Health Canada Santé Canada

GUIDANCE DOCUMENT

Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Rapid Diagnostic Tests (RDTs) for use at the Point of Care or for Self-Testing

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Health Products and Food Branch

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Également disponible en français sous le titre : *Ligne directrice : Ligne directrice à l'intention des fabricants de tests de diagnostic rapide (TDR) du virus de l'immunodéficience humaine (VIH) pour usage au point de soins ou pour l'autodépistage*

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1 INTRODUCTION

The purpose of this guidance document is to provide manufacturers of Class IV Human Immunodeficiency Virus (HIV) rapid diagnostic tests (RDTs) intended to be used at the point of care (POC) and/or for self-testing (home testing) with specific recommendations on: (1) the analytical and clinical data, and (2) device labelling, required to support a medical device licence application.

1.1 Policy Objective

To facilitate the submission of the analytical (pre-clinical), clinical and labelling content of a licence application filed pursuant to sections 32 and 34 of the *Medical Devices Regulations* (Regulations) for HIV rapid diagnostic tests intended to be used at the Point of Care and/or for self-testing.

1.2 Scope and Application

This guidance applies to Class IV HIV rapid diagnostic tests (RDTs) intended to be used at the POC and/or for self-testing.

It makes recommendations on the labelling requirements specific to an HIV POC or HIV self-test as per sections 21 to 23 of the Regulations and the analytical, clinical and near patient study design and data required as per sections 32(4) (i)(i) and 32(4)(k). It does not address other elements of safety and effectiveness, such as process validation, software validation and literature studies. Please refer to the guidance *Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications* and the guidance *Labelling of In Vitro Diagnostic Devices* for additional data and labelling requirements.

This guidance does not apply to HIV test kits which are used for patient management, donor screening or those intended for laboratory use. A separate guidance, *Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits Intended to be used in the Laboratory* is available for manufacturers of laboratory based kits.

This guidance does not address issues related to investigational testing (clinical trials). Manufacturers of HIV test kits wishing to conduct investigational testing in Canada should refer to the guidance document *Preparation of an Application for Investigational Testing - In Vitro Diagnostic Devices (IVDD)*. It is recommended that you contact Health Canada prior to beginning your studies to discuss protocol and study design.

The cited guidance documents can be found on the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents.html).

1.3 Background

The following documents, reviewed in the development of this guidance, may be useful to manufacturers of HIV rapid diagnostic tests as background information on the studies and performance requirements for RDTs used at the POC or for self-testing.

1. OraSure Technologies. Final Advisory Committee Briefing Materials: Available for Public Release, OraQuick In-Home HIV Test, Food and Drug Administration, Blood Products Advisory Committee, 2012.
2. PATH, Target Product Profile: HIV Self-Test, Version 4.1. White paper on the evaluation of current HIV rapid tests and development of core specifications for next-generation HIV tests. May 2014.
3. TGA. Clinical performance requirements and risk mitigation strategies for HIV tests. Version 1.0. March 2015.
4. Technical Specifications Series for submission to WHO Prequalification - Diagnostic Assessment: Human Immunodeficiency Virus (HIV) rapid diagnostic tests for professional use and/or self-testing. Geneva: World Health Organization; 2016.

In addition, international guidance documents prepared by the Global Harmonization Task Force (GHTF) and the International Medical Devices Regulator Forum (IMDRF) may also be helpful in the preparation of a medical device licence application.

These documents include:

1. The "Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices" (http://academy.gmp-compliance.org/guidemgr/files/GHTF-SG1-N063-2011-SUMMARY-TECHNICAL-DOCUMENTATION-IVD-SAFETY-CONFORMITY-110317.PDF)

2. "In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)" (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140630-rps-ivd-toc.pdf)

1.4 Definitions

Near Patient in vitro diagnostic device or near patient IVDD
an in vitro diagnostic device that is intended for use outside a laboratory, for testing at home or at the point of care, such as a pharmacy, a health care professional's office or the bedside. (*Medical Devices Regulations)*

Health care professional
a person who is entitled under the laws of a province to provide health services in the province. (*Medical Devices Regulations)*

Abbreviations and Acronyms

Ab: antibody
Ag: antigen
HCP: Health Care Professional
IVDU: Intravenous drug user
POC: Point of care
RDT: Rapid diagnostic test

2 GUIDANCE FOR IMPLEMENTATION

2.1 General Recommendations

2.1.1 Quality Control

2.1.1.1 External Material

External quality control (QC) material (both positive and negative) should be available for HIV RDTs intended for use at the POC. If you are the manufacturer of the external QC material, you may wish to consult with Health Canada on licensing requirements. For manufacturers that do not intend to provide external controls, the package insert should clearly include instructions on how to obtain appropriate external controls.

2.1.1.2 Internal Control

An internal or built in control should be included in the design of the kit. The internal control should verify the specimen and buffers/solutions have flowed through the device correctly. A control which appears even if a specimen is not added is not acceptable.

2.1.2 Performance Panels

Commercial or non-commercial panels which are used to establish performance claims should be well characterized. The data sheets or results of testing which confirm the reactivity of the samples should be provided. For non-commercial panels, the tests used to characterize the samples should be identified and the Canadian medical device licence number for these tests should also be provided.

2.1.3 Study Sites outside of Canada

When the data used to support the clinical performance claims of the device is obtained from sites outside Canada, the manufacturer should ensure the quality, integrity and scientific validity of the data. In addition, the studies should be conducted under good clinical practices, be appropriately monitored and protect the rights, safety, and well-being of the subjects providing the specimens used in the clinical performance studies.

Manufacturers should provide evidence that the laboratories in which data are generated meet the requirements of good laboratory practices (GLP) or equivalent. This evidence should be in the form of a certificate of accreditation or equivalent.

2.1.4 Study Protocol and Study Report

The complete study protocol and final study report for each analytical, clinical and near patient (including usability) study should be provided. Each protocol and report should be properly identified with a document reference number, version number and date.

The study protocol should include the objectives, study population, description of test method(s) and interpretation of results, specimen type, specimen collection, preparation, handling and storage, inclusion and exclusion criteria, limitations, warning and precautions, data collection/management, data analysis, required materials, number of study sites and if applicable, clinical endpoints/outcomes, and requirements for patient follow-up. It should also identify the key factors which may impact the completeness and significance of results, such as intended participant follow-up procedures, decision algorithms, discrepancy resolution process, masking/blinding, approaches to statistical analyses, and methods for recording endpoints/outcomes and, where appropriate, communication of test results.

The study report should include, as appropriate, any protocol amendments or deviations, and data exclusions with the appropriate rationale; explanations for any discrepant results and how they were resolved, test result summaries (for analytical data) with acceptance criteria and formatted raw data (individual data points) for clinical studies. Study conclusions should be stated. A summary of each study should also be provided.

For all studies done on behalf of a Manufacturer, a copy of the laboratory evaluation report, signed and dated by the principal investigator, should be provided. If the laboratory evaluation report is not prepared in English or French, a certified and notarized translation should be provided (i.e. an exact translation signed by the translator and verified by a notary public with the official notary seal affixed).

2.1.5 Presentation of Test Results

When feasible, it is recommended that photographs of the completed tests be provided. Reactive results should be graded according to the intensity of the observed reaction. The grading scale with photographs should be provided. Reactive results should not be reported as "+", "pos", or "positive" as these results cannot be properly evaluated.

2.1.6 Minimum Clinical Sensitivity and Specificity

Evidence that the RDT intended for use at the POC or for self-testing has a minimum sensitivity and specificity of ≥99% for HIV antibody detection should be provided and the 95% confidence intervals should be calculated.

2.2 Human Immunodeficiency Virus (HIV) Point of Care (POC) Tests

An HIV test that is intended to be used at the POC is considered a near patient in vitro diagnostic device (near patient IVDD). POC refers to a variety of settings which are outside a laboratory such as a pharmacy, a health care professional's office, sexual health clinics, or mobile outreach clinics. In the POC setting, it is a Health Care Professional (HCP) who administers the test.

2.2.1 Performance studies

The analytical, clinical and near patient studies used to establish the performance characteristics of an HIV test kit used at the POC should be designed to support all claims made by the manufacturer with respect to the device.

2.2.1.1 Analytical

The studies that are necessary to validate the analytical performance of the device will depend on whether it is a qualitative or quantitative test. However, in most cases, the following studies will be needed:

- Specimen type studies;
- Precision (repeatability and reproducibility);
- Analytical sensitivity (when claims for p24 antigen are made);
- Analytical specificity (interference and cross reactivity);
- Robustness;
- Stability

Please refer to Table 1 in Appendix A which provides additional details and recommendations regarding the analytical studies.

2.2.1.2 Clinical

Prospective clinical studies should be conducted to establish the clinical sensitivity and clinical specificity of the device.

2.2.1.2.1 Study Design

Clinical sensitivity and specificity studies should be designed as follows:

- Testing should be done using a minimum of three production lots;
- Testing should be done at a minimum of three geographically distinct POC sites (e.g. sexual health clinic, doctor's office) by the intended operators;
- The results from the POC device should be compared to serological results obtained on a sample collected at the time the POC test is administered. Serological testing should be done using, at a minimum, a 4th generation EIA test that is licensed in Canada. All reactive EIA tests should be confirmed by more specific methods. The test algorithm used by the collaborating laboratory should be provided to Health Canada and should be representative of the HIV test algorithms implemented in Canada.
- The number of samples that give indeterminate or invalid results should be provided;
- All discrepant results between the test under investigation and the test of reference should be clearly indicated and resolved using supplemental, specific assays, definitive clinical data, or clinical follow up; and,
- Sensitivity, specificity and their 95% confidence intervals should be calculated.

The clinical sensitivity and clinical specificity of a RDT intended to be used at the POC should be established using the sample numbers and sample types (e.g. confirmed HIV positive samples, low titer and seroconversion panels, HIV subtypes, clinical samples) described in Table 2 of Appendix A.

2.2.1.2.2 Study Population

Clinical studies should be performed using samples that represent an ethnically and genetically diverse population so as to be representative of the Canadian population. In addition, the performance of the tests should be established in a population with similar HIV prevalence rates to those seen in Canada.

2.2.1.2.3 Comparator Assays

For all clinical studies, the comparator assay should be licensed in Canada. A database listing of licensed medical devices is available on the Health Canada website (Medical Devices Active Licence Listing (MDALL) at www.mdall.ca).

If the comparator test used is not licensed in Canada, the manufacturer should contact Health Canada for further guidance.

2.2.1.2.4 Near Patient Studies (Usability studies)

Near patient studies which establish the performance of the device when used by the intended user, in the intended setting, without assistance and following the instructions provided in the labelling should be provided. Near patient studies include usability studies which establish whether untrained users can understand the key messages in the labelling and whether these users can correctly perform the test and interpret the test results.

If clinical sensitivity and clinical specificity are established using trained HCPs, near patient studies which establish diagnostic accuracy using untrained HCP should be provided along with studies that demonstrate the ability of the untrained HCP to interpret a variety of test results. The results from a questionnaire which assesses how well the untrained HCP understood how to use the device should also be provided. Additional details on these studies are provided in Table 3 of Appendix A.

2.2.1.3 Labelling

The version of the instructions for use (IFU) and Quick Reference Guide used for the clinical and near patient studies should be provided. In addition the final version of the labelling with the history and the reasons for all changes made (if applicable) should be provided.

2.3 Human Immunodeficiency Virus (HIV) Tests intended for Self-Testing

An HIV test that is intended to be used for self-testing is considered a near patient in vitro diagnostic device (near patient IVDD). The intended user of a self-test is a layperson.

2.3.1 Performance studies

The analytical, clinical and near patient studies used to establish the performance characteristics of an HIV test kit for self-testing should be designed to support all claims made by the manufacturer with respect to the device.

2.3.1.1 Analytical

The studies that are necessary to validate the analytical performance of the device will depend on whether it is a qualitative or quantitative test. However, in most cases, the following studies will be needed:

- Specimen type studies;
- Precision (repeatability and reproducibility);
- Analytical sensitivity (when claims for p24 antigen are made);
- Analytical specificity (interference and cross reactivity);
- Robustness;
- Stability

Please refer to Table 1 in Appendix A which provides additional details and recommendations regarding the analytical studies.

In cases where a manufacturer of a Health Canada licensed HIV POC test wishes to make a claim for self-testing; the analytical studies for the POC device may be used to support performance of the self-test device. If, however, the manufacturer has modified the POC device such that the device intended for POC use and the device intended for self-testing are not identical, additional studies will be needed to demonstrate that the analytical performance is unchanged. Additional studies may also be identified by the risk analysis conducted by the manufacturer for the self-test device.

2.3.1.2 Clinical

Prospective clinical studies should be performed to establish the clinical sensitivity and clinical specificity of the device. Manufacturers of HIV self-tests devices may establish clinical performance using trained users in a controlled setting (e.g. point of care) however near patient studies which establish the accuracy of the test using untrained lay users will be necessary (see section 2.3.1.2.4 below).

In cases where a manufacturer of a Health Canada licensed HIV POC test wishes to make a claim for self-testing; the clinical studies for the POC device may be used to support performance of the self-test device. However, near patient studies will still be required (see section 2.3.1.2.4 below).

2.3.1.2.1 Study Design

Clinical sensitivity and specificity studies should be designed as follows:

- Testing should be done using a minimum of three production lots;
- Testing should be done at a minimum of three geographically distinct sites using the intended operators;
- The results from the self-test device should be compared to serological results obtained on a sample collected at the time the self-test is administered. Serological testing should be done using, at a minimum, a 4th generation EIA test that is licensed

in Canada. All reactive EIA tests should be confirmed by more specific methods. The test algorithm used by the collaborating laboratory should be provided to Health Canada and should be representative of the HIV test algorithms implemented in Canada.

- The number of samples that give indeterminate or invalid results should be provided;
- All discrepant results between the kit under investigation and the test of reference should be clearly indicated and resolved using supplemental, specific assays, definitive clinical data, or clinical follow up; and,
- Sensitivity, specificity and their 95% confidence intervals should be calculated.

The clinical sensitivity and clinical specificity of an HIV self-test should be established using the sample numbers and sample types (e.g. confirmed HIV positive samples, low titer and seroconversion panels, HIV subtypes, clinical samples) described in Table 2 of Appendix A.

2.3.1.2.2 Study Population

Clinical studies should be performed using samples that represent an ethnically and genetically diverse population so as to be representative of the Canadian population. In addition, the performance of the tests should be established in a population with similar HIV prevalence rates to that seen in Canada.

2.3.1.2.3 Comparator Assays

For all clinical studies, the comparator assay should be licensed in Canada. A database listing of licensed medical devices is available on the Health Canada website (Medical Devices Active Licence Listing (MDALL) at www.mdall.ca).

If the comparator test used is not licensed in Canada, the manufacturer should contact Health Canada for further guidance.

2.3.1.2.4 Near Patient Studies (Usability studies)

Near patient studies which establish the performance of the device when used by the intended user, in the intended setting, without assistance and following the instructions provided in the labelling should be provided. Near patient studies include usability studies which verify whether untrained users can understand the key messages in the labelling (label comprehension study) and whether these users can correctly perform the test (accuracy study) and interpret the test results (test result interpretations study).

Additional details on these studies are provided in Table 3 of Appendix A.

2.3.1.3 Labelling

The instructions for use (IFU) and Quick Reference Guide used for the clinical and near patient studies should be provided. In addition the final version of the labelling with the history and the reasons for all changes made (if applicable) should be provided.

The IFU should make use of pictures or diagrams as much as possible with text targeted to a Grade 6 reading level. The intended use should be simple and clear. All components and steps for performing the assay should be clearly and simply described. Examples of positive, negative and invalid test results should be included.

Links to local support services must be provided.

It is strongly recommended that an on-line video be available to assist lay users in the correct performance of the test.

3 CUSTOMER SUPPORT SERVICES

Manufacturers should provide evidence that procedures are in place to ensure that self-testers have access to appropriate support and counselling services. Pre and post-test counselling is a critical component of HIV testing and functions to ensure that individuals are informed about their risk and are provided information on how to protect themselves and others from exposure to HIV. For individuals who test positive, they need to be connected with and have access to support services.

Manufactures should ensure the links and contact phone numbers that will provide local and national support and counselling services are valid and kept up to date.

4 APPENDIX A: RECOMMENDATIONS FOR ANALYTICAL, CLINICAL AND NEAR PATIENT STUDIES

Table 1: Analytical Studies for rapid diagnostic tests (RDTs) intended for use at the Point of Care (POC) and/or for Self-testing

Analytical Study	General recommendations	Specific recommendations
Specimen type: Sample type, Sample type equivalency Sample stability	▪ Equivalency for the claimed specimen types (e.g. serum, plasma, venous whole blood, fingerstick whole blood, saliva) should be demonstrated on matched specimens for each claimed analyte (e.g. HIV-1 antibody, HIV-2 antibody, p24 antigen). ▪ Equivalency for each claimed anticoagulant should be demonstrated. ▪ Sample stability should be demonstrated for all specimen types when applicable (e.g. stability for fingerstick specimens would not be expected). *Frequently the analytical studies are done using serum or plasma samples and therefore it is critical to establish equivalency if whole blood (capillary or fingerstick) or oral fluid or other sample types are claimed.*	▪ Identify the source of the specimens. ▪ Spiked, diluted or pooled samples may be acceptable but a rationale should be provided. ▪ Positive specimens should be near the cut off of the assay. ▪ 25 positive and 25 negative matched specimens are needed for each specimen type or anticoagulant.
Accuracy of measurement: Precision - Repeatability - Reproducibility	Refer also to CLSI EP5-A3: Evaluation of Precision of Quantitative Measurement Procedures. ▪ Repeatability estimates and information about the studies used to estimate within-run variability should be provided.	▪ Determined using panels consisting of HIV-1 positive samples (including Group O and Group N if claimed), HIV-2 positive samples, p24 antigen positive samples and negative samples depending on the intended use claims. ▪ The panel should include samples that are close to

	▪ Reproducibility estimates and information about the studies used to estimate variability between days, runs, sites, lots, operators, and instruments should be provided. ▪ Repeatability and Reproducibility studies should include the use of samples that represent the full range of expected analyte (measurand) concentrations that can be measured by the test as claimed by the manufacturer.	the cutoff (above and below). ▪ Reproducibility should be assessed using a minimum of three sites over five days using either • five replicates/panel member and 1 run/day or • three replicates/panel member and 2 runs/day ▪ Operators should reflect the intended users of the assay.
Analytical sensitivity	Applicable when claims for p24 antigen detection are made.	▪ The 2009 Common Technical Specifications (CTS) specifies a sensitivity of ≤2 IU/ml for WHO International Standard, NIBSC code 90/636
Analytical specificity - Interference - Cross reactivity	Refer also to CLSI EP7-A2 Interference Testing in Clinical Chemistry. Analytical specificity, as determined via the evaluation of potentially interfering and/or cross reacting substances, should be provided. The information should include the substance and concentration tested, sample type, analyte (measurand) test concentration, and results. Interferents and/or cross reacting substances which vary greatly depending on the assay type and design, could derive from exogenous or endogenous sources. Typically, interference studies involve adding the potential interferent to the sample and determining any bias of the test parameter relative to the control	This includes testing: • for interference due to prozone/hook effect, or interference due to human anti-mouse antibodies (HAMA), when applicable; • samples from individuals with medical conditions such as: non-HIV viral infections (e.g. Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Herpes simplex virus (HSV), Rubella); other retroviral infections (HTLV-I, HTLV-II); bacterial/parasitic diseases (syphilis, toxoplasmosis), autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus); polyclonal and monoclonal gammopathies (IgG or IgM hypergammaglobulinemia); other miscellaneous medical conditions (cancer, cirrhosis);

	sample to which no interferent has been added. It is recommended that the concentrations of interferents in these studies are provided in International Units (SI Units) and Conventional Units.	• samples from recipients of multiple blood transfusions and multiparous women; • for endogenous interferents including haemoglobin, lipids, bilirubin and protein concentration; and for exogenous interferents including therapeutic drugs and over-the-counter medications. Testing should include a minimum of 200 samples from individuals with medical conditions and a minimum of 100 samples with interfering substances. HIV positive and negative samples should be included as the impact of the interferent /cross reacting substance to produce false positive or false negative results needs to be assessed.
Robustness/Flex	Must demonstrate suitable robustness for the intended use and under a variety of conditions expected in the intended user setting. Factors to consider include: • Operator error/ human factors • Specimen integrity and handling • Reagent integrity (Reagent viability) • Environmental factors The steps taken to mitigate the errors that may occur should be specified including any changes	Potential sources of error: **Operator error/ human factors** • Use of incorrect specimen type • Incorrect application of the specimen to the device (e.g., incorrect placement, incorrect volume), • incorrect handling of reagents including those in self-contained unitized test devices, • incorrect placement of device (e.g., non-level surface), • incorrect placement of reagents, including strips,

	made to the IFU.	or other components that contain reagent, • use of incorrect reagents (for example, reagents that are not specific for the particular device or lot or generic reagents), • incorrect order of reagent application, • use of incorrect amount of reagent, • incorrect timing of procedures (e.g., specimen application, running the test, or reading results), • incorrect reading of test results, • incorrect reading due to color blindness, etc. **Specimen integrity and handling** • errors in specimen collection, • use of inappropriate anticoagulant, • clotted specimens, • error in specimen handling, • incorrect specimen transport and/or storage, • presence of interfering substances, • presence of bubbles in the specimen etc. **Reagent integrity (Reagent viability)** • use of improperly stored reagents, • use of outdated reagents, • use of improperly mixed reagents, • use of contaminated reagents, etc. **Environmental factors** • impact of key environmental factors (heat, humidity, barometric pressure changes, altitude (if applicable), sunlight, surface angle, device movement, etc.) on reagents, specimens, and test

		results.
Stability - Shelf life - In-Use - Shipping	Refer also to CLSI EP25-A: 2009 Evaluation of stability of in vitro diagnostic reagents and ISO 23640:2011 In vitro diagnostic medical devices - Evaluation of stability of in vitro diagnostic reagents. Using a panel that includes weak reactive samples, data should be provided for: • the recommended shelf life of the unopened kit under the recommended storage conditions (three lots); • the recommended product life of the opened kit (one lot); • the effects of freezing temperature (-20°C) and of extreme heat (≥ 37°C) on the performance characteristics and shelf life of the kit (one lot). Alternatively, the manufacturer may provide evidence that the kits are shipped under controlled conditions and that the kits are not exposed to temperatures outside the recommended range.	• The lots used should be production lots otherwise a rationale will be required. • The lots for the critical components (e.g. strips, buffers) should be unique for each kit lot. • The testing intervals should be stated. • Claims should be made at one time point less than the last time point tested. • Real time stability should be assessed after stressing the kits. The results should be reported so that changes in the device performance are evident. This means that the positive results should be graded (e.g. 4+ or 1+).

Table 2: Minimum number of samples for calculation of Sensitivity and Specificity

		HIV-1 Antibody	HIV-1/HIV-2 Antibody	p24 Antigen	Comments
Sensitivity	**Confirmed HIV positive samples**	1000 HIV-1	1000 HIV-1 200 HIV-2	100	The 1000 confirmed HIV-1 positive samples may include the 300 non-B subtype samples (referred to below under subtypes). These samples must be negative for HIV-2 antibody. The HIV-2 antibody positive samples must be negative for HIV-1 antibody.
	Low titer and Seroconversion Panels	25 panels			For p24 antigen assays the seroconversion panels should contain Ag+ Ab-/indeterminate samples. Provide the data sheets for every panel used.
	Subtypes	300 non-B subtypes		40 non-B subtypes	300 worldwide specimens, characterized as other than subtype B should be tested. All known non-B subtypes: A1, A2, C, D, F, G, H, J, K and recombinant AE (CRF01_AE; CRF02_AG) should be represented. No more than 75 specimens of any one subtype should be included in the total of 300 tested non-B subtypes. Both clinical samples and commercial panels may be used. Cell culture supernatants can be used to determine p24 antigen sensitivity in non-B subtypes.
Specificity	**Clinical samples**	2500			Prospective samples, tested at three intended use sites and representing the target population: pregnant women, hospitalized patients, people requesting testing (worried well), high risk etc.

Table 3: Near Patient Studies using Untrained Users

Intended User	Operator Questionnaire/Label Comprehension Study	Test results interpretation Study	(Diagnostic) Accuracy Study
Untrained HCP	Intended to assess if untrained HCPs, using only the labelling provided with the device, can understand how to use the device correctly, if they can correctly interpret test results and if they understand key warnings. The occupation of the HCP should be provided (doctor, nurse, HIV test counselor, etc.). The questionnaire should be completed by all HCPs participating in the diagnostic accuracy study. A list of the questions posed in the questionnaire and the results should be provided. It should be clear what version of the labelling was provided and whether any other instructions (e.g. Quick Reference Guide, Video or software application (App)) was	Intended to assess the ability of the untrained HCP to correctly interpret a variety of test results. Pre-made (contrived) devices should be used in order to mimic the different test results that might be observed. A pre-made device is one that has been fabricated by the manufacturer to display a specific test result. The pre-made devices should include all potential test results (i.e. non-reactive, reactive, weak reactive and invalids). The study should include: - a minimum of 3 POC sites - a minimum of 9 HCPs - 5 devices for each contrived result (non-reactive, reactive, weak reactive, invalids) should be interpreted by each operator.	Intended to assess the performance of the test relative to a licensed 4th generation test when used by an untrained HCP. The prospective study should include: - A minimum of 3 POC sites (different geographic locations), - A minimum of 9 HCPs, - 200 known HIV positive individuals and 400 individuals whose HIV status is unknown (200 should be from high risk populations). Results should be compared to a Health Canada licensed test. Positive and Negative Percent Agreement is calculated along with the lower bound of the two-sided 95% confidence interval for each. All invalid test results should be reported.

	made available to operators.		
Untrained Self-Tester	Intended to assess if untrained self-testers, using only the labelling provided, can understand how to use the device correctly, if they can correctly interpret test results and if they understand key warnings. A minimum of 200 self-testers should be included. The self-testers should be representative of the expected end user and should include persons at risk for HIV infection (IVDU, men who have sex with men, sex trade workers etc.). The demographic profile of the self-testers (gender, age, level of education, etc.) should be provided. The study report should list the questions included in the questionnaire and include any comments from study participants and the results. Any recommended actions to improve the labelling should be documented.	Intended to assess the ability of untrained self-testers to correctly interpret a variety of test results. Pre-made (contrived) devices should be used in order to mimic the different test results that might be observed. A pre-made device is one that has been fabricated by the manufacturer to display a specific test result. The pre-made devices should include all potential test results (i.e. non-reactive, reactive, weak reactive and invalids). The demographic profile of the self-testers (gender, age, level of education etc.) should be provided. A minimum of 400 self-testers should be used. The self-testers should be representative of the expected end user and should include persons at risk for HIV infection (IVDU, men who have sex with men, sex trade workers etc.).	Intended to assess the performance of the test relative to a licensed 4th generation test when used by an untrained lay person using only the instructional information provided. It should be designed so that the lay person is observed by a HCP trained in the use of the device while performing the test. Observations by the HCP should be documented and included in the study report. The demographic profile of the self-testers (gender, age, level of education etc.) should be provided. - Prospective study - 900 subjects with unknown HIV status including 400 persons at risk for HIV infection (IVDU, men who have sex with men, sex trade workers etc.). - The trained HCP also reads the results of the self-test within the stipulated reading time for the device allowing a comparison to be made between the trained and untrained groups. All invalid test results should be reported.

	It should be clear what version of the labelling was provided and whether any other instructions (e.g. Quick Reference Guide, Video or software application (App)) was made available to the self-testers.		