Health Canada Santé Canada

December 7, 2011

# Notice

Our file number: 11-121739-524

***Re: Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits intended to be used in the Laboratory***

Health Canada is pleased to announce the release of the final version of the *Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits intended to be used in the Laboratory*. A draft version of this guidance was first released for consultation in 2010. Comments from stakeholders have been considered in producing this final version.

This guidance document provides manufacturers of Class IV HIV test kits intended to be used in the laboratory with recommendations regarding the analytical (pre-clinical) and clinical data required to support a medical device licence application. The revisions to the previous 2001 guidance, contained herein, include:

- the removal of the requirement for Canadian investigational testing data in support of a medical device licence application;
- the elimination of the requirement for Canadian seroconversion samples;
- a decrease in the number of HIV-2 samples that should be tested to support an HIV-2 claim, from 300 to 200;
- an increase in the number of blood donor samples to support specificity claims, from 2500 to 5000; and,
- clarification on the number of non-B subtype positive samples that should be tested.

The revisions included in the *Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits intended to be used in the Laboratory* were developed in consultation with the Canadian Association of HIV Clinical Laboratory Specialists (CAHCLS), Canadian Blood Services (CBS), Héma-Quebec (HQ), the Public Health Agency of Canada (PHAC) and the medical devices industry.

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Canada

Health Canada Santé Canada

# GUIDANCE DOCUMENT

## Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits Intended to be Used in the Laboratory

Published by authority of the
Minister of Health

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| Date Adopted | 2011/11/14 |
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**Health Products and Food Branch**

Canada

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| Our mission is to help the people of Canada maintain and improve their health.<br>*Health Canada* | The Health Products and Food Branch's mandate is to take an integrated approach to managing of the risks and benefits to health related to health products and food by:<br>• minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,<br>• promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.<br>*Health Products and Food Branch* |



***Également disponible en français sous le titre : Ligne directrice : Ligne directrice à l'intention des fabricants de trousses de dépistage du virus de l'immunodéficience humaine (VIH) pour usage en laboratoire***

# 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) test kits intended to be used in the laboratory with recommendations on the analytical (pre-clinical) and clinical data required to support a medical device licence application.

The original version of this guidance document was issued in 1993 and has since undergone several revisions. For example, in 1996, the requirement for manufacturers to test panels of the various HIV subtypes or samples from geographic locations known to be prevalent for different subtypes was added. In 1997, the guidelines were updated to allow the use of positive samples collected from the continental United States of America. In September 2001, the guidelines underwent an editorial revision so as to be consistent with the *Medical Devices Regulations* issued July 1998.

The current version of the guidance document has been updated to reflect several changes including:

- the removal of the requirement for Canadian clinical trial data in support of a device licence application;
- the elimination of the requirement for Canadian seroconversion samples;
- a decrease in the number of HIV-2 samples that should be tested to support an HIV-2 claim from 300 to 200;
- an increase in the number of blood donor samples from 2500 to 5000 to support specificity claims; and
- clarification on the number of non-B subtype positive samples that should be tested.

The revisions included in this guidance were developed in consultation with the Canadian Association of HIV Clinical Laboratory Specialists (CAHCLS), Canadian Blood Services (CBS), Héma-Quebec (HQ), the Public Health Agency of Canada (PHAC) and the medical devices industry. Health Canada also considered data requirements from the European Common Technical Specifications (2009/886/EC)[1], as well as those outlined by the United States Food and Drug Administration (FDA)[2,3] as part of this guidance revision.

This guidance document is intended to be used in conjunction with the guidance *Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications* (GD008/Rev00-MDB) and the *Guidance for the Labelling of In Vitro Diagnostic Devices - Draft* (GD012/RevDR-MDB). These documents can be found on the Health Canada website at: http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php.

## 1.1 Policy Objective

To facilitate the submission of sufficiently detailed analytical (pre-clinical) and clinical data to Health Canada in support of a medical device licence application for an HIV test kit intended to be used in the laboratory, as required by section 32(4)(i)(i) of the Regulations (*Application for a Medical Device Licence*).

## 1.2 Policy Statements

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.

Human samples used to generate data in support of a medical device licence for an HIV test kit should be collected in accordance with generally accepted principles of Good Clinical Practice (GCP) or equivalent.

When available, international standards, reference reagents and international reference panels should be used.

## 1.3 Scope and Application

This guidance applies to Class IV HIV test kits intended to be used in the laboratory for diagnostic and/or donor screening purposes. This guidance does not apply to HIV test kits which are used for patient management, or HIV test kits intended to be used outside the laboratory, that is (i.e.), at the point of care and/or for home use. A separate guidance *Draft Guidelines for HIV Simple/Rapid Test Kit* is available for manufacturers of near patient HIV test kits upon request from the Medical Devices Bureau (MDB).

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)* (GD010/Rev00-MDB).

This guidance makes recommendations on the analytical and clinical data required as per section 32(4) (i)(i) of the Regulations, but 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* (GD008/Rev00-MDB) for additional data requirements.

# 2 GUIDANCE FOR IMPLEMENTATION

## 2.1 Performance Studies

The analytical (pre-clinical) and clinical studies used to establish the performance characteristics of an HIV test kit should be designed to support all claims made by the manufacturer with respect to the device.

Depending on the nature of the test [for example (e.g.), qualitative or quantitative, serological, Polymerase Chain Reaction (PCR) based], analytical testing should include studies to determine:

- matrix effect;
- assay cut-off;
- analytical sensitivity (limit of detection, dilutional sensitivity, sensitivity with different subtypes, sensitivity with seroconversion panels);
- analytical specificity (interference, cross-reactivity);
- precision;
- linearity; and
- kit and specimen stability.

Clinical studies should be done to establish:

- clinical (diagnostic) sensitivity; and
- clinical (diagnostic) specificity.

A detailed description of the design for all studies that enables a complete assessment of the data should be submitted. This should include, at a minimum, the study protocol, samples used, number of samples tested, results and conclusions. All data should be analysed using appropriate statistical methods. A description of the statistical methods used should be provided.

Panels (commercial or non-commercial) 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 all clinical studies done on behalf of a manufacturer, a copy of the laboratory evaluation report, signed and dated by the principal investigator, should be provided. This report should include a description of the study protocol, objectives and conclusions drawn by the investigator. 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).

## 2.2 Analytical Studies (pre-clinical)

### 2.2.1 Matrix Effect

Manufacturers claiming that their HIV test kit identifies HIV in serum or plasma should demonstrate equivalency. It is recommended that at least 50 serum and 50 plasma samples be used to validate this claim. A minimum of each of 25 positive and 25 negative serum and plasma samples should be used.

Manufacturers claiming that their HIV test kit identifies HIV in plasma should carry out a study with each anticoagulant [Ethylenediaminetetraacetic acid (EDTA), Na-citrate, heparin etc.] to verify performance using at least 50 samples (25 positive and 25 negative) for each anticoagulant.

Manufacturers claiming that their HIV test kit identifies HIV in a sample matrix such as urine or saliva, should conduct clinical studies to determine the performance of the device for these specimen types (see section 2.3.4).

Manufacturers claiming that their HIV test kit identifies HIV in cadaveric blood should refer to the FDA Guidance for Industry: *Recommendations for Obtaining a labelling Claim for Communicable Disease Donor Screening Tests using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based products (HCT/Ps)*[4].

### 2.2.2 Cut-off and/or Calibration Curve

The data, with a description of the study design and statistical methods used to determine the assay cut-off, should be provided. If the assay has an equivocal or grey zone, the rationale for its selection should also be included.

The accuracy and working range of calibration curves should be verified using serially diluted patient samples.

When applicable, the recommended intervals for calibration should be validated over the appropriate time intervals.

### 2.2.3 Analytical Sensitivity

When available, international standards, reference reagents and international reference panels should be used to establish the analytical sensitivity of HIV test kits.

The World Health Organization (WHO) 1st International Reference Reagent for p24 antigen (90/636) is an acceptable reference reagent to establish analytical sensitivity of a p24 antigen assay.

For nucleic acid based detection systems, the Limit of Detection (LOD) should be established using a dilution series of an international standard (e.g. WHO) or calibrated reference materials. A dilution series of at least ten unique HIV seropositive specimens with known numbers of HIV copies at levels around the LOD should also be tested. Manufacturers should demonstrate the 95% probability of detection at the LOD.

Manufacturers are also expected to evaluate the sensitivity of their assays using low titre and seroconversion panels and should evaluate the sensitivity of the assay for subtype detection (see tables 1, 3 and 4 below).

### 2.2.4 Analytical Specificity (Interference and Cross-Reactivity)

Manufacturers should refer to the Clinical and Laboratory Standards Institute (CLSI) document EP7-A2 *Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition*[5]. This guideline is intended to assist manufacturers in characterizing the susceptibility of their test kits to interfering substances.

Any potentially cross-reacting or interfering substances (endogenous and exogenous) or medical conditions should be evaluated using the assay system.

This includes testing:

- for interference due to prozone, high dose 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-1, HTLV-2);
  - 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);
- 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.

In addition, any potential for carry-over or cross-contamination with the assay should be evaluated.

Testing should include approximately 200 samples from individuals with medical conditions and approximately 100 samples with interfering substances.

### 2.2.5 Precision (Reproducibility/Repeatability)

Manufacturers should refer to CLSI document *EP5*-A2 *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition*[6] which describes protocols to establish an estimate of precision, and CLSI document *EP12-A User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline*[7].

Intra-assay (within run or repeatability), inter-assay (between run) and total precision should be determined using panels consisting of HIV-1 positive samples (including Group O and Group N if claimed), HIV-2 positive samples (if the assay makes a claim for HIV-2 detection), negative samples, and kit calibrators and kit controls. For assays that detect both antibody and antigen ("combo" assays), the panel should include p24 antigen positive samples. For qualitative tests, it is recommended that the panel consist of diluted positive samples, negative samples and kit positive controls. The panel should include samples that are close to the cutoff (both above and below).

Reproducibility should be assessed using a minimum of three laboratory sites (one of which can be in-house). Specimens should be tested in triplicate, using three lots over a minimum of five days. Operators should reflect the intended users of the assay (e.g. blood operators vs. clinical laboratory personnel). Other sources of variability (e.g. instruments) should also be considered.

Results provided should be reported as mean, standard deviation (SD), and coefficient of variation (CV) for each specimen.

### 2.2.6 Linearity

Manufacturers should refer to CLSI document EP6-A *Evaluation of the Linearity of Quantitative Measurement Procedures, A Statistical Approach; Approved Guideline*[8] which describes a statistical process for determining the linearity of a quantitative measurement procedure.

The linear range of a quantitative assay should be validated over the reportable range. Additionally, regression analysis should be performed on the data and the y-intercept, slope and $r^2$ obtained should be provided.

### 2.2.7 Stability

Manufacturers should refer to the European Standard EN 13640:2002 "Stability testing of in vitro diagnostic reagents"[9] which describes the general requirements for stability testing and specific requirements for real-time and accelerated stability testing.

#### (i) Kit, Reagents, Controls etc.

The data, along with the study design used to establish real time stability of the kit, reagents and controls for both storage and shipping temperatures are required.

Using a panel that includes weak reactive samples, data should be provided for:

- the recommended shelf life of the unopened kit, reagents, controls, etc., under the recommended storage conditions (three lots);
- the recommended product life of the opened kit, reagents, controls, etc. (one lot);
- the stability of on-board reagents (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, reagents and controls (one lot). This is to assess the effects of temperature fluctuation during shipment. 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. Please note that studies at freezing temperatures are not required for lyophilized reagents.

#### (ii) Specimen Collection and Handling

All sample collection, storage and transport claims should be validated. It should be verified that the recommended specimen storage conditions are compatible with the assay, i.e., can the specimen be frozen and thawed one or more times without affecting the detection of the analyte? The acceptable number of freeze/thaw cycles should be

specified in the package labelling. Data in support of the claims can be generated from real-time studies or provided from literature references. Where appropriate, on-board sample stability should be validated. This would apply, for example, to nucleic acid test systems where the samples are subjected to automated pipetting and incubation before extraction and processing.

## 2.3 Clinical Studies

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

### 2.3.1 Study Design

Clinical sensitivity and specificity studies should be designed as follows:

- testing should be done using a minimum of three master lots, one of which should be close to its expiry date;
- testing should be done at a minimum of three clinical sites;
- a detailed description of the testing algorithm used by the laboratory performing the testing should be provided;
- results should be expressed in terms of number of non-reactive (NR) samples, number of initially reactive (IR) samples, number of repeat reactive (RR) samples, and number of confirmed repeat reactive samples;
- the number of samples that give indeterminate or equivocal 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.

### 2.3.2 Study Population

Testing should be done using samples that represent an ethnically and genetically diverse population so as to be representative of the Canadian population.

### 2.3.3 Comparator Assays/Reference Methods

For all clinical studies, the comparator assay should be licensed in Canada (see http://www.mdall.ca).

In the absence of a licensed Canadian comparator test, a reference method or "gold standard" may be acceptable if published references supporting the methodology are provided. In this case, it is recommended that the manufacturer contact MDB for further guidance prior to testing.

### 2.3.4 Specimen Types

Tables 1 to 4 below show the types of samples (positive samples, seroconversion panels, blood donors, etc) and the minimum number of each sample type that should be tested when validating antibody, antigen and Nucelic Acid Testing (NAT) based assays.

Manufacturers claiming that their HIV test kit identifies HIV in a sample matrix such as urine or saliva, should conduct parallel testing with a Canadian licensed serological assay using serum or plasma from the same individuals. A listing of currently licensed devices for sale in Canada can be found at http://www.mdall.ca.

The sensitivity requirements for donor screening tests and diagnostic tests are the same.

Confirmed HIV positive samples used to determine assay sensitivity should reflect the different stages of infection, different antibody patterns, and include samples from different risk groups.

Manufacturers making a claim for Group O, Group N or Group P detection must provide validation data for these non M groups.

Manufacturers of test kits that detect both antibody and antigen ("combo kits") should meet the individual requirements specified for antibody detection and antigen detection.

Manufacturers of test kits which detect only HIV-2 antibodies and manufacturers of HIV-2 NAT tests should consult with MDB prior to submitting a licence application.

**Table 1: Minimum Number of Samples for Sensitivity for Donor Screening and Diagnostic Assays (Antibody Detection and NAT)**

| | Donor Screening and Diagnostic Assays | |
|---|---|---|
| | **Human Immunodeficiency Virus-1 (HIV-1)** | **Human Immunodeficiency Virus-1/2 (HIV-1/2)** |
| **Confirmed HIV positive samples** | 1000 HIV-1[a] | 1000 HIV-1<br>200 HIV-2 |
| **Low titre and seroconversion panels** | 25 panels | |
| **Subtypes** | 300 non-B subtypes[b] | |

[a] The 1000 confirmed Human Immunodeficiency Virus (HIV) positive samples may include the 300 non-B subtype samples.
[b] 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 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.

**Table 2: Minimum Number of Samples for Specificity for Donor Screening and Diagnostic Assays (Antibody Detection and NAT)**

| | **Donor Screening** | **Diagnostic** |
|---|---|---|
| **Blood Donors** | 5000[a] | not required |
| **Clinical Samples** | not required | 2500[b] |

[a] Unselected and include 1st time donors from at least three blood donation centres. These should be equally distributed among the testing centres and should be collected from geographically distinct regions. The results should include 300 fresh plasma samples matched to fresh serum samples.
[b] Prospective samples, tested at three centres and representing the target population: pregnant women, hospitalized patients, people requesting testing (worried well), high risk etc.

**Table 3: Minimum Number of Samples for Sensitivity and Specificity for HIV-1 Supplemental Assays (Western Blot, Strip Immunoblot, Indirect immunofluorescence assay (IFA), NAT)**

| | | |
|---|---|---|
| **Sensitivity** | Confirmed Human Immunodeficiency Virus-1 (HIV-1) positive samples | 300 HIV-1 |
| | Low titre and seroconversion panels | 25 panels |
| | Subtypes | 40 non-B subtypes |
| **Specificity** | Negative samples | 500[a] |

[a] 250 should be pedigreed false repeat reactive (RR) by Enzyme Immunoassay (EIA). False RR samples should not be selected using a single platform (for example, sample 1 would be a false RR on platform A, sample 2 a false RR on platform B, sample 3 a false RR on platform C etc). If possible, include false RR samples that are false RR on more than one platform (for example, sample 4 is a false RR on platforms A and B). The remaining 250 samples should come from a population representative of the Canadian population (ethnically/genetically).
If a claim is made for resolving indeterminate results of other supplemental assays, 250 samples which are indeterminate by these licensed assays should be tested.

**Table 4: Minimum Number of Samples for Sensitivity and Specificity for HIV-1 p24 Antigen and p24 Neutralization**

| | | **p24 antigen** | **p24 neutralization** |
|---|---|---|---|
| **Sensitivity** | Confirmed Human Immunodeficiency Virus-1 (HIV-1) positive samples[a] | 300 HIV-1 | |
| | Low titre and seroconversion panels[b] | 25 panels | not required |
| | Subtypes | 40 non-B subtypes | |
| **Specificity** | Negative samples | 2500 | 500 |

[a] For the p24 neutralization assay, the positive specimens should be p24 Ag repeat reactive (calculate % neutralization).
[b] For p24 antigen assays, the seroconversion panels should contain $Ag^{+}Ab^{-/indeterminate}$ samples.

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