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Haemoglobin A1c point of care analysers for professional use

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List of contributors

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

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[1] Joined by teleconference

A. Abbreviations

CAP	College of American Pathologists
DCM	designated comparator method
DM	diabetes mellitus
EQA	External Quality Assessment
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
IVD	in vitro diagnostic
POC	point-of-care
PRMP	primary reference measurement procedure
NGSP	National Glycohemoglobin Standardization Program
TSS	Technical specifications series
WHO	World Health Organization

B. 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 to be used:

- to monitor the therapy of 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

[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.

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 consistently and fulfil its indications for use. The clinical study described in part 2 is intended to verify 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 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. Other 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[3]
- Instructions for Compilation of a Product Dossier, WHO document PQDx_018 *(1)*
- Use of glycated haemoglobin (HbA1c) in diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. *(2)*

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 level in human 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);

[3] Available at https://extranet.who.int/pqweb/vitro-diagnostics/guidance-documents

- The intended use environment (e.g., for professional use in a laboratory setting, and/or POC (e.g., mobile testing facilities);
- The intended user (e.g., laboratory professionals4, 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 reference values (e.g., presence of haemoglobin variants, environmental conditions, pregnancy, age, ethnicity, drugs, renal disease etc.).

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,
- 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, the manufacturer is required to conduct a risk assessment to identify the substances that may interfere with the detection and appropriate interpretation of HbA1c. In some cases it may be due to biological changes. 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 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 summarized in this document correspond to IVDs that are designed to determine HbA1c levels in human blood by way of quantitative test result.

When establishing performance, the true HbA1c concentration of a specimen must be determined using a suitable quantitative designated comparison method (DCM) test, justification for which must be provided. The corresponding quantitative values of

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

HbA1c concentration (mmol/mol (%)), 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 the same DCM is not required to be used in the analytical and clinical performance studies in part 1 and part 2, however the chosen DCM is required to meet 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). *(3)*

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 assigned shelf 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, specimen types, 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 IMDRF document IMDRF/RPS WG/N13 FINAL:2019 (Edition 3) *(4).* 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 so as 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**	
3.05.01	**Stability of specimens(s)**	
	Specimen collection, storage, and transport	
3.05.02	**Validation of specimens**	
	a) Demonstration of validity of all specimen types	
	b) Demonstration of equivalence of claimed anticoagulants and/or frozen samples	
3.05.03	**Metrological traceability of calibrators and control material values**	
3.05.04	**Accuracy of measurement**	
3.05.04.01	Trueness	
3.05.04.02	Precision (repeatability & reproducibility)	
3.05.06	**Analytical specificity**	
	a) Potentially interfering substances and medical conditions	
	b) Endogenous	
	c) Exogenous	
3.05.08	**Measuring range of the assay**	
	Linearity	
3.05.10	**Validation of the assay procedure**	
	a) Validation of assay parameters	
	b) Carry over	
3.06.01	**Electrical systems: safety, mechanical and environmental protection, and electromagnetic compatibility**	
3.06.02.08	**software verification and validation**	
	a) Software validation	
	b) Error codes	
3.06.03	**Cleaning and disinfection validation**	
3.06.04	**Usability/human factors**	
	a) Flex studies/robustness	
	b) Qualification of usability for point of care testing by the intended user: label comprehension (including IFU) and results interpretation	
3.06.05	**Stability of the IVD**	
3.06.05.01	Claimed shelf-life (including transport stability)	
3.06.05.02	In-use stability (open pack or open vial stability)	
Part 2		
IMDRF ToC Chapter 4	**Clinical evidence**	
4.02.03	**Device specific clinical studies**	
	a) General requirements for clinical evaluation studies	
	b) Diagnostic accuracy performance	
	c) Variant interference 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
266.	**3.05.01 Stability of specimen(s)**			
267.	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 samples across the working 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 will 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 samples within a specified time frame 3. The IVD performance shall be established for each different storage condition at the beginning and end of the stated period of stability in the IFU	
268.	**3.05.02 Validation of specimens**			
269.	a) Demonstration of validity of all specimen types	The relationship between IVD performance in claimed specimen types shall be established 1. The specimen panel shall contain • 40 samples across the working range of the assay for each specimen type 2. Testing shall be conducted in 1 lot	1. All specimen types (capillary whole blood, venous whole blood) and anticoagulants claimed for use with the IVD must be validated 2. The values shall represent the analytical and clinically relevant ranges 3. 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 one or more of the claimed specimen types are equivalent, then not all specimen types need to be tested in some of the subsequent studies 4. It is known that some assays do not perform well with frozen samples therefore demonstration of equivalence of fresh and frozen specimens is required on at least one specimen type – if frozen samples are to be used in any part of the analytical or clinical study.	WHO TGS-3 *(6)* Lenters-Westra E, English E. *(7)*
270.	b) Demonstration of equivalence of claimed anticoagulants and/or frozen samples	1. For each claimed anticoagulant, testing shall be conducted to demonstrate equivalent performance in at least: • 40 samples across the working range of the assay for each specimen type 2. Testing shall be conducted in 1 lot		

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
		3. When frozen specimens are used for the analytical or clinical performance analysis, then these also need to have been shown to have equivalence to fresh specimens (see note 4): 4. Testing shall be conducted using 40 fresh and paired frozen specimens across the working range of the method 5. Testing shall be conducted in 1 lot		
271.	**3.05.03 Metrological traceability of calibrators and control material values**			
272.	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 part of the analytical or clinical performance analysis, then the manufacturer of the IVD medical device may provide any information from the manufacture of the specified control materials where applicable	Jeppsson et al *(8)* NGSP *(9)*
273.	**3.05.04 Accuracy of measurement**			
274.	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 (this is the designated comparator method (DCM)) 1. The specimen panel described below shall be tested by the IVD and the reference method (see note 1-5): • A total of at least 100 specimens with HbA1c concentration covering the entire linear range of the IVD (see note 5 and 6)	1. The DCM shall be authorized for use by a recognized stringent regulatory authority [5] and acknowledged in the literature as representing state of the art 2. In addition: The device/analyser and HbA1c test used for comparison must pass IFCC certification and NGSP certification prior to use in any performance assessment. The IVD manufacturer IFCC certification shall be provided – it is not necessary for the individual DCM device to have a certificate	CLSI EP9 *(10)* WHO PQDx_173 *(11)* EurA1c Trial Group *(12)* NGSP *(13)*

[5] The document PQDx_173 Abridged prequalification assessment contains a list of recognized regulatory authorities.

<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</th></tr>
<tr><td></td><td></td><td>2. 100 specimens shall be tested on each of 2 lots
3. Testing in one specimen type unless no equivalence demonstrated (see section 3.05.02)</td><td>3. The comparator HbA1c test cannot be from the same manufacturer as the device under evaluation
4. Additionally, the comparator test shall be externally validated through an EQA process such as a through a national EQA programme, (with accuracy based values) or the EurA1c study or CAP survey in USA
5. 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 sample concentrations chosen shall be provided
6. The distribution of samples across the working range shall include:
<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>7. Correlation of results between the IVD and the established method shall be demonstrated statistically</td><td></td></tr>
<tr><td>275.</td><td>3.05.04.01 Precision repeatability & reproducibility</td><td>1. Both repeatability (within-batch) and reproducibility (between-batch) shall be estimated using panels with defined analyte levels.
2. Repeatability and reproducibility specimen panels shall at least include:
• 3 different HbA1c levels at appropriate clinically relevant concentrations (note 2)
3. Testing in 1 whole blood specimen type unless no equivalence demonstrated (see section 3.05.02)
4. Each HbA1c level shall be tested:</td><td>1. E.g., within- or between-run, -lot, -day, -site, 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. The concentrations of HbA1c in the specimens shall span the linear range of the assay, including the lower and upper limit of quantification. Suggested values are approx. 35, 50 and 75 mmol/mol
3. Lots shall be composed of different batches of critical components</td><td>WHO TGS 3 (6)
CLSI EP-15-A3 (14)
ISO 13612 (15)
CLSI EP05-A3 (16)</td></tr>
</table>

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	• in duplicate at 2 points in the day such as the morning and the afternoon (minimum of at least 2 hours in between runs) • using 2 different lots of reagents and instruments (note 3) • over 20 days (not necessarily consecutive) with two runs/day (preferably in the morning and in the afternoon with at least 2 hours in between) at each of 2 different testing sites (also see note 4) 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 HbA1c levels (see note 2) • Using at least 3 lots of reagents (see note 3) • At 3 different sites (also see note 4) 6. If the effect of operator-to-operator variation on IVD performance is considered to be of significance (see note 8) then it shall be included as part of the precision studies. Manufacturers shall provide a justification for not including operator-to-operator variation studies. Testing shall be performed: • by 1 operator/site (see notes 5 and 8) • by operators 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)	4. To understand irregularities in results obtained, at least 2 lots shall be tested at each of the testing sites 5. The operator of the devices shall not be an employee/representative of the IVD device manufacturer 6. Results must be statistically analysed (e.g., using ANOVA to identify and isolate the sources and extent of any variance) 7. The numbers of invalid tests must be reported 8. If operators are considered a significant source of test results variation (for example tests that need a significant proportion of manual manipulations), then at least 1 different operator per site shall be used 9. 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 10. Alternative methods used to establish repeatability and reproducibility performance of the assay shall be discussed with WHO in advance of dossier submission	

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
276.	**3.05.06 Analytical specificity**			
277.	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 (see note 1 and 2)	1. In some cases (refer those identified in the adjacent "Testing Requirements" column), access to appropriate compounds or specimens may be challenging. Provided justification is given, it may be possible to address these potential sources of interference as part of clinical studies in representative populations (part 2) 2. The risk assessment conducted for an IVD should identify substances at medically relevant levels for which the potential for interference can reasonably be expected for the analyte being detected • 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 3. 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 4. Results shall be reported with respect to each condition and not be reported as an aggregate of the total number of specimens tested in the study 5. HbA1c concentrations chosen should be clinically relevant 6. Exogenous substances shall be spiked at the highest medically relevant concentrations	EU IVDR *(18)* CLSI EP07 *(19)* CLSI EP 37 *(20)*
278.	b) Endogenous	The interference of endogenous substances in whole blood on the performance of the device shall be investigated, such as: 1. Triglycerides, unconjugated bilirubin (5 high concentration specimens) 2. Haemolysis (5 high concentration specimens) 3. Frozen specimens (40 samples across the clinically relevant HbA1c range) 4. Lyophilized specimens (10 samples across the clinically relevant HbA1c range) 5. Carbamylated HbA1c (5 high concentration specimens) 6. Labile HbA1c (10 high concentration specimens) 7. Abnormally high and abnormally low haematocrit concentrations (10 high haematocrit and 10 low haematocrit specimens) 8. Haemoglobinopathies and synthesis disorders such as sickle cell trait, thalassemia (elevated A2) • Manufacturer is required to test variant haemoglobin (D, E, S, C (20 samples of each heterozygous Hb variant covering the full analytical HbA1c range of the device) • Manufacturer is required to test 10 samples with different A2 and HbF concentrations covering the full analytical HbA1c range of the device		

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
279.	c) Exogenous	1. The interference of exogenous substances on the performance of the device shall be investigated as per manufacturer IFU claim (see note 5, 6). See also section C.2 of this document		
280.	**3.05.08 Measuring range of the assay**			
281.	Linearity	The linear range shall be established: 1. Using a dilution series with 10 concentrations that span the measurement range shall be tested where possible 2. 2 to 4 replicates shall be tested at each concentration 3. Using 1 lot 4. Testing in EDTA venous blood specimens only	1. It may be difficult to obtain very high HbA1c concentration specimens – justification shall be provided for the use of samples which do not cover the full analytical range of the IVD method 2. 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) 3. 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	CLSI EP06-A *(21)*
282.	**3.05.10 Validation of the assay procedures**			
283.	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 must be ascertained for each device (note 2) 3. The parameters specified in the IFU commonly include: • time between drawing sample, handling and loading • volumes (specimen and reagent) • temperatures • humidity 4. Validation of parameters shall be documented as required in 1 specimen type 5. Validation shall be performed using a minimum of 2 different reagent system lots:	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 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	IMDRF TOC *(3)* WHO PQDx_018 *(1)*

<table>
<tr><td></td><td>IMDRF ToC Chapter heading and aspect</td><td>Testing requirements</td><td>Notes on testing requirement</td><td>Source documents</td></tr>
<tr><td></td><td></td><td>• Freshly made reagents
• Reagent towards the end of their assigned shelf lives
4. At least 3 specimens shall be tested with the following HbA1c concentrations
<table><tr><th>Interval</th><th>HbA1c concentration</th></tr><tr><td>1</td><td>35 mmol/mol</td></tr><tr><td>2</td><td>50 mmol/mol</td></tr><tr><td>3</td><td>75 mmol/mol</td></tr></table></td><td>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 ranges of humidity tested shall be risk-based, taking into consideration likely operational conditions in resource limited settings</td><td></td></tr>
<tr><td>284.</td><td>b) Carry over</td><td>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 samples low (L), medium (M), high (H) and analyse in the following order: MHLMMLLHHM (see note 1)</td><td>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</td><td>CLSI EP10 (22)</td></tr>
<tr><td>285.</td><td colspan="3">3.06.01 Electrical systems; safety, mechanical and environmental protection, and electromagnetic compatibility</td><td></td></tr>
<tr><td>286.</td><td>Electrical safety, mechanical and environmental protection, and electromagnetic compatibility</td><td>1. Evidence supporting electrical safety, mechanical and environmental protection, and electromagnetic 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</td><td>1. Electromagnetic compatibility (EMC) testing
2. Electrostatic discharge/Electromagnetic interference testing
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.</td><td>IEC 61326-1 (24)
IEC 61326-2-6 (25)
IEC 61010-1 (26)</td></tr>
<tr><td>287.</td><td colspan="3">3.06.02.08 Software verification and validation</td><td></td></tr>
<tr><td>288.</td><td>a) Software validation</td><td>1. Software validation shall include:
• Verification of built-in fail-safe and alert mechanisms
• Verification of quantitative results detection
• Verification of quantitative results calculation</td><td>1. Software validation procedures shall be conducted according to IEC 62304.</td><td>IEC 62304 (27)</td></tr>
</table>

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
289.	b) Error codes	1. Provide evidence to demonstrate that appropriate error codes are provided		US FDA *(23)* IEC 62304 *(27)*
290.	**3.06.03 Cleaning and disinfection validation**			
291.	Cleaning and disinfection validation	Disinfection efficacy studies shall be performed to 1. Demonstrate effectiveness of the chosen disinfectant against Hepatitis B virus (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) 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)	1. The studies conducted shall be based on the design of the device and risk assessment. 2. The disinfectant product should 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 *(28)* ASTM E1053-11 *(29)*
292.	**3.06.04 Usability/human factors**			
293.	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 3 specimens shall be tested with the following HbA1c concentrations	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 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 4. For the purposes of this document, ruggedness means the ability to resist environmental shocks of a variety of kinds	WHO PQDx_018 *(1)*

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
		<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> 2. IVD instrument sturdiness (including the effect of non-level work surface) 3. Ruggedness such as mechanical vibration testing, shock testing (see note 5)	5. Robustness testing generally takes the form of statistically designed experiments to evaluate the effect of simultaneous "small but deliberate changes" in method parameters	
294.	b) Qualification of usability for point of care testing by the intended user: label comprehension study (including IFU)	1. Questionnaire-based testing and/or peer observation (see note 2) of trained operators shall be conducted to assess their ability to correctly comprehend key messages from packaging and labelling such as: • Test procedure comprehension • Understanding of key warnings, limitations and/or restrictions • Ease of following instructions 2. Pre-testing and post-testing questionnaire shall be administered to at least 10 intended users, including those whose native language may not be the language of the IFU if necessary, to demonstrate comprehension of key messages (see note 3) 3. The study shall be conducted at 2 geographically diverse populations to demonstrate comprehension of key messages in each user group	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 3. Videography of the test procedure to be recorded (with appropriate consent procedures) to assess the trainability of the device. Alternatively, newly trained operators can be observed by trained laboratory or healthcare professional. The observing professional does not tutor or interact with subject conducting test but notes errors and other observations	IEC 62366-1 *(30)* Backinger CL and Kingsley PA *(31)* EU IVDR *(18)*
295.	b) Qualification of usability for point of care testing by the intended user:	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:	1. To include a range of HbA1c values in the study to initiate different status/key symbols on the device. This can be done on fresh whole blood specimens taken from a range of pre-screened HbA1c values	IEC 62366-1 *(30)* Backinger CL and Kingsley PA *(31)* EU IVDR *(18)*

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirement	Source documents
	Device output interpretation study	• 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		
296.	**3.06.05 Stability of the IVD**			
297.	3.06.05.01 Claimed shelf life (including transport stability)	Stability studies shall be evaluated for the shelf life of the test kit. The following conditions shall be investigated: 1. Transport stability • Conditions to mimic extremes of conditions (temperature, humidity, pressure) exposed to during transport (see note 2) • IVD in final packaging also subjected to drop-shock testing • 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. The stability panel shall consist of 40 specimens with HbA1c concentrations across the claimed analytical range of the IVD device 5. Each specimen shall be tested in duplicate at each time point/condition 6. All claimed specimen types shall be tested (unless equivalence has been shown – see section 3.05.02) 7. Multiple Instruments may be used to allow simultaneous testing at each time point	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 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	ISO 23640 *(32)* CLSI EP25-A *(33)* WHO TGS-2 *(34)* ASTM D4169-22 *(35)*
298.	3.06.05.02 In-use stability	1. The operating temperature and humidity range shall be tested: • Using a minimum of 1 lot		

<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>

At least 3 specimens shall be tested with the following HbA1c concentrations
<table>
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<tr><td>Medium</td><td>50 mmol/mol</td></tr>
<tr><td>High</td><td>75 mmol/mol</td></tr>
</table>

Each specimen shall be tested in duplicate 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
</td><td></td><td></td></tr>
</table>

Part 2: IMDRF ToC Chapter 4 Clinical evidence

299.	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source documents
300.	**4.02.03 Device specific clinical studies**			
301.	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 representative of intended use (minimum of 2 regions, including at least 1 region where there is increased prevalence of Hb variants) 3. In at least 2 different POC settings 4. By a variety of intended users representing relevant intended use settings (e.g., different levels of health care facilities) (see note 3) 5. 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 samples may be anticoagulated (EDTA preferably) capillary or venous blood specimens if equivalence has been demonstrated (see chapter 3.05.02) 6. All specimens shall be tested by the DCM (see note 4, 5 and 8) 7. 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 8. The procedure for selection of study specimens, how these represent the intended use population and how bias has been addressed shall be clearly described	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. For prequalification purposes, these shall be considered as the intended user, rather than a laboratory professional. • In addition, the operator shall not be linked in any way to the manufacture of the device 4. Comparator HbA1c testing: The device/analyser and HbA1c test used for comparison (the DCM) shall be approved by a stringent regulatory authority and must pass manufacturer IFCC certification and NGSP certification. prior to use in any performance assessment. The DCM cannot be from the same manufacturer as the device under evaluation. 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 USA. Where participation in an EQA programme is not possible then a sample exchange using 40 externally validated samples (these can be frozen), with HbA1c concentrations covering the clinically relevant range, can be used if the method used for the external validation meets the above criteria. 5. Furthermore, the DCM shall not be affected by the presence of Hb variants	CLSI H26 *(36)* EurA1c Trial Group *(12)* NGSP *(13)*

<table>
<tr><th>299.</th><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></td><td>9. Before any clinical study commences the manufacturer shall demonstrate that the IVD devices in use in the study are working within expected parameters, (see note 10)</td><td rowspan="2">6. Problematic specimens, those with unexpected results but which otherwise meet selection criteria for a study, shall not be systematically excluded from analysis. All invalid results shall be recorded
7. All results shall be included in the denominator data for analysis.
8. Correlation between the IVD and the DCM shall be established statistically
9. Clinical performance study protocols shall specify how results in the IVD under evaluation and the DCM will be compared and how results in the two assays will be statistically determined to be equivalent or not (e.g., Bland Altman analysis)
10. The manufacturer may consider protocols such as EP-15 or similar appropriate process for initial performance assessment and a justification of choice of process should be provided.
11. Each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents, representative of routine manufacture
12. Testing of each device with reagent lot 1 and 2, separately</td><td></td></tr>
<tr><td>302.</td><td>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 11, 12)
4. HbA1c values (in mmol/mol) of tested subjects shall cover a range of 30 -120 mmol/mol 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>EU IVDR (18)</td></tr>
<tr><td>303.</td><td>Variant interference study</td><td>This study is only required if the IVD POC 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 haemoglobin (D, E, S, C and HbF)
2. Testing in 20 specimens of each variant covering the full analytical range of the device</td><td>1. The comparator method used shall be described</td><td></td></tr>
</table>

E. Source documents

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