



INVITATION TO SUBMIT APPLICATIONS FOR FUNDING

from the

Government of Canada

(Canadian International Development Agency, Public
Health Agency of Canada and Industry Canada)

and

the Bill & Melinda Gates Foundation

on behalf of the

Canadian HIV Vaccine Initiative

for a

**Pilot Scale HIV Vaccine
Manufacturing Facility in Canada for
Clinical Trial Lots**

April 15, 2008

DISCLAIMER

The Government of Canada and the Bill & Melinda Gates Foundation are under no obligation to provide funding, or enter into Funding Agreements as a result of this *Invitation to Submit Applications*.

THE GOVERNMENT OF CANADA AND THE BILL & MELINDA GATES FOUNDATION ALSO RESERVE THE RIGHT TO:

- **reject any or all applications received in response to this *Invitation to Submit Applications*;**
- **accept any application as a whole or in part; and**
- **cancel and/or re-issue this *Invitation to Submit Applications*.**

Please note that the Government of Canada or the Bill & Melinda Gates Foundation will not reimburse an Applicant for costs incurred in the preparation and/or submission of a *Letter of Intent* or *Application* in response to this *Invitation to Submit Applications*.

NOTES TO APPLICANTS

- Ce document est disponible en français.
- This *Invitation to Submit Applications* is available electronically in WordPerfect and MS Word formats. To receive an electronic version of this *Invitation to Submit Applications*, please email the contact person identified below.
- Any questions or requests for clarification of this document must be submitted in writing by email to the contact person identified below. All questions and requests, along with the associated responses, will be posted anonymously on a “Questions, Answers and Corrections” website page on www.chvi-icvv.gc.ca. Any corrections to the *Invitation to Submit Applicants* will also be posted on the “Questions, Answers and Corrections” website page on www.chvi-icvv.gc.ca. Applicants to the Pilot Scale HIV Vaccine Manufacturing Facility in Canada for Clinical Trial Lots initiative are encouraged to check this website page daily to keep up-to-date with any posted questions, answers and corrections. Questions and requests for clarifications will be answered if received at least seven (7) calendar days prior to the date stipulated for submission of completed *Letter of Intent Forms*.
- Applicants are strongly encouraged to direct all inquiries relating to this *Invitation to Submit Applications* ONLY to the contact person named below. The information gained from all other contacts may be factually incorrect, may not necessarily reflect the opinions of the Government of Canada or the Bill & Melinda Gates Foundation as related to this project and should not be used for the basis of completing any element of a Letter of Intent or Application. Only the information contained in this *Invitation to Submit Applications*, accompanying *Letter of Intent Form* and *Application Form* and subsequent written information posted on www.chvi-icvv.gc.ca should be considered to accurately reflect the intent of the Government of Canada and the Bill & Melinda Gates Foundation as related to this project.
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TABLE OF CONTENTS

GLOSSARY	iv
PREAMBLE	1
INTRODUCTION	2
Vaccines and HIV/AIDS	2
Global HIV Vaccine Enterprise	2
Canadian HIV Vaccine Initiative	3
PRIORITY FOR THIS INVITATION	5
Pilot Scale Manufacturing Facility in Canada for Clinical Trial Lots	5
FACILITY PRINCIPLES	5
FACILITY MODEL	7
Key Objectives	7
Description and Capability of the Facility	9
Roles and Responsibilities	11
OVERVIEW OF THE INVITATION PROCESS	13
ELIGIBILITY	14
FINANCIAL	15
Funding	15
Applicant Contribution	16
Eligible Expenses	16
Ineligible Expenses	16
INVITATION AND APPROVAL PROCESSES AND TIME LINES	17
General	17
Invitation Process (April 15, 2008 to late October 2008)	17
Approval Process (October 2008 to May 2009)	18
LETTER OF INTENT AND APPLICATION REVIEW CRITERIA	18
FUNDING AGREEMENTS	22
Terms and Conditions	23
Audit	23
ADMINISTRATIVE CONTACT	24

GLOSSARY

This glossary defines specific terms as they apply to the Invitation to Submit Applications, Letter of Intent Form and Application Form and related documents.

Applicant	An eligible organization that submits a completed Letter of Intent form and, if invited, a completed Application Form. (See Eligibility Criteria)
Developer	The entity or individual from Canada or abroad that has the legal right to develop and commercialize the HIV vaccine candidate and applies to bring the HIV vaccine candidate to the facility to be manufactured. The Developer may also be the Discoverer of the HIV vaccine candidate and may be responsible for taking the HIV vaccine candidate to clinical trials.
Discoverer	The entity or individual from Canada or abroad that discovered the HIV vaccine candidate. The Discoverer has the legal right to develop and commercialize the HIV vaccine candidate and may either retain this right or may transfer this right to a Developer.
Funding Agreements	Generic term to encompass both the Government of Canada's contribution agreement and the Bill & Melinda Gates Foundation's grant agreement that provides funding to the successful Applicant.
Funding Authorities	The Government of Canada Ministers responsible for PHAC, IC and CIDA and the President of Global Health of the Bill & Melinda Gates Foundation.
Global Access	For the purposes of this project, global access is achieved when: the knowledge gained from the manufacturing of clinical trial lots (at the facility) and the conduct of clinical trials with those lots is shared with the international community; and any viable candidate (whose clinical trial lot was manufactured at the facility) is made available at an affordable price to all those who serve to benefit from it, particularly in low- and middle-income countries.
LMICs	An abbreviation for "low- and middle-income countries".
Not-for-Profit Corporation (NPC)	A Not-for-Profit Corporation (NPC) incorporated under appropriate legislation, or act of parliament or foreign equivalent for non-Canadian corporations.
Partner	An entity or individual that has a formal agreement with the Applicant to specifically assist in the establishment, operation and/or maintenance of a pilot scale HIV vaccine manufacturing facility in Canada for clinical lot trials by providing their money, property, knowledge, skills, time, personnel and/or other resources.

Universal Candidacy	For the purposes of this project, universal candidacy is achieved when vaccine candidates from all over the world are sought and given equal and equitable consideration for their development within the pilot scale HIV vaccine manufacturing facility that is the subject of this project.
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PREAMBLE

The purpose of this Invitation to Submit Applications is to solicit Letters of Intent and Applications to establish a pilot scale HIV vaccines manufacturing facility in Canada for clinical trial lots.

The envisioned facility would be capable of manufacturing a diverse number of HIV vaccines including current candidate technologies such as but not limited to, DNA vaccines and recombinant subunit vaccines and viral vectors (non-replicating and replication-competent). The facility should also be flexible enough to adapt to candidate technologies that will emerge in the future.

The successful Applicant would seek promising and suitable HIV vaccine candidates from Discoverers/Developers from around the world for pilot scale manufacturing conducted by the Applicant within the facility. The manufactured vaccine would be used for clinical trials to be conducted at locations around the world as arranged by the originating Discoverer/Developer.

Applications will only be accepted from Not-for-Profit Corporations (NPCs). While the NPC is not required to be headquartered in Canada, it should have a presence in Canada. Applicants are expected to partner with other organizations and/or individuals to access the necessary expertise to carry out this project.

The Government of Canada and the Bill & Melinda Gates Foundation (Gates Foundation) are collaborating to support a Canadian HIV Vaccine Initiative (CHVI), a key component of which is the establishment of the pilot scale HIV vaccine manufacturing facility which is the subject of this Invitation to Submit Applications. The CHVI collaborates with the Global HIV Vaccine Enterprise which has identified manufacturing capacity as a critical gap in the effort to develop a successful HIV vaccine.

The maximum available funding contribution from the Government of Canada and the Gates Foundation for this project to establish a pilot scale HIV vaccine manufacturing facility is limited to \$88 million¹ which is expected to be paid out over a four year period. In addition to the contribution provided by the Government of Canada and the Gates Foundation, the successful Applicant (i.e., a Not-for-Profit Corporation (NPC)) is expected to attract and provide additional funding from other public and/or private sector sources to establish, operate, maintain and sustain the facility. Government of Canada and Gates Foundation funding is limited to covering costs associated with the creation but not ongoing operations and maintenance of the pilot manufacturing facility. Certain conditions of the Funding Agreements dealing with the use and disposal of the facility may extend for approximately 20 years following the expiry or termination of the Funding Agreements to ensure that the facility continues to be used for the purposes for which funding was provided (i.e., consistent with the principles of CHVI and specific facility principles as described herein).

¹ All monetary amounts in this Invitation to Submit Applications are in Canadian dollars unless otherwise annotated.

INTRODUCTION

Vaccines and HIV/AIDS

One of the greatest public health interventions in the past 100 years has been the discovery and widespread use of vaccines. More than 30 common infectious diseases are preventable with vaccines, and one of the most deadly, smallpox, was eliminated from human populations in 1979. The cost to eradicate smallpox was US\$300 million, whereas the benefit has been estimated at US\$27 billion over 20 years. Vaccines are one of the most cost-effective public health interventions available.

In the absence of a vaccine or cure, HIV/AIDS continues to spread at an alarming rate, devastating individuals and communities around the world. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2006 AIDS Epidemic Update, an estimated 38.6 million people were living with HIV/AIDS worldwide at the end of 2005 – almost half of whom are women (17 million) and 8 million of whom are young people (15-24 years). Since the epidemic began, AIDS has killed over 25 million people and approximately 15 million children have lost one or both parents to this disease.

Safe, effective, affordable and globally accessible preventative HIV vaccines represent the most promising breakthrough needed to reverse the devastating inequalities that have been exacerbated by HIV/AIDS especially in the developing world.

Global HIV Vaccine Enterprise

The Global HIV Vaccine Enterprise (the Enterprise), first proposed in 2003, was developed as an alliance of independent organizations around the world dedicated to accelerating the development of a preventive HIV vaccine through:

- ***A shared Scientific Strategic Plan (SSP)***: Implementing a strategic plan for HIV vaccine research that spans vaccine discovery, product development and manufacturing, and clinical trials;
- ***Increased resources***: Mobilizing significant new funding to achieve the scientific plan; and
- ***Greater collaboration***: Promoting more efficient, faster ways for researchers to share successes and failures and avoid unnecessary duplication of efforts.

The SSP of the Enterprise, published in February 2005, describes the major challenges facing the field and makes recommendations in six priority areas: vaccine discovery, laboratory standardization, product development and manufacturing, clinical trials capacity, regulatory issues and intellectual property issues. An update on these activities can be found in *The*

Enterprise Report of Activities 2005-2007 published in August 2007.

Specifically in the area of product development and manufacturing, the SSP recommends “increasing global manufacturing capacity closely linked to vaccine discovery consortia and clinical trial sites. Such efforts will be particularly important as more HIV vaccine candidates are discovered, developed and advanced through clinical trials mostly in and for the ultimate benefit of low and middle income countries (LMICs). Private industry involvement is critical because most vaccine manufacturing expertise resides in the private sector”.

Canadian HIV Vaccine Initiative

In February 2007, the Prime Minister of Canada and Bill Gates jointly announced a new collaboration between the Government of Canada and the Bill & Melinda Gates Foundation (Gates Foundation) to support the Canadian HIV Vaccine Initiative (CHVI). The overall goal of the CHVI is to coordinate HIV/AIDS vaccine research, development and access activities with international efforts in support of the Enterprise. The Government of Canada is committing up to \$111 million² (\$85 million of new funding) to the CHVI, and the Gates Foundation is contributing up to \$28 million². A maximum of \$88 million² of this \$139 million² has been set aside by the Government of Canada and the Gates Foundation for the establishment of a pilot scale HIV vaccine manufacturing facility. In addition to the contribution provided by the Government of Canada and the Gates Foundation, the successful Applicant (i.e., a Not-for-Profit Corporation (NPC)) is expected to attract and provide additional funding from other public and/or private sector sources to establish, operate, maintain and sustain the facility.

The Gates Foundation is an independent, privately endowed charitable foundation. One of its missions is to reduce global health inequities by accelerating the development, deployment and sustainability of health interventions that will save lives and dramatically reduce the disease burden in developing countries.

The CHVI is guided by the following principles:

- ***Strategic Coordination and Integration*** - The CHVI's alignment with the Enterprise will focus Canadian and international expertise on addressing key objectives of the Enterprise's SSP;
- ***Multi-Sectoral Collaboration and Engagement*** - The CHVI will promote active involvement and collaboration among governments, private sector, academic researchers,

² All monetary amounts in this Invitation to Submit Applications are in Canadian dollars unless otherwise annotated.

non-governmental organizations (NGOs), civil society, people living with HIV/AIDS and other relevant stakeholders. It will strengthen domestic and international linkages to foster collaboration among researchers, policy makers and regulators by promoting the use of most appropriate and up-to-date technologies. The CHVI will also explore new collaborations and mechanisms for leveraging additional investments;

- ***Promotion of Human Rights and Global Access*** - CHVI will help ensure that all activities are consistent with established international principles and best practices to promote and protect human rights and support the meaningful involvement of people living with HIV/AIDS. It will focus on evidence-based interventions and foster support for social justice and gender equality. And, it will actively support the principles of Global Access, striving to make the benefits from the initiative relevant and accessible to all, especially those in LMICs where the burden of HIV/AIDS is the highest and the needs are the greatest; and
- ***Accountability and Transparency*** - Recognizing the multi-sectoral nature of this initiative and the scope of the projects to be undertaken, the CHVI will be implemented through open, integrated and transparent processes with regular, publicly available progress reports.

The CHVI builds on the Government of Canada's commitment to a long-term comprehensive approach to fighting HIV/AIDS globally and domestically of which the development of new HIV prevention technologies is a component. The CHVI represents an approach involving the Canadian International Development Agency, the Public Health Agency of Canada, Industry Canada, the Canadian Institutes of Health Research, Health Canada and the Gates Foundation.

The CHVI activities will focus on:

- ***Discovery and social research***: Through this component, support will be provided to HIV vaccine discovery and social research while strengthening the capacity and promoting greater involvement and collaboration amongst researchers in Canada and LMICs;
- ***Clinical trial capacity building and networks***: Support will be given to researchers and research institutions, particularly in LMICs, that will strengthen their capacity to conduct high-quality clinical trials of HIV vaccines and other related prevention technologies;
- ***Pilot scale manufacturing facility for clinical trial lots***: A pilot scale manufacturing facility will be established in Canada to increase the global capacity to produce HIV vaccine candidates for use in clinical trials. These trials will be conducted mostly in and particularly for the benefit of LMICs;

- ***Policy and regulatory issues, community and social dimensions:*** This component will improve the regulatory capacity in LMICs, particularly those where clinical trials are planned or ongoing, and will address policy issues that will ultimately promote Global Access to a HIV vaccine. The CHVI will support the development and strengthening of community, legal, ethical and human rights frameworks for HIV vaccines in Canada and in LMICs; and
- ***Planning, coordination and evaluation:*** The CHVI will coordinate its activities with Canadian and international HIV vaccine research and development partners to ensure the Canadian contribution to the Enterprise is most effective.

PRIORITY FOR THIS INVITATION

Pilot Scale Manufacturing Facility in Canada for Clinical Trial Lots

Under the CHVI, the Government of Canada (specifically the Canadian International Development Agency, the Public Health Agency of Canada and Industry Canada) and the Gates Foundation have made it a priority to fund the establishment of a pilot scale manufacturing facility in Canada to increase the global capacity to produce HIV vaccine candidates for use in clinical trials. In addition to the contribution provided by the Government of Canada and the Gates Foundation, the successful Applicant (i.e., a Not-for-Profit Corporation (NPC)) is expected to attract and provide additional funding from other public and/or private sector sources to establish, operate, maintain and sustain the facility. The ability of the successful Applicant to work within the global environment to identify promising vaccine candidates and negotiate with the Developers to manufacture their vaccines in order to conduct clinical trials in the desired locations is absolutely critical to the success of this project to establish a pilot scale HIV vaccine manufacturing facility.

FACILITY PRINCIPLES

The establishment of the envisioned facility is for the global public good. The facility should be established, operated, maintained and sustained in a manner consistent with the objectives of the Enterprise and the principles of CHVI as stated in the Introduction, and the following specific facility principles:

- ***Integration with global efforts*** - The scale of the HIV/AIDS epidemic requires a global

effort. Within the framework of the Enterprise, the proposed pilot scale HIV vaccine manufacturing facility is intended to be one piece in a worldwide process to bring an HIV vaccine from discovery to equitable and universal access and use. To be effective, the facility must be operated in concert with global efforts and actively seek to involve the best minds and resources worldwide;

- ***Multi-sectoral collaboration*** - The unique strengths of a number of parties such as, but not limited to, an NPC, industry and academia will be harnessed to successfully establish and operate the facility;
- ***Global Access***- The knowledge gained from the manufacturing of clinical trial lots and the conduct of clinical trials with those lots will be shared with the international community and any viable candidate (whose clinical trial lot was manufactured at the facility) will be made available at an affordable price to all those who serve to benefit from it, particularly in LMICs;
- ***Universal Candidacy*** - Vaccine candidates from all over the world will be sought and given equal and equitable consideration for their development within the facility;
- ***Tangible benefits to LMICs*** - LMICs will tangibly benefit from the facility including, but not limited to, an ability to have their vaccine candidates considered for pilot scale manufacture, the increase in the conduct of clinical trials in their countries and their affordable access to successful HIV vaccines;
- ***Technology*** - The technology employed within the facility will be flexible enough to accommodate future advances in technical requirements associated with future vaccine candidates (i.e., those candidates coming down the “pipeline”) that can be reasonably anticipated and to accommodate multiple candidates simultaneously including those with different bio-safety requirements up to and potentially including bio-safety level 3 (BSL 3);
- ***Self-sustainability*** - The facility will mobilize diverse and extensive resources and world-class capabilities to produce a creative business model that is self-sustaining; and
- ***Open and transparent processes*** - Openness and transparency will be the hallmarks by which the facility will be established and operated.

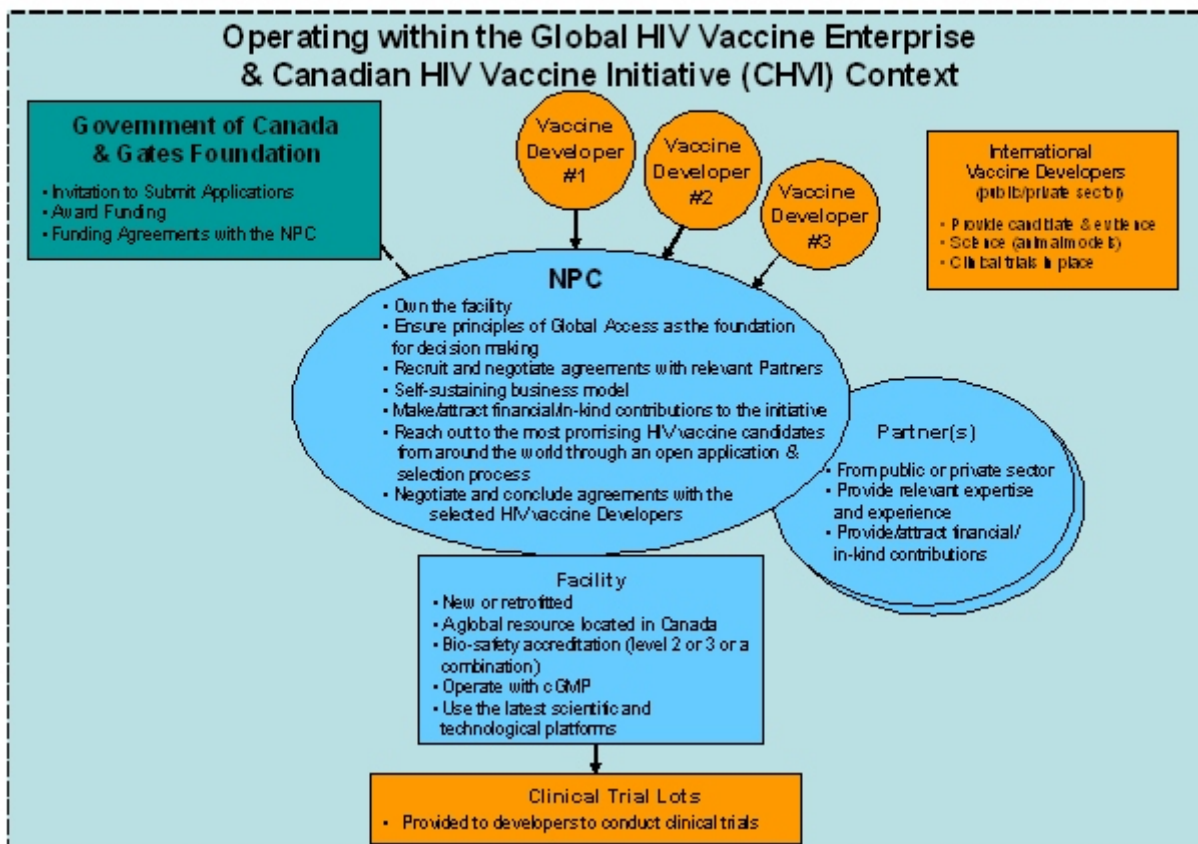
FACILITY MODEL

Figure 1 presents an overview of the envisioned model for the operation of the clinical trial lot manufacturing facility within the global and Canadian environments. This section outlines the key objectives of the model, the minimum requirements of the facility and describes the roles and responsibilities of the Applicant and its Partner(s). An Applicant will detail how it proposes to meet the key objectives and minimum requirements in its submission.

Key Objectives

- The pilot scale facility will be a global resource for the production of clinical trial lots of HIV vaccine candidates particularly for LMICs where the burden of HIV is highest;

Figure 1 – Pilot Scale HIV Vaccine Manufacturing Facility



- The facility will have the capacity to produce clinical trial lots using the latest scientific and technological platforms tailored to the most promising HIV vaccine candidates

- currently in the development pipeline;
- The successful Applicant will reach out to public (e.g., academic and research institutes) and private sector researchers and vaccine Developers from around the world in an open and transparent process to ensure that the most promising vaccine candidates are identified and considered for pilot scale manufacturing within the facility;
 - The successful Applicant will develop and manage an open and transparent process by which HIV vaccine candidates that are suitable and ready for clinical trials are selected and prioritized for manufacture in the facility in accordance with the objectives of the Enterprise and the general principles of CHVI and the specific principles of the facility as set forth in this document and which meaningfully involves leading experts in the field not formally associated with the Applicant (e.g., not a Partner);
 - The objectives of the Enterprise, the general principles of CHVI and the specific principles of the facility will guide the manner by which the successful Applicant will evaluate vaccine candidates to select those to be manufactured in the facility. For example, vaccine candidates should be evaluated on the basis of such factors as, but not limited to:
 - demonstrated evidence of effectiveness in animal models,
 - the ability to manufacture the candidate vaccine (i.e., the vaccine candidate's "manufacture-ability"),
 - secured funding and the capacity to seek ethical approval for clinical trials,
 - ability or capacity to obtain regulatory approval for clinical trials in the countries planned for clinical trials,
 - candidate targeted for HIV in LMICs, and
 - adequate provisions for Global Access;
 - The facility output - clinical trial lots - will be provided to those responsible and authorized for the conduct of the clinical trials as agreed with the vaccine Developer when their vaccine candidate was accepted for manufacturing;
 - A self-sustaining business model will be developed and adopted which does not require additional funding from the Government of Canada or the Gates Foundation beyond the scope of the financial contribution associated with this Invitation to Submit Applications. Applicants may explore other uses of the facility and other mechanisms to achieve self-sustainability provided this is done within an overall not-for-profit framework, and the uses and mechanisms are consistent with the objectives of the Enterprise and the general principles of CHVI and the specific principles of the facility as set forth in this document and do not diminish the Applicant's ability to manufacture HIV vaccine clinical trial lots; and

- The principles of Global Access, as defined in the glossary, will be a foundation for all decision making. The Applicant will outline an approach to ensure that Global Access is fully respected in all aspects of the operation of the facility for the duration of its existence, including appropriate preconditions related to intellectual property issues. Preconditions will be established by the successful Applicant for the acceptance of vaccine candidates from Developers for manufacturing at its facility (i.e., the pilot scale HIV vaccine manufacturing facility funded through the Funding Agreements). These preconditions will require the vaccine Developer to accept contractual obligations guaranteeing that any vaccine candidate making use of the facility would be rapidly and widely available to LMICs at an affordable price and in sufficient quantities should its vaccine candidate be proven safe and effective in efficacy clinical trials. In addition, commitments must be obtained from Developers to ensure that knowledge gained through clinical trials will be promptly and broadly made available to the scientific community .

Description and Capability of the Facility

The facility:

- will be located in Canada;
- will be designed, built (or retrofitted) and operated in compliance with all applicable municipal, provincial, territorial and federal laws and regulations including environmental assessment requirements;
- will operate in accordance with applicable Canadian and foreign Good Manufacturing Practices (GMPs);
- will be subject to regulatory review by applicable Canadian departments and agencies;
- may be co-located with existing infrastructure, such as laboratories or similar manufacturing operations in order to leverage associated facilities (e.g., formulation, filling, packaging, and storage); and
- may only be disposed of in accordance with the provisions specified in the Funding Agreements.

Applicants will identify and describe the technical and operational characteristics and capabilities of the most suitable facility for pilot scale HIV vaccine manufacturing that they can establish within the available budget based on their experience and expertise. Applicants' descriptions should specify such facility characteristics as:

- the manufacturing platforms/technologies that will be employed (e.g., peptide synthesis, mammalian cell culture or bacterial fermentation), etc., as appropriate);
- the candidate technologies that will be accommodated (e.g., DNA vaccines and recombinant subunit vaccines and viral vectors (non-replicating and replication-competent), etc., as appropriate);
- whether it will be capable of simultaneously manufacturing a number of diverse HIV vaccines and, if so, how;
- whether it will be capable of adapting to new vaccine technologies and platforms that currently exist and that may evolve in the future and, if so, how and what implications are associated with such a capability;
- whether the manufacturing platforms can be readily scaled up to increase production of clinical trial lots and to ease the transfer of manufacturing from this facility to full scale (commercial) manufacturing and, if so, how such a capacity may be achieved and what additional risks and considerations would be associated with the enhanced process;
- whether the Applicant believes that the facility should have the capacity for BSL3 accreditation and, if so, to what extent (i.e., the entire facility, a specific portion or portions, at a later date, etc., as appropriate);
- examples of the minimum number of clinical trial lots and their respective sizes that can be manufactured each year given the technical platforms being proposed;
- the process by which appropriate manufacturing processes will be developed and designed for each accepted vaccine candidate in collaboration with its Developer;
- how the Applicant would store clinical trial lots until they can be delivered to locations for clinical trials;
- the process by which the regulatory requirements for clinical trials in appropriate foreign

countries (e.g., certificate of GMPs, notarized certificate of conformance, etc.) will be met during the manufacturing process; and

- the process by which industry standards for productivity and quality will be met from inception to manufactured vaccine.

Roles and Responsibilities

As part of the invitation process, the Applicant will demonstrate its capacity to:

- recruit one or more potential relevant Partners within the public and/or private sectors to assist in implementing the project;
- identify financial or in-kind contributions (from itself and its Partner(s)) and any other potential sources of funding;
- continually monitor advances such as those in the HIV vaccines pipeline and scientific research and manufacturing techniques and secure funding from outside of the Funding Agreements to incorporate these advances in the facility in the future;
- make suitable arrangements to gain access to the land upon which the facility will be established or in the event of an existing facility, to the facility itself;
- identify a business model to ensure the self-sufficiency of the facility; and
- develop a Global Access Plan that clearly describes the commitment to Global Access and how it will be implemented.

The successful Applicant will sign Funding Agreements with the Government of Canada and the Gates Foundation and will:

- design, build (or retrofit) and operate the facility in compliance with all applicable municipal, provincial, territorial and federal laws and regulations including environmental assessment requirements;

- own the facility;
- adhere to the relevant national regulatory authorities applicable to the manufacturing and release of vaccines;
- develop and manage an open and transparent process by which HIV vaccine candidates that are suitable and ready for clinical trials are selected and prioritized for manufacture in the facility in accordance with the objectives of the Enterprise and the general principles of CHVI and the specific principles of the facility and which meaningfully involves leading experts in the field not formally associated with the Applicant (e.g., not a Partner);
- negotiate and conclude agreements with selected HIV vaccine Developers that are consistent with the Funding Agreements, and include among other things intellectual property provisions and commitments to meet the Global Access objectives;
- ensure linkages with key international bodies and vaccine Developers/researchers;
- conduct public relations and communications with domestic and international stakeholders; and
- be an active player in the Enterprise and in the CHVI and conduct itself in a manner consistent with CHVI Guiding Principles.

In order to obtain the specialized expertise and capabilities that it may not have but are required to construct and operate the pilot scale clinical trial lot manufacturing facility, it is anticipated that the successful Applicant will partner with one or more organizations. The Partner(s):

- may be public or private sector organizations and/or individuals with experience in some or all of the following:
 - HIV research,
 - vaccine research,
 - design, construction/retrofit, licensing and/or operations of a relevant manufacturing facility, and
 - working with LMICs in the areas of scientific research (preferably HIV/AIDS related) or vaccine development and manufacturing, or
 - creating synergy by bringing together activities such as, but not limited to:

- not-for-profit and private sector expertise,
 - research and manufacturing expertise,
 - researchers from LMICs and Canada, or
 - scientific researchers from various fields of study; and
- will deliver specific activities according to the negotiated agreement between the Partner(s) and the Applicant.

OVERVIEW OF THE INVITATION PROCESS

This Invitation to Submit Applications (ISA) has been developed as a result of a thorough consultation process. It solicits responses from Applicants interested in establishing and operating a pilot scale HIV vaccine manufacturing facility in Canada. The ISA is a results oriented process and Applicants are expected to provide details such as how, where and when the facility will be established and operated in their Applications.

Responses will be solicited in two stages. Initially, an interested Applicant will provide a Letter of Intent (LOI) by completing the LOI Form provided. The completed LOI will clearly identify the NPC and demonstrate its capability to establish and operate the envisioned facility. Those Applicants deemed most capable to undertake the project as determined by the review committee described in the next paragraph will then be invited to submit an Application which details the facility and its operation. Applications will be submitted by completing the Application Form that will be provided to those Applicants deemed most capable on the basis of their completed LOIs.

A review committee established by the Government of Canada and the Gates Foundation will formally evaluate the Letters of Intent and Applications received against the criteria defined in a subsequent section of this ISA document. The review committee will be comprised of technical experts internal and external to the Government of Canada and the Gates Foundation. Following evaluation of the Letter of Intent submissions, the review committee will recommend to the Government of Canada and the Gates Foundation those Applicants most suitable to be invited to submit Applications. Applicants and their submissions will be reviewed in light of the key objectives and principles as well as specific evaluation criteria. Key evaluation criteria will include such factors as methodology, capability, cost, feasibility, self-sustainability, adherence to Global Access and budget details. Following evaluation of the Applications, a recommendation will be made to the applicable government Ministers and the Gates Foundation. Funding for this project is conditional upon the successful Applicant entering into two Funding Agreements to establish and operate the facility – one with the Government of Canada and one with the Gates Foundation.

The Government of Canada funds will be administered by the Public Health Agency of Canada in a manner consistent with Treasury Board's Transfer Payment Policy, and Public Health Contribution Program Terms and Conditions and in a manner consistent with the Funding Agreements with the successful Applicant. The Gates Foundation funds will be administered by it in a manner consistent with applicable legal requirements, as well as its internal policies and practices and consistent with the Funding Agreements.

ELIGIBILITY

To be eligible for funding, Applicants must meet the following:

- be a Not-for-Profit Corporation (NPC) incorporated under appropriate legislation, or act of parliament or foreign equivalent for non-Canadian corporations;
- have structure, governance and funding arrangements that allow objective execution of its not-for-profit mandate;
- are competent, credible and accountable in carrying out activities;
- are guided by objectives and principles consistent with CHVI objectives;
- have an elected, voluntary Board of Directors; and
- bear a portion of the costs associated with this initiative, particularly for its ongoing operations, through the contribution of its own funds and/or the contribution of funds and/or in-kind contributions to the facility that it attracts from others.

A university, post-secondary college or educational institution is considered eligible if it has its own board of directors.

The geographic location of the Applicant's headquarters will not be restricted although the location of the facility must be in Canada. While the NPC is not required to be headquartered in Canada, it should have a presence in Canada.

For-profit organizations and not-for-profit organizations that are agencies of government will not be eligible for funding. However, it is expected that the Applicant will partner with for-profit and other organizations and/or individuals to access the necessary expertise and resources for this project.

An Applicant that is not certain whether it is eligible should contact the contact person named in the Notes to Applicants section for assistance in determining its eligibility. The contact person may request additional information to make a determination.

FINANCIAL

Funding

The maximum amount of funding available from the Government of Canada and the Gates Foundation for this project to establish a pilot scale HIV vaccine manufacturing facility is \$88M³. This amount includes Government of Canada and Gates Foundation funding of \$60M³ and \$28M³ respectively. Applicants will provide a detailed budget associated with these funds. It is expected that the funds will be paid out over four years subject to the terms of the Funding Agreements. At present, this period is anticipated to be May 2009 to March 2013 but will be confirmed at the time that the Funding Agreements are signed. Although the Funding Agreements will be for a four-year period, certain conditions dealing with the use and disposal of the facility may extend for approximately 20 years following the expiry or termination of the Funding Agreements to ensure that the facility continues to be used for the purposes for which funding was provided (i.e., consistent with the principles of CHVI). In addition to the contribution provided by the Government of Canada and the Gates Foundation, the successful Applicant (i.e., a Not-for-Profit Corporation (NPC)) is expected to attract and provide additional funding from other public and/or private sector sources to establish, operate, maintain and sustain the facility.

³ All monetary amounts in this Invitation to Submit Applications are in Canadian dollars unless otherwise annotated.

Applicant Contribution

The successful Applicant will be expected to bear a portion of the associated costs through the contribution of its own funds and/or in-kind contributions to the facility, particularly for its ongoing operation. The Applicant is expected to seek funding from other sources. Funding and planned funding from other sources must be disclosed in the Application. The Applicant's capability in this regard will be a factor in the evaluation of its Application.

Eligible Expenses

Eligible expenses include such necessary and reasonable costs that relate directly to the establishment of a pilot scale HIV vaccine manufacturing facility. They may include, but are not limited to, costs of personnel, travel and accommodation, design costs, costs of environmental reviews/assessments, construction and/or retrofit costs, costs of services and equipment rentals and licensing and certification costs.

The Government of Canada cannot fund start-up costs such as, but not limited to, initial recruitment and training of facility staff and training materials and supplies. However, such start-up costs are eligible expenses for funding from the Gates Foundation.

Ineligible Expenses

Ineligible expenses include but are not limited to:

- the costs associated with the preparation and submission of the Letter of Intent and Application ; and
- operating expenses such as the costs of vehicle purchases, rent and utilities and material and supplies related to ongoing operations. Some of these expenses may be eligible for partial funding as overhead or indirect costs from the Gates Foundation.

INVITATION AND APPROVAL PROCESSES AND TIME LINES

General

The invitation and approval processes and associated time lines are summarized as follows:

- Invitation Process:
 - Stage 1 - Letter of Intent (LOI) - April 15, 2008 to June 10, 2008
 - Stage 2 - Application - July 8, 2008 to late October 2008

- Approval Process - October 2008 to May 2009

It is expected that the design and construction/retrofit of the facility and the required certification and licensing will occur from approximately May 2009 to March 2013. This is the expected term of the Funding Agreements although certain conditions of the Funding Agreements dealing with the use and disposal of the facility may extend for approximately 20 years following the expiry or termination of the Funding Agreements to ensure that the facility continues to be used for the purposes for which funding was provided (i.e., consistent with the principles of CHVI).

Invitation Process (April 15, 2008 to late October 2008)

The process involves the following two stages:

Stage 1: Letter of Intent (April 15, 2008 to June 10, 2008)

In this stage all Applicants must complete a Letter of Intent (LOI). The LOI will be reviewed to determine the eligibility of the organization and its capability to create a pilot scale HIV vaccine manufacturing facility in Canada for clinical trial lots (see LOI document for details). The Canadian International Development Agency, Public Health Agency of Canada, Industry Canada and the Gates Foundation, having regard to the recommendations of the review committee on eligibility and capability, will select Applicants to submit an Application for Funding. Only successful LOI Applicants may be invited to submit an Application for funding. Unsuccessful Applicants will be notified in writing once a decision has been made.

Stage 2: Application (July 4, 2008 to late October 2008)

Selected Applicants who have successfully completed the LOI stage will be invited to submit an Application. Completing the Application will require each selected Applicant to fully define its organizational, management, technical, business and financial plans as detailed in the Application Form document.

Approval Process (October 2008 to May 2009)

Following its evaluation, the review committee will make recommendations to the Funding Authorities. The Funding Authorities have final approval over selection of the successful Applicant and the Funding Agreements. It is anticipated that it may take up to seven months for the final approvals to be obtained and the Funding Agreements to be negotiated. Consequently it is expected that the Funding Agreements with the successful Applicant should be finalized by April 2009 and the project should begin by May 2009.

LETTER OF INTENT AND APPLICATION REVIEW CRITERIA

The LOI Form and Application Form outline the type of information that should be provided by the Applicant. In addition to the completeness of the information provided, the following criteria will be used to assess completed LOI Forms and Application Forms, as applicable:

Applicant and Partner Information, Understanding and Commitment:

- the relevance of the Applicant's corporate background and general corporate description to this project;
- the extent to which the Applicant has successfully completed relevant programs, activities and/or initiatives;
- the similarity of the Applicant's values and principles to those of the Enterprise and CHVI;
- the clarity and completeness of the Applicant's Strategic Plan and its relevance to this project;
- the qualifications of the Applicant's Board of Directors;
- roles, responsibilities and contributions of any and all Partners are clearly explained with complementary strengths explained and evident and all necessary experience to complete this project is available from the Applicant or its Partner(s);
- the Applicant demonstrates that any and all proposed partnerships are appropriate and strategic for the activities proposed and will contribute to successfully achieving the

project/implementation of project activities;

- the qualifications and capabilities of any and all Partners and their fit with the Applicant;
- the quality of any and all formal agreements with Partners (e.g., completeness, consistency with CHVI's principles, etc.);
- ability of the Applicant and/or its Partner(s) to communicate with the public and vaccine candidate Discoverers/Developers in both official languages of Canada in accordance with the Treasury Board Policy on Official Languages for Transfer Payments;
- compliance with the Conflict of Interest Act, Values and Ethics Code for the Public Service and its predecessor Code⁴;
- the degree to which the Applicant demonstrates an understanding of key objectives, minimum requirements, issues, opportunities and challenges; and
- the Applicant's demonstrated commitment to the principles behind this project such as Global Access (which includes appropriate intellectual property ownership and management strategies), facility ownership, financial security and self-sustainability .

Applicant/Partner Experience and Capability:

- the quality and breadth of the demonstrated experience that the Applicant and/or its Partner(s) has/have in commercial vaccine development and manufacturing;
- the quality and breadth of the demonstrated experience that the Applicant and/or its Partner(s) has/have with HIV/AIDS research;
- the quality and breadth of the demonstrated experience that the Applicant and/or its Partner(s) has/have engaging with LMICs in the areas of scientific research (preferably HIV/AIDS-related) or vaccine development and manufacturing;
- the quality and breadth of the demonstrated experience the Applicant and/or its Partner(s) has/have in bringing together disparate activities and talents to create a result that would not have been otherwise achievable; and
- the quality and breadth of the demonstrated experience the Applicant and/or its Partner(s) has/have with regulatory approval processes (e.g., operating GMP compliant facilities, operating a BSL 2 or 3 facility, etc.) in Canada and foreign locations where clinical trials can be expected to be conducted.

⁴ These references are to Government of Canada legislation and policies.

Management Details and Work Plan:

- the quality of the Applicant's proposed organizational structure, reporting relationships and key individuals for the Applicant's proposed Establishment Team and on-site personnel;
- the adequacy of the linkages described between the Applicant, its Partner(s), the Establishment Team and on-site personnel;
- the clarity and completeness of the responsibilities described for individuals for the various functions and activities and the quality of their stated qualifications;
- the proposed work plan and schedule are detailed, realistic, feasible, consistent with requirements and measurable;
- adequate performance management provisions are described;
- suitable provisions for performing liaison with the Government of Canada and the Gates Foundation are described;
- the extent to which a thorough understanding of the regulatory environment is shown;
- the degree to which the Applicant is able to meet the criteria related to facility ownership and land ownership or access;
- the clarity and completeness of the Applicant's concept for operating and maintaining the facility and its consistency with the objectives of the Enterprise and CHVI;
- the suitability of the described interfaces with the Enterprise, LMIC scientific researchers and/or vaccine Developers/manufacturers and other parties;
- the appropriateness and quality of criteria and processes described for identifying and selecting vaccine candidates;
- the quality of governance that will be applied to the Applicant's efforts; and
- the quality of the proposed approach for administrating the establishment and operation of the facility.

Technical Details:

- the adequacy of the description of the proposed location of the facility, its size, design layout, features (e.g., independent master seed and product seed areas, independent fermentation areas, independent down stream purification areas and independent fill, finish and lyophilization areas), capability, capacity, processes, process flow and change-over procedures from one product to another;
- examples of the minimum annual clinical trial lot manufacturing capacity of the facility given the technologies proposed by the Applicant to be used;
- the types and range of manufacturing platforms/technologies that will be employed (e.g., peptide synthesis, mammalian cell culture or bacterial fermentation), etc.;
- the types and range of candidate technologies that will be accommodated (e.g., DNA

vaccines and recombinant subunit vaccines and viral vectors (non-replicating and replication-competent), etc.);

- the adequacy of the description of the different technologies/processes that are anticipated to be performed in the facility and whether they will be performed in parallel or simultaneously;
- the capacity of the facility to simultaneously manufacture vaccines using different technologies that could reasonably be anticipated to accommodate HIV vaccine candidates now and in the future;
- the capacity of the facility to promote containment and to prevent mix-ups and contamination;
- the capacity of the manufacturing platforms to be readily scaled up to increase production of clinical trial lots and to ease the transfer of manufacturing from this facility to full scale (commercial) manufacturing and the manner by which this would be accomplished;
- the technical and manufacturing provisions incorporated to ensure that a successful vaccine candidate can subsequently be successfully manufactured at a full scale (commercial) manufacturing facility;
- the implications of the additional risks and considerations associated with any scalable production capability related to clinical trial lots and the ease of the transfer of manufacturing from this facility to full scale (commercial) manufacturing;
- the adequacy of the details of the common services needed to support the diverse manufacturing platforms/technologies and the description of how access to these services will be managed; and
- the adequacy of the description of supporting elements such as, but not limited to, work control systems, records management systems, inventory control systems, quality assurance plans and GMPs for clinical trial vaccines.

Global Access Plan:

- the degree to which the described provisions to ensure Global Access as defined in the Invitation to Submit Applications, as well as the development of pathways and strategies meant to ensure that the Global Access objectives are met, are consistent with objectives of the Enterprise and CHVI;
- the appropriateness of the described process, the composition of the Applicant's associated review committee, the evaluation criteria by which vaccine candidates will be identified and selected in order that they address and adhere to Global Access requirements, and the structure of the relationships with the related Discoverers/Developers; and
- the extent to which the described provisions for the management of technologies and intellectual property rights (which will include clearly defined provisions stating the ownership and other rights of the successful Applicant and those of the vaccine candidate Discoverer/Developer with respect to licensing of the vaccine and licensing of proprietary manufacturing technologies regarding both LMICs and non-LMICs) are relevant and

appropriate.

Financial Details and Self-Sustainability Plan:

- demonstrates the financial resources and stability to effectively manage the project (e.g., operational cash flow requirements);
- demonstrates a proven capability in managing financial obligations and reliably secure funding;
- maximizes financial and in-kind contributions to be made by the Applicant and/or its Partner(s);
- describes a plan to avoid cost overruns;
- the extent to which the proposed budget (preliminary and final) clearly breaks out applicable major categories of facility establishment costs such as, but not limited to, design, construction/retrofit, laboratory equipment, manufacturing equipment, facility validation/certification, etc.;
- the extent to which the proposed budget (preliminary and final) clearly breaks out applicable major categories of facility start-up costs such as, but not limited to, initial hiring/recruitment, initial training and training supplies and materials, etc.;
- the extent to which the proposed budget (preliminary and final) clearly breaks out applicable major categories of facility operating costs such as, but not limited to, governance, utilities, rent, hiring, personnel, travel, material, etc. and associated cost schedule;
- the extent to which the proposed budget clearly differentiates between establishment (i.e., construction/ retrofit), start-up and operating costs, as applicable;
- the extent to which funding expenditure estimates (i.e., basis of payments) for the duration of the Funding Agreements are consistent with the proposed budget and progress on activities;
- the degree to which the Applicant offers value for money for the funding requested; and
- the quality of the self-sustainability plan and its ability to achieve its objective (i.e., self-sustainability) as supported by pro forma income statements including identification of funding sources over the proposed operation of the facility.

FUNDING AGREEMENTS

The successful Applicant will be required to sign formal Funding Agreements with the Government of Canada and the Gates Foundation. Under the terms of the Funding Agreements, the Applicant will be required, among other things, to:

- indemnify the Crown and the Gates Foundation for any loss, claim or damages resulting from

the Applicant's and/or its Partner's(s') creation (or establishment), operation of the facility including the manufacture and use of clinical trial lots;

- meet administrative requirements, such as, but not limited to, financial and narrative reporting, progress reporting, and other monitoring activities;
- provide a financial plan that describes how the Applicant will plan, monitor, control, record and verify revenues and expenditures during the term of the Funding Agreements;
- submit monthly progress and cash flow reports;
- submit a monthly reconciliation report with the established milestone payment schedule;
- submit a final report upon successful establishment of the facility;
- participate in on-site visits during establishment of the facility, as required;
- conduct/participate in periodic evaluations to determine the impact of CHVI funding;
- agree to conditions related to the disposal of the facility; and
- on an ongoing basis, for a period of approximately 20 years after expiry of the Funding Agreements, submit productivity/activity reports during facility operations in accordance with the terms and conditions of the Funding Agreements.

Terms and Conditions

It is expected that the Funding Agreements with the successful Applicant will last from approximately May 2009 to March 2013. However, certain conditions of the Funding Agreements dealing with the use and disposal of the facility are expected to extend for approximately 20 years following the expiry or termination of the Funding Agreements to ensure that the facility continues to be used for the purposes for which funding was provided (i.e., consistent with the principles of CHVI

Audit

The Government of Canada and the Gates Foundation may conduct audits and/or evaluations of any aspect of the work associated with these Funding Agreements up to six years following its expiration or termination. Audit details will be outlined in the Funding Agreements.

ADMINISTRATIVE CONTACT

For further information, please contact:

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