Health Canada Santé Canada

DRAFT GUIDANCE DOCUMENT

HIV Simple/Rapid Test Kits

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Également disponible en français sous le titre : *Ébauche de la ligne directrice : Les trousses de dépistage simple/rapide du VIH*

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 BACKGROUND

An application for a Medical Device Licence for HIV test kits must be prepared in accordance with Section 32 of the *Medical Devices Regulations*.

The Guidelines for HIV Simple/Rapid Test Kits are intended to give additional details specific to Class 4 HIV test kits on the requirements of Section 32 (4) (a) to (p). This document is a complement to the guidance document "Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications"[1] and, therefore, manufacturers must ensure that all subsections found in the guidance document are fully addressed in their application, not only those mentioned in these Guidelines.

These Guidelines were developed by representatives from the Provincial Laboratory B.C. Centre for Disease Control, Alberta's Provincial Laboratory of Public Health, the Laboratoire de Santé Publique du Québec, the Ontario Ministry of Health Central Laboratories, the B.C. Centre for Excellence in HIV/AIDS, the Canadian Red Cross Society, the Laboratory Centre for Disease Control (LCDC) and the Medical Devices Bureau (MDB).

The Medical Devices Bureau reserves the right to ask for more information than is requested in these Guidelines if it is felt that such data are necessary to substantiate the safety and effectiveness of the kit.

2 GENERAL INFORMATION ON THE EVALUATION PROCESS OF HIV DEVICE LICENCE APPLICATIONS

In support of their Device Licence Application, all manufacturers of HIV test kits will be required to conduct prospective investigational studies in the intended target population (intended users). Investigational studies can only be undertaken once the Manufacturer has obtained an "Authorization for Investigational Testing" from the Medical Devices Bureau in accordance with Sections 79 to 88 of the *Medical Devices Regulations*.

Some laboratory studies (e.g. sensitivity studies, panel studies) can be conducted in Canadian laboratories without a prior "Application for Investigational Testing Authorization" from the Medical Devices Bureau, provided these studies are conducted on repository specimens of **known** HIV status (e.g. repository confirmed HIV positive samples, panels, etc.). In these cases, the kits must be labelled "For Research Use Only".

The following subsections are numbered in accordance with those found in the "Guidance Document: The Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications" Section 7.0 Format of a Class IV Review Document (IVDDs) - They are intended to complement this Guidance Document and, therefore, Manufacturers must ensure that

[1] Guidance Documents can be found on the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/index-eng.php)

all 8 sections of the Guidance Document, which cover the requirements of Section 32, subsection (4) paragraphs (a) to (p) of *the Medical Devices Regulations*, are fully addressed in their application, not only those mentioned below.

7.4.1 MATERIAL SPECIFICATIONS

As part of the information required in this section, include details regarding the strain of the virus, the cell line for the cultivation of the virus, sequences of relevant nucleic acids and amino acids, etc., used in the manufacturing process of viral lysate, purified proteins, recombinant and synthetic proteins, primers, probes, etc.

7.4.2 MANUFACTURING PROCESS SPECIFICATIONS

As part of the information required in this section, include a flow chart of the manufacturing process on which all Quality Control (QC) steps are indicated. Provide detailed information of the QC procedures.

The information should also include details of the manufacturing process and of the Quality Assurance Program in place for the preparation of viral lysate, purified proteins, recombinant and synthetic proteins, primers, probes, immunoglobulin, immunoglobulin-proteins conjugate, positive and negative controls, coated plates, etc.

3 SAFETY AND EFFECTIVENESS STUDIES

Manufacturers are strongly encouraged to contact a designated Canadian laboratory (see attached list) for a pre-investigational evaluation of their kits and to submit this data in support of an "Application for Investigational Testing Authorization".

In cases where the data are generated in laboratories (Canadian or foreign) other than those mentioned in the attached list, provide a certificate of accreditation, or equivalence, for the said laboratories, attesting that the laboratory meets the requirements of Good Laboratory Practices, or equivalent.

For all studies done on behalf of a Manufacturer, a copy of the laboratory evaluation report, signed and dated by the principal investigator, must be provided.

3.1 Sensitivity/Specificity

3.1.1 Specificity

- A prospective study in the intended Canadian target population on 2,500 individuals, 500 of which must be from a high risk population. The study must be conducted in at least three different cities, two of which should be Montreal, Vancouver or Toronto. Samples should be distributed equally among the different investigational sites. This

study can only be undertaken once the Manufacturer has received an Investigational testing authorization from the Medical Devices Bureau in accordance with sections 79 to 88 of the *Medical Devices Regulations*.

- At this time, the results obtained from simple/rapid test kits must be compared to conventional serological testing done in designated laboratories.

- The study must be performed on three (3) master lots, one of which should be close to its expiry date.

- Results must be expressed in terms of: # of non-reactive samples, # of reactive samples, # of indeterminates for both the rapid test kit and the test of reference. Calculate specificity and 95% confidence intervals.

- All discrepant results between the kit under investigation and the test of reference must be clearly indicated and resolved using supplemental, specific assays, or definitive clinical data or clinical follow up.

- If applicable, studies must be conducted to determine if the users understand the purpose of the test, the conditions for its use, the tests limitations, the meaning of the result (positive, negative or indeterminate) and the appropriate follow-up.

Table 1. **Sensitivity** data required from Manufacturers of Rapid HIV test kits in order to obtain a Medical Device Licence

Intended use of the kit	confirmed HIV positive		Commercial sero-conversion panels [B]	panels of the various clades[C]	recent Canadian seroconverted samples[D]
	HIV-1[A]	HIV-2			
Rapid Test Kits (serum or whole blood)					
HIV-1	1,000	NR	25	Yes	50
HIV-1/HIV-2	1,000	300	25	yes	50
Rapid Test Kits (saliva or urine)					
HIV-1	1,000	NR	as available	Yes	as available
HIV-1/HIV-2	1,000	30	as available	yes	as available

[A] This data must be from Canadian or Continental USA seropositive individuals and must be generated on a minimum of three master lots, one of which should be close to its expiry date. Calculate sensitivity and 95% confidence intervals. In some cases, the data can be generated from repository samples. In other cases, fresh samples will have to be obtained from seropositive individuals under an "Application for Investigational Testing Authorization", if this is done in Canadian settings.

[B] Characterized commercial panels. In some instances (e.g. saliva, urine) there are no commercial panels available. If and when such panels become available, the Guidelines will be modified accordingly.

[C] In instances where there are no panels available, data from confirmed positive samples from geographic locations known to be prevalent with the different clades should be included in the application.

[D] Specimens from individuals that have seroconverted within the last 12 months obtained from at least two different geographic location (e.g. Montreal, Toronto, Vancouver). This testing must be done by designated Canadian Laboratories (see attached list). Samples should be distributed equally among the different locations. In some instances (e.g. saliva, urine, nucleic acid based detection system) Canadian samples of this type are not available. If and when such samples become available, the Guidelines will be modified accordingly.

NR = Not Required

Note: Deficiencies in the evaluation of the kit due to the unavailability of panels or samples will need to be addressed in the package insert, .e.g. under "limitations of the assay".

3.1.2 Additional Instructions for Specificity and Sensitivity Studies

For all studies conducted in laboratories other than the designated Canadian Laboratories, data presentation should include a summary of the data in the form of Tables, as well as the detailed results (actual OD values, WB bands, other read-out values) of individual specimens obtained with both the investigational kit and the kits of reference. For photographs of gels and blots, only originals are acceptable.

For studies conducted in designated Canadian Laboratories, summaries of the data, in the form of Tables and Figures, is sufficient.

For all studies done on behalf of a Manufacturer, a copy of the laboratory evaluation report, signed and dated by the principal investigator, must be provided.

3.1.3 Criteria of Acceptability for Sensitivity and Specificity of HIV Rapid Test Kits

1) OTC HIV Home Test Kits: to be considered for receiving a Medical Device Licence, the predictive values in the intended target population will need to be equivalent to those obtained by the testing algorithm in practice in Canadian Provincial Laboratories. A built-in (internal) control must be included in the design of the kit.

2) For other rapid test kits, such as those used in Health Care settings, the manufacturers will have to demonstrate that the performance characteristics of the kits agree with their intended use (objective). A built-in (internal) control should be included in the design of the kit.

3.2 Interference

Any potentially cross-reacting or interfering substances or conditions potentially encountered in specific specimen types should be tested using the assay system. For example:

- if the antigen utilized in the device is a recombinant, test sera containing antibodies against the organism in which vectors were induced

- if the antisera utilized in the devices were produced by using recombinant(s) as the immunogen(s), test sera containing antibodies against the organism in which the vectors were induced.

- verify that 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 qualitative detection of the analyte? Both the possibility of false positivity or false negativity due to storage conditions of the specimens should be evaluated.

- Samples from individuals with non-HIV viral infections (Hepatitis C virus, Hepatis B virus, Hepatitis A virus, Epstein-Barr virus, Herpes simplex virus, Rubella, Cytomegalovirus, etc.), other retroviral infections (Human T-cell Lymphotropic virus type I/II), bacterial/parasitic diseases (syphilis, toxoplasmosis), autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus), other miscellaneous medical conditions (cancer, cirrhosis, etc.), polyclonal and monoclonal gammopathies (IgG or IgM hypergammaglobulinemia), recipients of multiple blood transfusions, lipemia, haemolysis, etc.

3.3 Reproducibility

Intra- and inter-assay variations must be determined with a panel consisting of:

- dilutions of an HIV-1 positive specimen (4 above end point with one near cutoff value and 2 below end point and one near cutoff value).

- dilutions of an HIV-2 positive specimen (4 above end point with one near cutoff value and 2 below end point and one near cutoff value).

- 2 negative specimens

- positive control

The specimens should be tested in triplicate on 3 different days (runs) in at least 3 sites on 3 lots (total number of replicates of each member = 3 x 3 x 3 x 3 = 81).

3.4 Stability

Using a panel similar to the one described in the Reproducibility studies, provide data for each of the three (3) master production lots:

- the recommended shelf life of the unopened kit, reagents, controls, etc., under the recommended storage conditions.

- the recommended product life of the opened kit, reagents, controls, etc.

- the stability of on-board reagents, where applicable.

- the effects of freezing temperature and of extreme heat ($\geq 37^{O}C$) on the performance characteristics and the shelf life of the kit. This is to assess the effects of temperature fluctuation during shipment. If the kits are shipped under special conditions (e.g. dry ice) and there is evidence that the kits are not exposed to temperature outside the recommended range, even during summer days, the studies at the higher temperature are not required.

3.5 Other Studies

Prozone effect, robustness of the kit, etc.

4 DEVICE LABEL

The final package insert must clearly describe the performance characteristics of the test kit, i.e. specificity, sensitivity, reproducibility, stability, earliest clinical detection in comparison with tests of reference, etc., and how these were determined.

In accordance with Sections 86(c), 86(d) and 86(e) of the *Medical Devices Regulations*, all labels to be used in connection with a device that is sold for investigational testing must include the statements “Investigational Device”, “To Be Used By Qualified Investigators Only” and “The performance specifications of this product have not been established”.

Labelling may be an option to address deficiencies in the evaluation of the performance characteristics of kits due to the unavailability of panels or samples, depending on the nature of the deficiency.

APPENDIX 1:

The following complements the guidance document, "Preparation of an application for Investigational Testing - *In Vitro* Diagnostic Devices (IVDD)".

Manufacturers must provide the information described in Sections 79-88 of Part 3 of the *Medical Devices Regulations* in order to obtain an Authorization for Investigational Testing.

The investigational protocol must clearly indicate that the results obtained with the investigational kit are not to be used for clinical patient management since its performance characteristics have not yet been established.

In accordance with the *Medical Devices Regulations*, all labels to be used in connection with a device that is sold for investigational testing must include the statements "Investigational Device" and "To Be Used By Qualified Investigators Only" and "The performance specifications of this product have not been established".

Designated Laboratories in Canada

Contact Person and Address		Contact Person and Address	
LCDC	Dr. J. Kim A/Chief, National Lab for HIV Reference Services Laboratory Centre for Disease Control Health Canada Virus Building, Tunnel's Pasture, Postal Locator 1002A1 Ottawa, Ontario K1A 0L2 Tel: (613) 957-9666 Fax: (613) 957-7258	CBS	Dr. Wesley Rees VP of Safety and Performance Management 1800 Alta Vista Drive Ottawa, Ontario K1G 4J5 Tel: (613) 739-2300 Fax: (613) 731-1411
Nfld	Dr. S. Ratnam Newfoundland & Labrador Public Health Laboratories PO Box 8800 St. Johns, Newfoundland A1B 3T2 Tel: (709) 737-6568 Fax: (709) 737-7070	SASK	Dr. E. Chan/Mr. F. Sidaway Microbiology and Communicable Diseases Provincial Laboratory 3211 Albert Street Regina, Saskatchewan S4S 5W6 Tel: (306) 787-3135 Fax: (306) 787-1525
PEI	Dr. L. P. Abbott Provincial Health Laboratory Queen Elizabeth Hospital PO Box 6600, Riverside Drive Charlottetown, PEI C1A 2M7 Tel: (902) 894-2309 Fax: (902) 566-6385	ALB[1]	Dr. K. Fonseca Provincial Laboratory of Public Health 3030 Hospital Drive, NW PO Box 2490 Calgary, Alberta T2P 2M7 Tel: (403) 670-1200 Fax: (403) 270-2216
NS	Dr. S. Lee Department of Virology and Immunology Victoria General Hospital D.J. Mackenzie Building 5788 University Avenue Halifax, Nova Scotia B3H 1V8 Tel: (902) 473-6885 Fax: (902) 473-7971	ALB[2]	Dr. J. Preiksaitis Provincial Laboratory University of Alberta Walter Mackenzie Health Sciences Centre 114th Street Edmonton, Alberta T6G 2J2 Tel: (403) 492-4134 Fax: (403) 492-3684

BC[1]	Mr. D. Cook Provincial Laboratory B.C. Centre for Disease Control 828 West 10th Avenue Vancouver, British Columbia V5Z 1L8 Tel: (604) 660-6045 Fax: (604) 660-6073	BC[2]	Dr. C. Sherlock Diagnostic Virology & Reference Laboratory 6th floor, Burrard Building 631-1081 Burrard St., St. Pauls Hospital Vancouver, British Columbia V6Z 1Y6 tel: (604) 631-5426 Fax: (604) 631-5421
ON	Ms. C. Major Ontario Ministry of Health Central Laboratories PO Box 9000, Terminal "A" Toronto, Ontario M5W 1R5 Tel: (416) 235-6096 Fax: (416) 235-6194	QC	Ms. M. Fauvel Laboratoire de Santé Publique du Québec 20045, chemin Ste-Marie Ste-Anne-de-Bellevue, Québec H9X 3R5 Tel: (514) 457-2070 Fax: (514) 457-6346
MAN	Dr. T. Williams Cadham Provincial Laboratory PO Box 8450 750 William Avenue Winnipeg, Manitoba R3C 3Y1 Tel: (204) 945-6123 Fax: (204) 786-4770		

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