Questionnaire-based testing and/or peer observation of trained operators shall be conducted to assess their ability to correctly comprehend key messages from packaging and labelling such as: • Test procedure comprehension	1. The trained operator (the intended user) shall be from the routine working environment and in no way linked with the manufacturer 2. Instructions for use and labelling should be clear and easy to understand; use of pictorial instructional material is encouraged	IEC 62366-1 (*29*) Backinger CL and Kingsley PA (*30*)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
study (including IFU)	• Understanding of key warnings, limitations and/or restrictions • Ease of following instructions 2. The questionnaire shall be administered to at least 15 intended users, including those whose native language may not be the language of the IFU if necessary, to demonstrate comprehension of key messages 3. The study shall be conducted at 2 geographically diverse populations to demonstrate comprehension of key messages		EU IVDR (*17*)
3.06.04 c Qualification of usability: Result interpretation study	1. Intended users shall be requested to interpret key symbols provided to guide interpretation of the outputs (including errors) of the HbA1c POC device (see note 1) 2. Testing subjects shall consist of: • at least 15 intended users, including those whose native language may not be the IFU language • in their usual working environment, not employees of the manufacturer • from 2 geographically diverse populations to demonstrate correct interpretation of device outputs	1. The manufacturer shall include a range of HbA1c concentrations that trigger different status/key symbols (including range of error messages) on the device. This can be partially conducted using fresh whole blood specimens taken from a range of pre-screened HbA1c specimens	IEC 62366-1 (*29*) Backinger CL and Kingsley PA (*30*) EU IVDR (*17*)
3.06.05 Stability of the IVD			
3.06.05.01 Claimed shelf life (including transport stability)	Stability studies shall be evaluated for the shelf life of the test kit and control solution if applicable. The following conditions shall be investigated: 1. Transport stability studies	1. Lots must comprise different batches of critical components. 2. Determination of transport (shipping) stability shall be performed using simulated extreme stress conditions, ensuring that application of those conditions is consistent and controlled	ISO 23640:2011 (*31*) CLSI EP25 (*32*)

<table>
<tr><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirement</th><th>Source documents</th></tr>
<tr><td></td><td>

Conditions to mimic extremes of conditions (temperature, humidity, pressure, drop-shock) exposed to during transport (see note 2)
Conditions shall be applied to the IVD in final packaging
These conditions shall be applied to the kit firstly, before placing the kits onto real time stability studies

2. Shelf life storage temperature and humidity range
3. Testing shall be conducted in at least 3 lots
4. At least 3 specimens shall be tested with the following HbA1c concentrations
<table>
<tr><th></th><th>HbA1c concentration</th></tr>
<tr><td>Low</td><td>35 mmol/mol</td></tr>
<tr><td>Medium</td><td>50 mmol/mol</td></tr>
<tr><td>High</td><td>75 mmol/mol</td></tr>
</table>
5. Each specimen shall be tested in triplicate at each time point/condition
6. All claimed specimen types shall be tested (unless equivalence has been demonstrated – see section 3.05.02)
</td><td rowspan="2">
3. Claims for stability must be based on the second-last successful data point from the least stable lot, with, if lots are different, a statistical analysis showing that the bulk of lots will be expected to meet the claimed life. For example: for testing conducted at 3, 6, 9, 12 and 15 months, if stability was still observed at 15 months, then the maximum stability claim can be 12 months
4. Accelerated studies do not replace the need for real time studies.
5. In-use stability of labile components shall be conducted using components in their final configuration
6. The number of invalid tests with each kit lot shall be reported
</td><td rowspan="2">WHO TGS-2 (33)
ASTM D4169-22 (34)</td></tr>
<tr><td>3.06.05.02 In-use stability</td><td>
1. The operating temperature and humidity range shall be tested:

Using a minimum of 1 lot

</td></tr>
</table>

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	• At least 2 specimens shall be tested at different HbA1c levels (approximately 50mmol/mol and 75mmol/mol) • Each specimen shall be tested in triplicate at each of the time points 2. All labile components shall be evaluated (see note 5) 3. Only 1 claimed specimen type is required to be tested		

Part 2: IMDRF ToC Chapter 4 Clinical evidence

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source documents
4.02 Overall clinical evidence summary			
4.02.03 Device specific clinical studies			
4.02.03 a General requirements for clinical evaluation studies	Testing shall be conducted: 1. On specimens from all sections of the population for which claims are made in the IFU (for example across the stated age range) (see note 1, 2) 2. In different geographical settings • minimum of 2 regions, including at least 1 region where there is increased prevalence of Hb variants 3. By a variety of intended users representing POC intended use settings (e.g., different levels of health care facilities) (see note 3) 4. All primary specimens (i.e., those used on the POC IVD HbA1c device under evaluation) shall be fresh capillary blood specimens at a minimum. The comparator specimens may be capillary or venous blood specimens (EDTA preferably) if equivalence has been demonstrated (see chapter 3.05.02) 5. All specimens shall be tested by the DCM 6. Specimens with discrepant results (a difference of 3 standard deviations or more) shall be further evaluated. Where possible, follow-up testing shall be done to determine the cause (see note 9) 7. The procedure for selection of study specimens, how these represent the intended use population	1. Clinical performance shall be established using specimens that correspond directly to claims made in the IFU. 2. Not all subjects need to have been diagnosed with diabetes 3. Prequalified HbA1c POC IVDs will generally be used by trained health care workers and professionals • In addition, the operator shall not be linked in any way to the manufacture of the device 4. Comparator HbA1c test: The device/analyser and HbA1c test used for comparison (the DCM) shall be approved by a stringent regulatory authority and shall pass manufacturer IFCC certification and NGSP certification prior to use in any performance assessment. Additionally, the DCM shall be externally validated through an EQA programme such as a national EQA programme (with accuracy-based values) or the EURA1c study or CAP survey in the USA 5. The DCM shall not be affected by the presence of Hb variants 6. Product name, manufacturer name, product code and IFU version of the DCM used shall be provided 7. The manufacturer may consider protocols according to CLSI EP15 for initial performance assessment of the DCM. A justification for the choice of the protocol shall be provided 8. Problematic specimens, those with unexpected results but which otherwise meet selection criteria for a study, shall not	EurA1c Trial Group (*13*) NGSP CAP survey (*14*) CLSI EP09 (*11*) CLSI EP15-A3 (*15*)

<table>
<tr><th>IMDRF ToC Chapter heading and aspect</th><th>Testing requirements</th><th>Notes on testing requirements</th><th>Source documents</th></tr>
<tr><td></td><td>and how bias has been addressed shall be clearly described
8. Before any clinical study commences the manufacturer shall demonstrate that the DCM is working within expected parameters (see note 7)</td><td>be systematically excluded from analysis. All invalid results shall be recorded
9. All results shall be included in the denominator data for analysis
10. Correlation between the IVD and the DCM shall be established statistically
11. Clinical performance study protocols shall specify how results of the IVD under evaluation and the DCM will be compared and how results of the two assays will be statistically determined to be equivalent or not (e.g., Bland Altman analysis)
12. Each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents, representative of routine manufacture
13. Testing of each device with reagent lot 1 and 2, separately</td><td></td></tr>
<tr><td>4.02.03 b Diagnostic accuracy performance</td><td>The study shall be conducted as follows:
1. At different geographical settings (min. 2 regions)
2. At least 100 subjects shall be tested per region (see note 1, 2)
3. Testing of at least 2 reagent lots on at least one device (see note 12, 13)
4. HbA1c values (in mmol/mol) of tested subjects shall cover a range of 30 -120 mmol/mol and be as evenly distributed across the clinical range as possible
<table>
<tr><th>Distribution of subjects</th><th>HbA1c concentration range</th></tr>
<tr><td>10%</td><td>30-36 mmol/mol</td></tr>
<tr><td>60%</td><td>37-65 mmol/mol</td></tr>
<tr><td>30%</td><td>>65mmol/mol</td></tr>
</table></td><td></td><td></td></tr>
<tr><td>4.02.03 c Variant interference study</td><td>This study is only required if the HbA1c device variant interference study (see chapter 3.05.06) has been performed using frozen specimens and fresh to frozen specimen equivalence has not been demonstrated. Testing of the following specimens shall be conducted:
1. Haemoglobinopathies and synthesis disorders such as heterozygous sickle cell anaemia, thalassemia (elevated A2), variant Hb (D, E, S, C and HbF)</td><td>1. The comparator method used shall be described</td><td></td></tr>
</table>

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source documents
	2. Testing in 20 specimens of each variant covering the full measuring range of the device		

E. Source documents

1. Technical Guidance Series: WHO prequalification of in vitro diagnostics (IVDs) (website) https://extranet.who.int/prequal/vitro-diagnostics/guidance-documents Accessed 2 October 2023
2. World Health Organization. (2023). Instructions for compilation of a product dossier, fifth edition. Prequalification of in vitro diagnostics. World Health Organization; Available from https://extranet.who.int/prequal/vitro-diagnostics/contents-dossier Accessed 13 December 2023
3. World Health Organization. (2011). Use of glycated haemoglobin (HbA1c) in diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. World Health Organization. https://apps.who.int/iris/handle/10665/70523
4. World Health Organization. (2016). Reportable changes to a WHO prequalified in vitro diagnostic medical device. World Health Organization https://apps.who.int/iris/handle/10665/251915. License: CC BY-NC-SA 3.0 IGO
5. International Medical Device Regulators Forum (2019). In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC). IMDRF/RPS WG/N13 FINAL:2019 (Edition 3). https://www.imdrf.org/documents/vitro-diagnostic-medical-device-market-authorization-table-contents-ivd-ma-toc
6. World Health Organization. (2017). Principles of performance studies TGS-3. World Health Organization. https://apps.who.int/iris/handle/10665/258985. License: CC BY-NC-SA 3.0 IGO
7. Lenters-Westra E, English E. Are hemoglobin A1c point-of-care analyzers fit for purpose? The story continues. Clinical Chemistry and Laboratory Medicine. 2021 Mar 1;59(4):765-774. https://doi.org/10.1515/cclm-2020-1308
8. Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures, First Edition. CLSI EP35. Wayne, PA: Clinical and Laboratory Standards Institute; 2019. https://clsi.org/standards/products/method-evaluation/documents/ep35/
9. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, Miedema K, Mosca A, Mauri P, Paroni R, Thienpont L, Umemoto M, Weykamp C. International Federation of Clinical Chemistry and Laboratory Medicine. Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med 2002; 40:78-89. DOI: 10.1373/clinchem.2003.024802
10. Traceability and the EU Directive (website) NGSP: IFCC Traceability Accessed 23 November 2023
11. Measurement Procedure Comparison and Bias Estimation Using Patient Samples, Third Edition. CLSI EP09. Wayne, PA: Clinical and Laboratory Standards Institute; 2018 https://clsi.org/standards/products/method-evaluation/documents/ep09/
12. World Health Organization. (2021). Abridged prequalification assessment: prequalification of in vitro diagnostics, PQDx_173 V4 4 January 2021. World Health Organization. https://iris.who.int/handle/10665/350642. License: CC BY-NC-SA 3.0 IGO
13. EurA1c trial group (website) EurA1c trial (ifcchba1c.org) Accessed 23 November 2023
14. College of American Pathologists (CAP) Survey Data (website) NGSP CAP Survey Data Accessed 23 November 2023

15. User Verification of Precision and Estimation of Bias, 3rd Edition; Approved Guideline - Third Edition. CLSI EP15-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2014 https://clsi.org/standards/products/method-evaluation/documents/ep15/
16. Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition. CLSI EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2014 https://clsi.org/standards/products/method-evaluation/documents/ep05/
17. Regulation (EU) 2017/756 of the European Parliament and of the Council of 5 April 2017 on in-vitro diagnostic medical devices. O.J.E.U. 2017 L 117/176. European Parliament; 2017. EUR-Lex - 32017R0746 - EN - EUR-Lex (europa.eu)
18. Interference Testing in Clinical Chemistry. Approved Guideline - Second Edition. CLSI EP07-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2018 EP07 | Interference Testing in Clinical Chemistry (clsi.org)
19. Supplemental Tables for Interference Testing in Clinical Chemistry, 1st Edition. CLSI EP37. Wayne, PA: Clinical and Laboratory Standards Institute; 2018 EP37 | Supplemental Tables for Interference Testing in Clinical Chemistry (clsi.org)
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32. Evaluation of Stability of In Vitro Medical Laboratory Test Reagents; 2nd edition. CLSI EP25-Ed2. Wayne, PA: Clinical and Laboratory Standards Institute; 2023 EP25Ed2 | Evaluation of Stability of In Vitro Medical Laboratory Test Reagents, 2nd Edition (clsi.org)
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34. ASTM D4169-22, Standard Practice for Performance Testing of Shipping Containers and Systems, ASTM International, West Conshohocken, PA, 2022 D4169 Standard Practice for Performance Testing of Shipping Containers and Systems (astm.org)

Prequalification of in vitro diagnostics
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Switzerland
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Website: https://extranet.who.int/prequal/vitro-diagnostics/prequalified-vitro-diagnostics

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