Health Canada Santé Canada

November 7, 2011

Notice

Our reference number: 11-120556-783

Release of the Draft Guidance Document: Clinical Trial Sponsors - Clinical Trial Applications

Health Canada is please to announce the release of the *Draft Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*. This Guidance serves to assist sponsors in seeking authorization from Health Canada to conduct a clinical trial with a drug (pharmaceutical and/or biologic and radiopharmaceuticals) in human subjects pursuant to Part C, Division 5 of the *Food and Drug Regulations*. This guidance document clarifies application and post-authorization requirements and procedures.

Noteworthy updates include:

- Harmonizing Module 1 with the newly proposed Common Technical Document (CTD) format (please refer to the draft consultation document entitled "*Revised draft guidance document preparation of drug submissions and applications in the common technical document (CTD) format*" posted on the Health Canada website;
- Outlining application requirements with respect to comparative bioavailability studies for pharmaceuticals;
- Providing additional guidance on clinical and quality amendments vs. notifications;
- Adding filing requirements for the importation of clinical trial drugs;
- Elaborating on adverse drug reaction (ADR) reporting criteria and;
- Changing the policy on the 7 day administrative review target.

The document is being released for a 90-day comment period. Health Canada will review the comments received during this comment period and revise the Guidance as necessary. A final version of this document will then be posted.

This consultation is open for comment starting November 7, 2011 until February 4, 2012. Please submit your comments via email, fax or by mail to:

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Health Canada Santé Canada

DRAFT GUIDANCE DOCUMENT FOR CLINICAL TRIAL SPONSORS

Clinical Trial Applications

This guidance document is being distributed for comment purposes only.

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Health Products and Food Branch

Canada

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

Également disponible en français sous le titre : Ébauche de la ligne directrice à l'intention des promoteurs d'essais cliniques - demandes d'essais cliniques

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 *Food and Drugs Act* and supporting regulations provide authority to Health Canada to regulate the sale and importation of drugs for use in human clinical trials in Canada. This document provides guidance on the regulatory obligations pursuant to Part C, Division 5 of the *Food and Drug Regulations* (herein referred to as the *Regulations*), Drugs for Clinical Trials Involving Human Subjects.

1.1 Policy Objectives

To provide Guidance to sponsors seeking authorization to conduct a clinical trial in Canada that supports the protection of clinical trial subjects and contributes to the high standards of excellence in research and development in Canada. This document clarifies application and post-authorization requirements and outlines procedures for obtaining authorization.

1.2 Policy Statements

Clinical trial sponsors must submit a clinical trial application (CTA) to Health Canada for authorization to sell or import a drug for the purpose of a clinical trial.

Clinical trial sponsors must conduct clinical trials according to generally accepted principles of good clinical practice that ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons.

Research Ethics Boards (REBs) have an important role in the oversight of the conduct of clinical trials. Sponsors are required by the *Regulations* to obtain REB approval for each clinical trial site prior to commencing the trial at that site.

The *Regulations* are generally consistent with the principles, definitions and standards found in the International Conference on Harmonisation (ICH) guidance documents on clinical trials. Where inconsistencies exist, the *Regulations* take precedence.

The format for CTAs as outlined in this guidance document is consistent with that used for other types of drug submissions filed to Health Canada, based on the format of the ICH Common Technical Document (CTD). Although the scope of the ICH CTD does not include applications at the clinical research stage of development, the modular format of the CTD is being extended to CTAs to facilitate the preparation of drug submission information throughout the lifecycle of a drug.

1.3 Scope and Application

The information provided in this guidance document is for clinical trials involving drugs (pharmaceuticals and/or biologics and radiopharmaceuticals) in human subjects. In the *Regulations* a clinical trial is an investigation in respect of a drug that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

This guidance document applies to:

- Clinical trials for Phases I through III of drug development and comparative bioavailability studies.
- Clinical trials for marketed drugs where the proposed use of the drug is outside the parameters of the Notice of Compliance (NOC) or Drug Identification Number (DIN) application.
- Clinical Trial Amendments (CTA-A) [C.05.008] and Notifications (CTA-N) [C.05.007].

This guidance document does not apply to clinical trials involving medical devices or natural health products.

1.4 Background

The regulatory requirements respecting drugs to be used for the purposes of clinical trials were originally developed in the early 1960s. On September 1, 2001, the regulatory amendments to Part C, Division 5 of the *Food and Drug Regulations* (Drugs for Clinical Trials Involving Human Subjects) came into force to strengthen protections for clinical trial subjects in Canada.

Health Canada completed a review of the clinical trials regulatory framework through 2006-2008 that included assessing input received from stakeholders, and considering best practices in other countries, as well as Health Canada's experience with the existing regulatory framework (refer to Appendix 2). Subsequently, Health Canada proceeded with a series of initiatives, one of which included consultations on the type of guidance required by industry to assist in meeting regulatory obligations (Spring/Summer 2008). During the consultations, stakeholders noted the need for better guidance on processes, requirements, and roles and responsibilities in clinical trial activities. Stakeholders called for clear and consistent definitions and guidance on the requirements for various types of clinical trials. Clarification was also requested on information requirements for Health Canada to review CTAs within 30 days and on which applications qualify for the seven-day administrative review target.

Additionally, some stakeholders raised concerns regarding the requirements for CTA-As, which they believed to be burdensome to some groups. Respondents identified the need to clarify the regulatory requirements, streamline processes and review the amount of information that is required. In particular, comments indicated that Health Canada should consider limiting full amendment submissions to filing only substantive changes and to further define "minor" and "major" changes.

In response to these consultations, the *Guidance for Clinical Trial Sponsors - Clinical Trial Applications* has been updated to reflect stakeholder concerns and improve clarify and communication. The guidance includes new information for sponsors regarding information needs and processes related to CTAs, CTA-As and notifications.

2 GUIDANCE FOR IMPLEMENTATION

2.1 Abbreviations/Definitions

2.1.1 Abbreviations

ADR	Adverse Drug Reaction
BGTD	Biologics and Genetic Therapies Directorate
CIOMS	Council for International Organizations of Medical Sciences
CR	Central Registry
CTA	Clinical Trial Application
CTA-A	Clinical Trial Application-Amendment
CTA-N	Clinical Trial Application-Notification
CTSI	Clinical Trial Site Information
CTD	Common Technical Document
DIN	Drug Identification Number
DMF	Drug Master File
GCP	Good Clinical Practice
HPFBI	Health Products and Food Branch Inspectorate
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
ITA	Investigational Testing Application
NOC	Notice of Compliance
NOL	No Objection Letter
NSN	Not Satisfactory Notice
PSEAT-CTA	Protocol Safety and Efficacy Assessment Template - Clinical Trial Application
QIS	Quality Information Summary
QIS-PER	Quality Information Summary - Positron-Emitting Radiopharmaceuticals

QIS-R	Quality Information Summary - Radiopharmaceuticals
QIU	Qualified Investigator Undertaking
QOS	Quality Overall Summary
QOS-CE	Quality Overall Summary - Chemical Entities (Clinical Trial Applications)
REB	Research Ethics Board
TPD	Therapeutic Products Directorate

2.1.2 Definitions

Most of the definitions listed below were taken from the *Regulations*, and the Health Canada / ICH Guidance Documents *E6: Guideline for Good Clinical Practice: Consolidated Guideline* (ICH E6) and *E8: General Considerations for Clinical Trials*.

Adverse Drug Reaction: Any noxious and unintended response to a drug that is caused by the administration of any dose of the drug.

Adverse Event: Any adverse occurrence in the health of a clinical trial subject who is administered a drug that may or may not be caused by the administration of the drug, and includes an adverse drug reaction.

Authorized Clinical Trial Application: For the purposes of this document, an authorized clinical trial application is one that has been filed with Health Canada and has been granted a No Objection Letter (NOL).

Clinical Trial: An investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

Clinical Trial Site: The location where trial-related activities are actually conducted.

Date of Commencement of a Clinical Trial: For the purpose of the Clinical Trial Site Information Form, this is defined as the date when the clinical trial site will be ready to enrol patients in the clinical trial.[1]

Drug: For the purpose of this document, a drug for human use that is to be tested in a clinical trial and includes pharmaceuticals, biologics, gene therapies, blood products, vaccines and radiopharmaceuticals. Consistent with the *Food and Drugs Act*, a drug is

[1] Before commencement of a trial, the sponsor must ensure that Health Canada and the Research Ethics Board have raised no objections to the Clinical Trial Application.

defined as including any substance used in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, and in restoring, correcting or modifying organic functions.

Good Clinical Practices: Generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons. These are the good clinical practices referred to in section C.05.010 of the *Regulations.*

Import: To import a drug into Canada for the purpose of sale in a clinical trial.

Importer: The sponsor or person designated by the sponsor who is responsible for the import of the drug into Canada for the purpose of sale in a clinical trial. Individual investigators at the clinical trial sites in Canada may serve as Canadian Importers.

Informed Consent Document/Form[2]**:** Written informed consent, given in accordance with the applicable laws governing consent is obtained from every person before that person participates in a clinical trial but only after that person has been informed of:

a) The risks and anticipated benefits to his or her health arising from participation in the clinical trial; and

b) All other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial.

Institution/Investigator-initiated Clinical Trial: A clinical trial that is initiated and conducted by an institution or an individual investigator. For such trials, the institution or investigator is considered to be the sponsor of the trial and must fill all the regulatory obligations of the sponsor as outlined in the *Regulations*.

Investigator's Brochure: In respect of a drug, a document containing the nonclinical and clinical data on the drug that are described in section C.05.005(e) of the *Regulations*.

Phase I: Clinical trials designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses. Pharmacokinetic studies as well as drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development. Phase I trials are generally conducted in

[2] For further guidance regarding the informed consent process, please see International Conference on Harmonisation E6, in particular section 4.8, and the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, in particular chapter 3.

healthy volunteers, but may be conducted in patients when administration of the drug to healthy volunteers is not ethical.

Phase II: Clinical trials to evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with the drug. If a new indication for a marketed drug is to be investigated, then those clinical trials may generally be considered Phase II trials.

Phase III: Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated. These are intended to gather the additional information about the clinical effectiveness and safety under the proposed conditions of use.

Phase IV: All studies performed within the approved indication after the drug has been approved by the regulator for the market. These studies are often important for optimizing the drug's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the approved indication, for example (e.g.) mortality and morbidity studies, or epidemiological studies.

Protocol: A document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial.

Qualified Investigator: The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and

b) in any other case a physician and a member in good standing of a professional medical association.

Research Ethics Board: A body that is not affiliated with the sponsor, and

a) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being; and

b) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents under the *Immigration Act*, that is composed of both men and women and that includes at least:

i) two members whose primary experience and expertise are in scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline,

ii) one member knowledgeable in ethics,

iii) one member knowledgeable in Canadian laws relevant to the biomedical research to be approved,

iv) one member whose primary experience and expertise are in a non-scientific discipline, and

v) one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted.

Senior Medical or Scientific Officer: A scientific or medical officer residing in Canada, representing the sponsor, who is responsible for providing an attestation with respect to the Clinical Trial Application/Amendment at the time of filing, as outlined in Appendix 3 of the Drug Submission Application Form (HC/SC 3011).

Serious Adverse Drug Reaction: An adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death.

Serious Unexpected Adverse Drug Reaction: A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.

Sponsor: An individual, corporate body, institution or organization that conducts a clinical trial. The sponsor must comply with its obligations as set out in the *Regulations* (C.05.010-C.05.015) in adhering to good clinical practices for the proper use of the drugs, drug labelling requirements, record keeping, submission of information, reporting of ADRs, and trial discontinuation reporting requirements.

2.2 Pre-Clinical Trial Application (CTA) Consultation Meeting

Health Canada invites sponsors to request a pre-CTA consultation meeting. Such consultations may be particularly useful for new active substances or applications that will include complex issues that may be new to Health Canada.

The pre-CTA consultation meeting provides an opportunity for the sponsor to present relevant data, discuss concerns and issues regarding drug development. It also gives Health Canada an opportunity to provide guidance on the acceptability of the proposed trial(s). Sponsors may invite the qualified investigator(s) who will be involved in the proposed trial(s) in Canada to attend the meeting.

2.2.1 Request for a Pre-Clinical Trial Application (CTA) Consultation Meeting

Requests for a pre-CTA consultation meeting should be submitted in writing by the sponsor to the appropriate Directorate (refer to Appendix 1).

Requests should be submitted in the form of a cover letter proposing four dates and times suitable for a pre-CTA consultation meeting. The cover letter should be accompanied by the following information:

- A brief synopsis of the proposed study;
- A list of questions to be addressed by the Directorate during the meeting; and
- Sufficient information for Health Canada to assess the utility of the meeting and identify the appropriate staff necessary to discuss the proposed issues. This will assist in ensuring efficient use of Health Canada resources.

The Directorate will acknowledge the request for consultation. If the Directorate agrees with the request, the acknowledgement letter will indicate the number of copies of the pre-CTA information package to be provided and confirm the pre-CTA consultation meeting date.

2.2.2 Pre-Clinical Trial Application (CTA) Information Package

The Information Package should contain:

a) proposed agenda, any prepared slides, and a complete list of attendees
[it is recognized that the slides may change prior to the meeting]

b) a brief summary of all data including:

i) a tabular listing of completed nonclinical and clinical studies,

ii) an outline of the observed toxicological manifestations and a discussion of their impact on the use of the drug in humans,

iii) an outline of the observed adverse events and a discussion of potential safety problems;

c) a proposed global clinical plan for the current stage of drug development including regulatory status in other countries;
[It is recognized that this plan is subject to change as new information becomes available.]

d) details of the proposed clinical trials to be conducted in Canada, within the scope of the intended CTA, including:

i) a statement of trial design,

ii) parameters, values, ranges or limits for indication(s) and clinical use(s), patient study population(s) and routes of administration,

iii) parameters, values, ranges or limits for dosage form(s), dosage regimen(s) and formulation(s),

iv) proposed procedures and/or criteria for patient monitoring, clinical efficacy and safety assessments, alternative treatments, premature patient discontinuation and other considerations, as appropriate;

e) a summary of significant Quality (Chemistry and Manufacturing) aspects of the drug;

i) a listing of all production site(s) - **only for biologics and radiopharmaceuticals**,

ii) a summary of the method of manufacture for both drug substance and dosage form,

iii) relevant flow charts,

iv) a listing of quality control procedures and specifications, and

v) a summary of product characteristics.

Should the pre-CTA package be found deficient, the sponsor may be requested to reschedule or postpone the meeting to allow the sponsor to assemble a more thorough package. Please note that the Directorate reserves the right to modify or truncate the proposed agenda as it sees fit to better achieve the stated goals of the meeting.

2.2.3 Pre-Clinical Trial Application (CTA) Consultation Meeting Record

The sponsor should prepare and send to the appropriate Directorate a written record of the discussions and conclusions of the consultation meeting within 14 days of the consultation date. All records of this consultation will be added to the Central Registry (CR) file for the drug.

Meeting minutes approved by all parties in attendance at the meeting should be included in the subsequent CTA.

2.3 Clinical Trial Applications (CTAs)

The sponsor must file a CTA **prior** to the initiation of the trial [C.05.005]. CTAs are required for human drug clinical trials in Phases I through III of drug development and comparative bioavailability studies; this includes trials involving marketed drugs, where the proposed use of the drug is outside the parameters of the NOC or DIN, e.g., one or more of the following is different:

a) Indication(s) and clinical use;

b) Target patient populations(s);

c) Route(s) of administration; or

d) Dosage regimen(s).

Sponsors are *not* required to file a CTA for clinical trials involving marketed drugs where the investigation is to be conducted within the parameters of the approved NOC or DIN [C.05.006(2)]; these trials are referred to as Phase IV clinical trials.

Sponsors must conduct all clinical trials, including Phase IV trials, in accordance with the principles of GCPs [C.05.010] and obtain REB approval.

2.3.1 Filing a Clinical Trial Application (CTA)

CTAs should be sent directly to the appropriate review Directorate (refer to Appendix 1).

The outer label should be clearly identified with "**Clinical Trial Application**".

2.3.1.1 Joint Reviews

CTAs or CTA-As that involve the use of:

i) pharmaceuticals **and** biologics or radiopharmaceuticals;
ii) a medical device and drug combination that is classified as a drug; or
iii) a natural health product and a drug, must be submitted to the appropriate lead Directorate / Bureau **in duplicate**.

Authorization for the sale and importation of all investigational products to be used within a CTA or CTA-A must be obtained prior to the initiation of the clinical trial or implementation of the protocol amendment.

The lead Directorate / Bureau will be responsible for communicating the regulatory decision to the sponsor.

For CTAs that involve the use of an unlicensed class 2, 3, or 4 medical device, a separate ITA and CTA must be filed and authorized before the trial can commence.

2.3.2 Clinical Trial Application (CTA) Format

The CTA is composed of three parts (modules):

- Module 1 - contains administrative and clinical information about the proposed trial;
- Module 2 - contains Quality (Chemistry and Manufacturing) summaries about the drug product(s) to be used in the proposed trial; and
- Module 3 - contains additional supporting Quality information.

The CTA should be submitted in hard copy and in electronic copies in a file format accepted by Health Canada. In accordance with electronic specifications, all documents should be submitted in electronic format and must be identical to the hard copies provided in the CTA.

Refer to Appendix 2 for guidance documents that may be useful in the preparation of the application.

For Biologics and Radiopharmaceuticals: if the CTA contains both Clinical and Quality (Chemistry and Manufacturing) information, Module 1 (Administrative / Clinical Information) should be submitted in **duplicate**.

Module	Type of submission	Contents of submission package
1		**Administrative and Product Information for Canada**
1.0		**Correspondence**
1.0.1	**CTA/CTA-A**	Cover letter For CTA-As, a cover letter indicating the original CTA(s) and previous CTA-As with file number and control number(s).
1.0.5	**CTA/CTA-A**	Meetings Including e.g., a copy of the record of the discussions and conclusions of the pre-CTA consultation meeting or other relevant correspondence with Health Canada, if applicable.
1.1	**CTA/CTA-A**	Table of Contents A listing of the contents of Module 1 (Administrative / Clinical Information), Module 2 (Common Technical Document Summaries) and Module 3 (Quality), if applicable.
1.2		**Administrative Information**
1.2.1	**CTA/CTA-A**	Application Forms A completed and signed Drug Submission Application Form (HC/SC 3011) including Appendix 3, signed by the Senior Medical or Scientific Officer in Canada and the Senior Executive Officer. (Appendices 1 and 2 of the HC/SC 3011 Form should be completed and submitted if applicable). Please refer to Appendix 2 of this document for the relevant URL address. For Institution/Investigator-initiated clinical trials, Appendix 3 of the Drug Submission Application Form (HC/SC 3011) may be signed by the appropriate Department head in lieu of the Senior Executive Officer and the Qualified Investigator in lieu of the Senior Medical or Scientific Officer.

1.2.3	**CTA/CTA-A**	Certification and Attestation Forms Including a Letter of Attestation for electronic documents in accordance with the electronic specification requirements for CTAs and CTA-As (refer to Appendix 2 for link).
1.2.5.1		Clinical Trial Site Information
	CTA	The Clinical Trial Site Information (CTSI) Form should be provided for each proposed clinical trial site, if known at the time of the application as per C.05.005(c). The CTSI Form must be submitted prior to commencement of a clinical trial. Please refer to section 2.7.3 for additional information. If any changes are made to the CTSI Form (for example, change of qualified investigator) a revised CTSI Form should be submitted.
	CTA-A (Clinical)	An updated CTSI form should be provided for each site participating in the clinical trial to report that the amendment has been implemented. Health Canada recognizes that not all information required in the CTSI form may be available at the time of filing a CTA-A. In this case, sponsors are requested to state a commitment to filing the completed form prior to implementation of the amendment at a site as per C.05.008(c). Please see section 2.7.3 for additional information.

1.2.6	**CTA/CTA-A**	Authorization for Sharing Information Letters authorizing Health Canada to access related files (for example, a previously authorized CTA, Drug Master Files, Manufacturing Site Reference Files), if applicable. For example, a letter of access may be required to satisfy requirements for a CTA if a sponsor is utilizing a drug in a clinical trial that has not received a NOC and/or a DIN and the manufacturer of the drug does not wish to disclose confidential information about the drug to the clinical trial sponsor. **Reference to a Drug Master File (DMF):** - A letter written by the holder of the DMF permitting Health Canada to reference information in the DMF in support of the sponsor's CTA should be submitted. - The CTA sponsor should ensure that the supporting DMF (including submission of the letter of access and payment of related fees) has been submitted to and accepted by Health Canada prior to filing a CTA. **Reference to an application previously submitted to and authorized by Health Canada:** - A letter written by the sponsor of the referenced application authorizing Health Canada to access the information in support of the sponsor's CTA should be submitted. - The referenced information should meet the regulatory requirements for CTAs. - The letter of access should include the file number and control number(s) of the referenced submission(s). **For Pharmaceuticals:** Where chemistry and manufacturing information is referenced, sponsors are still required to complete the appropriate Quality Overall Summary (QOS) template (Module 2, [2.3]) including the introduction and any sections not covered by the letter of access.
1.2.7	**CTA/CTA-A (Clinical)**	International Information Information regarding refusals by regulatory authorities outside Canada, if applicable.

1.2.9	**CTA/CTA-A**	Other Administrative Information This section is for any administrative information that does not have a designated location in the CTD format. This section should NOT contain any scientific information.
1.3		**Product Information**
1.3.4		Investigator's Brochure for Clinical Trial Applications (CTA)/CTA-A
	CTA	A copy of the current Investigator's Brochure (IB), supplemented as appropriate with up-to-date safety, non-clinical and clinical data. The IB containing all information regarding the product to date should be prepared in accordance with the ICH E6, and should be reviewed at least annually and revised as necessary. If the IB has been updated relative to a version contained within a previously authorized CTA or CTA-A, a tabulated summary of the changes should be provided, including a rationale for each change that includes any omissions or deletions from previous versions. Sectional reports should not be submitted unless requested. Please refer to section 2.8.4 for additional information. For products marketed in Canada, a reference to the Canadian Product Monograph (PM) may be submitted if an updated IB is not available.
	CTA-A (Clinical)	If the CTA-A proposes to extend the duration of the trial, an updated IB with supporting toxicological studies and clinical safety data to support the extension should be provided. The amendment to the IB may be included as an addendum.
	CTA-A (Quality)	**For Biologics and Radiopharmaceuticals only:** a revised IB or an Addendum to the IB describing any new Quality (Chemistry and Manufacturing) information, including supporting data as required, if applicable.
1.4		**Health Canada Summaries**
1.4.1	**CTA**	Protocol Safety and Efficacy Assessment Template - Clinical Trial Application (PSEAT-CTA) A Protocol Synopsis in the format of the Protocol Safety and Efficacy Assessment Template - Clinical Trial Application (PSEAT-CTA).

1.7		**CTA Specific Requirements**
1.7.1		Protocol
	CTA	A copy of the final proposed protocol(s), including version number.
	CTA-A (Clinical)	A copy of the **amended or working protocol** with a clear description of the changes that are being proposed (that is, original wording vs. revised wording), a rationale for ***each*** proposed change, and a copy of the most recently authorized protocol, including version number. The changes may be listed in a separate document or an annotated version of the protocol. Cross-referencing is not acceptable.
1.7.2		Informed Consent Forms
	CTA	A copy of the Informed Consent Forms/Document(s) (ICDs) to be used in conjunction with the clinical trial, including a statement regarding the risks and anticipated benefits to the clinical trial subjects as a result of their participation in the clinical trial. ICDs to be used in conjunction with the clinical trial should be prepared in accordance with applicable laws governing consent. The ICH E6 and the Tri-Council Policy Statement (TCPS) provides standards for the ICD.
	CTA-A (Clinical)	The revised ICDs must be submitted if the changes to the study protocol(s) or other supporting documentation (nonclinical study results, adverse events, revisions to the IB) affect the information in the ICD. The ICD with changes clearly indicated (annotated) should be provided.
1.7.3	**CTA/CTA-A (Clinical)**	Research Ethics Board (REB) Refusals The name, address and telephone number and, if applicable, the fax number and electronic mail address of any REB that has previously refused to approve the clinical trial protocol or amendment, its reasons for doing so and the date on which the refusal was given, if known at the time of submitting the application as per C.05.005(d) and C.05.008(c). Please refer to section 2.7.1 for additional information.

1.7.4	**CTA/CTA-A**	Information on Prior-related Applications A list of ongoing clinical trials in Canada for which authorization has been granted by Health Canada, if applicable.
2		**Common Technical Document Summaries** This module contains Quality (Chemistry and Manufacturing) Information only. **This section does not apply if the drug product to be used in the clinical trial has received a NOC and/or DIN and has not been modified.** If the Quality information was previously submitted to, and authorized by, Health Canada and **has not changed**, re-submission of the applicable Quality Summary may not be required. However, sponsors should refer to the control number of the prior application.
	CTA-A (Quality)	The Common Technical Document Summaries Module should include: An applicable updated Quality Overall Summary (QOS) or Quality Information Summary (QIS). The rationale for each proposed change should be submitted. Revised information should be clearly identified. The changes may be listed in a separate document or a marked up annotated version of the QOS/QIS-R/QIS-PER, as applicable. Cross-referencing is not acceptable.
2.1	**CTA/CTA-A (Quality)**	Common Technical Document Table of Contents A listing of the contents of Modules 2 and 3, if applicable.
2.2		

2.3	**CTA**	Quality Overall Summary (QOS) a) **For Pharmaceuticals:** a QOS is required (refer to Appendix 2 for links). b) **For Biologics and Radiopharmaceuticals:** There are four QOS guidance documents to be used as direction for the completion of the quality section for biologic drug submissions and two QIS (Quality Information Summary) templates for radiopharmaceutical drug submission applications (refer to Appendix 2 for links). The applicant should submit a completed QOS/QIS with, as a minimum, those subsections or parts which have a check mark (✓) beside the guidance or heading, including the facility information. Note that these guidances were not written specifically for CTAs and may not necessarily apply to the same extent. It is understandable that depending upon the stage of drug development, a limited amount of information may be available for a CTA; in which case, the sponsor should provide whatever data are available at that time. Sponsors should also refer to the applicable Health Canada quality guidance documents and updated notices for additional information. c) **For Placebo-controlled studies:** a qualitative list of the ingredients in the placebo should be submitted.
3		**Quality** (if submitted)
3.1	**CTA/CTA-A (Quality)**	Table of Contents of Module 3 A listing of the contents of Module 3.
3.2	**CTA/CTA-A (Quality)**	Body of Data Where there is additional supporting quality information to that provided in the QOS-CE (Module 2), this information should be provided separately in the appropriate Module 3 section and cross-referenced in the applicable QOS/QIS. Sponsors should refer to the applicable Health Canada quality guidance documents for additional information. **For Biologics and Radiopharmaceuticals:** For a product early in development, submission of Module 3 is not always necessary if sufficient information is provided in the QOS/QIS-R/QIS-PER, as appropriate.

3.3	**CTA/CTA-A (Quality)**	Literature References Literature references related to quality information should be provided here if applicable.

2.3.3 Comparative Bioavailability Trial Application Requirements

This section outlines the application requirements for sponsors wishing to conduct comparative bioavailability studies for pharmaceuticals only where:

- The studies are performed on healthy adult volunteers;
- The reference drug product is marketed in Canada, United States, European Union, Australia, Switzerland or Japan; and
- The maximum single or total daily dose of the study drug does not exceed that specified in the labelling of the reference drug product; or the simultaneous administration of a radioactive labelled and unlabelled drug product.

This section does not apply to biologics, radiopharmaceuticals and cellular therapies, which includes Phase I trials using somatic cell therapies, xenografts, gene therapies, prophylactic vaccines or reproductive and genetic technologies. Additionally, this section does not apply to comparative bioavailability studies involving different formulations of investigational drugs or comparing different routes of administration (please refer to section 2.3.2 for filing requirements).

CTAs for comparative bioavailability studies should be filed directly to the Therapeutic Products Directorate, addressed to the attention of the Director. The outer label of the shipping carton should be clearly identified with "**Clinical Trial Application for Bioavailability Studies**". In general, the CTA filing requirements (Section 2.3.2) also apply to the comparative bioavailability studies that meet the criteria provided above, with some exceptions as follows:

- The cover letter to the application should include a rationale for the study and be provided in hard copy and in electronic format;
- A hard and electronic copy of the current labelling or PM/Prescribing Information for the reference product in lieu of the IB; and
- A completed Quality Overall Summary - Chemical Entities (Clinical Trial Application - Bioavailability Studies) (QOS-CE (CTA-BA)) template, as well as any additional quality information as outlined in the template.

CTA-A and CTA-Notification (CTA-N) filing requirements (refer to sections 2.4 and 2.6, respectively) also apply to comparative bioavailability studies.

2.4 CTA Amendments (CTA-As)

CTA-As are applications in which a sponsor proposes information to support changes to a **previously authorized** application [C.05.008]. CTA-As are required for changes to clinical trial drug supplies that affect the quality or safety of the drug, changes to an authorized protocol that alter the risk to clinical trial subjects, or both.

CTA-As must be authorized by Health Canada prior to implementation of the changes [C.05.008]. However, if the sponsor is required to immediately make one or more of the amendments referred to in subsection (2) of C.05.008 because the clinical trial or the use of the drug for the purposes of the clinical trial endangers the health of clinical trial subjects or other persons, the sponsor may immediately make the amendment without prior review by Health Canada. Sponsors must notify Health Canada of this change, provide the relevant rationale in support of the immediate implementation and file a CTA-A that clearly identifies the change and the rationale for immediate implementation of the change within 15 days after the date of implementation of the amendment [C.05.008(4)].

Amendments submitted when the CTA is under review will not be accepted. Where a sponsor wishes to make changes to the CTA under review, the sponsor should withdraw the active CTA and submit the amendment as a new CTA. Changes requested by Health Canada during the review process may be filed later as amendments or notifications, as appropriate.

2.4.1 Clinical Trial Application-Amendments (CTA-A): Clinical

Sponsors are required to file CTA-As for changes to the protocol made after the original CTA that will impact on the safety of the subjects or will affect the analysis and the interpretation of the safety and efficacy of the drug(s) under investigation. As per section C.05.008(2), a CTA-A must be filed when the proposed amendments to the protocol:

a) Affect the selection, monitoring, or dismissal of a clinical trial subject;
b) Affect the evaluation of the clinical efficacy of the drug;
c) Alter the risk to the health of a clinical trial subject;
d) Affect the safety evaluation of the drug; and
e) Extend the duration of the clinical trial.

Examples of protocol changes that require a CTA-A are provided below to aid in determining whether a CTA-A should be filed. These examples are not all inclusive, when in doubt of whether a CTA-A is warranted, sponsors should contact the corresponding Directorate.

CLINICAL AMENDMENTS
Examples include, but are not limited to:
1. Criteria, tests or procedures required to select or dismiss a clinical trial subject. These include changes to eligibility criteria, tests or procedures for selecting the study population, as well as tests, procedures, or criteria for dismissing clinical trial subjects prematurely or at the end of the trial;
2. Criteria, tests or procedures required for the monitoring of clinical trial subjects, including monitoring of safety, or evaluation of safety and efficacy. This includes protocol changes as a result of serious unexpected ADRs;
3. Study design, study population, duration of use, objectives, or hypotheses, including adding or discontinuing a study arm that was not included as a provision in the original CTA protocol;
4. Changes in the primary efficacy endpoint(s), important secondary efficacy endpoints (e.g., those that could be used in support of a marketing application), safety endpoints, sample size estimation, or addition of interim analyses that will affect the analysis and interpretation of the study results;
5. Dose level, dosage schedule, or treatment duration;
6. The follow-up period, in particular if the follow-up period is being shortened;
7. Adding or removing a concomitant medication, which may impact on the analysis of efficacy or increase the risk to clinical trial subjects;
8. Criteria for expedited reporting of serious, unexpected adverse drug reactions;
9. Blood volume, procedure, repeat testing, or confirmatory testing in PK studies that were not specified in the original CTA protocol; and/or
10. Aspects of the conduct of the study that may increase the risk to the health of clinical trial subjects.

Protocol changes should be reflected in a revised ICD, as applicable. Additionally, new information related to the safety of the drug may affect a subject's decision to participate in the trial, and hence should be added to the risks section of the ICD. An updated copy of the ICD should be included in the CTA-A, as applicable, with changes clearly indicated (annotated).

Protocol changes that extend the duration of the clinical trial pertain to extensions in the treatment period of individual study subjects. All protocol changes that involve an extension in treatment duration or treatment period require filing of a CTA-A; such CTA-As must be accompanied by an IB or equivalent information to support the extension in treatment duration. Changes in the projected duration of the entire trial are normally not considered to require a CTA-A.

2.4.2 Clinical Trial Application-Amendments (CTA-A): Quality (Chemistry and Manufacturing)

a) For Biologics and Radiopharmaceuticals: A list of all proposed quality changes from the authorized application should be provided in the cover letter.

It should be noted that for Biologics and Radiopharmaceuticals, differences in manufacturing strategies can lead to the production of a novel drug product requiring both non clinical and clinical data to support its use and are considered **beyond the scope** of an authorized CTA. In such cases, a new CTA is required. Examples of differences in manufacturing strategies include, but are not limited to:

1. Change in the source of drug substance (e.g., from a fermentation process to transgenic milk);
2. Change in the host cells used to express the same coding sequence;
3. Use of an alternate expression cassette;
4. Change in the strain of virus used in manufacturing a vaccine;
5. Change in the strain of oncolytic virus used in cancer treatment;
6. Change in the animal source of an immune globulin (e.g., from rabbit to sheep);
7. Change in the source of a radionuclide (e.g., from nuclear reactor to cyclotron or linear accelerator) for labelling kits;
8. Change in the source of the parent radionuclide (e.g., from nuclear reactor to cyclotron or linear accelerator) used in a generator;
9. Change in the design, structure and operation of a radionuclidic generator.

For additional guidance regarding the classification of a quality change, sponsors are encouraged to consult with BGTD.

Sponsors must file a CTA-A or CTA-N to a previously authorized application when changes that may affect the quality or safety of the clinical trial drug supplies are proposed. Changes to the Quality summary subsections of Module 2.3 and Module 3 (if applicable) including, but not limited to those listed below, warrant the filing of a CTA-A or a CTA-N.

For a product commercially available and used in clinical trials for which a quality change has been made and approved according to the post-NOC Changes guidance document, supporting data are not required in support of the same change affecting the clinical product. The change can be notified to the BGTD with cross-reference to the approved submission filed for the commercial product. In the situation where a change made to the commercial product has not yet been approved and is affecting the clinical material, a CTA-A or a CTA-N must be submitted according to the tables below.

DRUG SUBSTANCE (Biologics and Radiopharmaceuticals)	
1. Replacement or addition of a manufacturing site and/or manufacturer involving:	
a. production of the starting material, intermediate, or drug substance	Amendment
b. testing (e.g., release, stability)	Notification
2. Change in the manufacturing process for the drug substance or intermediate, involving:	
a. the fermentation process (e.g., scale-up, new bioreactor technology, use of new raw materials of biological origin); or change in the route of synthesis of the radiopharmaceutical drug substance or critical component*	Amendment
b. the purification process (e.g., addition/removal/replacement of a purification step)	Amendment
3. Change in the specifications for the drug substance involving:	
a. deletion or replacement of a test, relaxation of an acceptance criterion or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
4. Change in the primary container closure system(s) for the storage and shipment of the drug substance	
5. Change in the shelf life for the drug substance, involving:	
a. Extension	
i. if the approved shelf life is less than or equal to 18 months	Amendment
ii. if the approved shelf life is more than 18 months	Notification
b. Reduction (due to stability concerns)	

*For the manufacture of some radiopharmaceuticals, “critical components” (e.g., F-18 radionuclide used to manufacture F-18-FDG and F-18-NaF) are considered analogous to drug substance (consult BGTD).

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DRUG PRODUCT (Biologics and Radiopharmaceuticals)	
1. Replacement or addition of a drug product manufacturing site / manufacturer, involving:	
a. production of a drug product (including primary packaging)	Amendment
b. secondary packaging	Notification
c. testing (e.g., release, stability)	Notification
2. Change in the drug product manufacturing process (e.g., scale-up, changes to the formulation process); change from manual synthesis of positron-emitting radiopharmaceutical to use of Automatic Synthesis Unit (ASU) or change in type of ASU	Amendment
3. Deletion of a drug product manufacturer / manufacturing site, secondary packaging site or testing site	Notification
4. Change in the specifications for the drug product, involving:	
a. deletion or replacement of a test, relaxation of an acceptance criterion or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
5. Change in the shelf life for the drug product, involving:	
a. Extension	
i. if the approved shelf life is less than or equal to 18 months	Amendment
ii. if the approved shelf life is more than 18 months	Notification
b. Reduction (due to stability concerns)	Amendment
6. Change in the storage conditions for the drug product	Amendment
7. Changes in drug substance and/or final product dosage form (e.g., liquid to lyophilized formulation);	Amendment
8. Changes in drug substance and/or final product strength	Amendment
9. Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution; change in radiolytic protective agent or antioxidant	Amendment

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712 **b) For Pharmaceuticals:**
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DRUG SUBSTANCE (Pharmaceuticals)	
1. Replacement or addition of a manufacturing site and/or manufacturer involving:	
a. production of the starting material, intermediate, or drug substance	Amendment
b. testing (e.g., release, stability)	Notification
2. Change in the manufacturing process for the drug substance or intermediate	Amendment
3. Change in the batch size for the drug substance (no impact on quality)	Notification
4. Change in the specification for the drug substance involving test and acceptance criteria:	
a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification
5. Change in the re-test period (or shelf life) for the drug substance, involving:	
a. Extension	Notification
b. Reduction	Amendment
DRUG PRODUCT (Pharmaceuticals)	
6. Addition of a dosage form or strength	Amendment
7. Change in the composition of a dosage form	Amendment
8. Qualitative or quantitative addition, deletion or replacement of a colour or flavour with no negative impact on stability	Notification
9. Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution	Amendment
10. Replacement or addition of a drug product manufacturer / manufacturing site involving:	
a. Production of an immediate release drug product (tablet, capsule, liquids, semi-solids) within the same Company	Notification
b. Production of an immediate release drug product (tablet, capsule, liquids, semi-solids) to a new Company	Amendment
c. Production of a modified release product	Amendment

d. Production of a sterile drug product	Amendment
e. Primary packaging (non-sterile products)	Notification
f. Testing (e.g., release, stability)	Notification
11. Change in the drug product manufacturing process	Amendment
12. Change in the specification for the drug product tests and acceptance criteria, involving:	
a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification
13. Change in the shelf life for the drug product, involving:	
a. Extension	Notification
b. Reduction (due to stability concerns)	Amendment
14. Change in the storage conditions for the drug product	Amendment

2.4.3 Filing a Clinical Trial Application-Amendments (CTA-A)

CTA-As should be filed directly to the appropriate Directorate (Appendix 1). The outer label should be clearly labelled with **"Clinical Trial Application - Amendment".**

For joint reviews, refer to Section 2.3.1.1.

2.4.4 Clinical Trial Application-Amendments (CTA-A) Format

Similar to CTAs, CTA-As should be organized and numbered as per the CTD format.

CTA-As should be submitted in hard copy and in electronic copy in a format accepted by Health Canada.

2.4.4.1 Clinical Amendments

Please refer to Section 2.3.2 CTA Format for guidance in completing filing requirements for Clinical CTA-As; subsection 1.4.1 is not applicable.

2.4.4.2 Quality (Chemistry and Manufacturing)

Please refer to Section 2.3.2 CTA Format for guidance in completing filing requirements; subsections 1.2.5.1, 1.2.7, 1.4.1, 1.7.2-1.7.4 are not applicable.

2.5 Clinical Trial Application (CTA) and Clinical Trial Application-Amendments (CTA-A) Review Process

Health Canada reviews the documents submitted in CTAs and CTA-As to assess the quality of the products and determine that the use of the drug for the purposes of the clinical trial does not endanger the health of clinical trial subjects or other persons, the clinical trial is not contrary to the best interests of a clinical trial subject, and the objectives of the clinical trial may be achieved [C.005.006(1)(b)(ii)]. All CTAs including those for comparative bioavailability studies are subject to the 30 day default period from the date of receipt of the completed application as per C.05.005 or C.05.008. However, comparative bioavailability studies that meet the criteria provided in Section 2.3.3 are targeted to be reviewed within **7 days**; sponsors are reminded that this expedited review process is an administrative target. An acknowledgement letter will be issued to indicate the start of the review period and to indicate that the Minister is in receipt of a complete application.

2.5.1 Screening Process

All CTAs and CTA-As will be screened for completeness and if deficiencies are identified at screening, these will be addressed by a Request for Clarification or a Screening Rejection Letter.

2.5.1.1 Requests for Clarification during screening

Requests for Clarification that are issued during screening should be responded to within 2 calendar days. If the application is considered complete, an acknowledgement letter will be issued to indicate the commencement of the 30-day default period.

2.5.1.2 Screening Rejection Letter

A Screening Rejection Letter may be issued when information required under C.05.005 or C05.008 has not been included in the CTA or CTA-A or responses to Requests for Clarification have not been received in a timely manner. Sponsors will be issued a letter itemizing each deficiency. If the sponsor wishes to resubmit the information and material at a future time, it will be processed as a new CTA or CTA-A, and will be assigned a new control number as per the *Management of Drug Submissions Guidance*.[3]

[3] *Management of Drug Submissions Guidance 2011/04/01* is located on the Health Canada website.

2.5.2 Review process

The sponsor is responsible for resolving issues identified by Health Canada during the review process. Sponsors must provide the requested information within 2 calendar days [C.05.009].

Should the sponsor be unable to provide the requested information within the specified time frame, the submission may be withdrawn and resubmitted without prejudice.

A Not Satisfactory Notice (NSN) may be issued if significant deficiencies are identified during the review of the CTA or CTA-A, or if a timely response to information requested has not been provided. If the sponsor wishes to resubmit the information and material at a future time, it will be processed as a new CTA or CTA-A, and will be assigned a new control number as per the *Management of Drug Submissions Guidance.*[5]

If the CTA or CTA-A is deemed acceptable, a No Objection Letter (NOL) will be issued within the review period.

2.6 Notifications

Notifications must be provided for changes to CTAs that do not meet the criteria for CTA-As. The changes may be implemented immediately, but Health Canada must be informed in writing, within 15 calendar days of the day of the change [C.05.007]. Information regarding the change should be submitted in the form of a cover letter and any supporting documentation. This information will be reviewed and added to the file.

Notifications include the following:

a) Changes to the protocol that do not affect the safety of the trial participants and which would not be considered an amendment under section 2.4. Examples include, but are not limited to the following:

NOTIFICATIONS
1. Minor changes to the inclusion and exclusion criteria, such as laboratory chemistry cut-off values that reflect clinical practice and improve the safety of clinical trial subjects;
2. Increasing the screening period or other administrative changes to accommodate logistical constraints in study conduct that do not affect the safety of the trial participants;
3. Changes to administrative information such as new contact names and numbers and addresses of individuals, organizations, or other entities, involved in the conduct of the trial;
4. Updating the ICD with new safety information that does not require a protocol amendment.

b) Changes to Quality (Chemistry and Manufacturing) information that does not affect the quality or safety of the drug (refer to section 2.4.2 CTA-As: Quality (Chemistry and Manufacturing)).

2.7 Additional Requirements Prior to Commencing a Clinical Trial

Prior to initiating a clinical trial or implementing an amendment to a clinical trial at a site, the sponsor must ensure that the REB Attestation and Qualified Investigator Undertaking forms have been completed, and that the Clinical Trial Site Information form has been filed with Health Canada. For all biologics, the BGTD requires that the lot release information be provided by the CTA sponsor/manufacturer before its use in the trial (see section 2.7.4).

The information required on the Qualified Investigator Undertaking, REB Attestation, HC/SC 3011, and Clinical Trial Site Information Form, is necessary because of differences in signing authority and attestation.

2.7.1 Research Ethics Board Review

Prior to initiating a clinical trial or implementing an amendment to a clinical trial at a site, the proposed trial protocol and ICD must be reviewed and approved by a REB as defined in the *Regulations*.

The sponsor must:

a) Submit the name of the REB that approved the trial or trial amendment prior to the commencement of the trial or trial amendment at that site (see Clinical Trial Site Information Form);

b) Retain as records a REB Attestation, signed by the REB Chair that approved the protocol or protocol amendment at each site in a manner consistent with GCPs. REBs may wish to use the REB Attestation form provided on Health Canada's website or develop similar documentation that meets the requirements of the *Regulations* (see additional information below); and

c) Submit information pertaining to the refusal of the protocol for any reason by a REB.

A REB may use its own letter of attestation in lieu of the form provided by Health Canada. If a REB uses its own letter, it must attest to the following 3 points:

- The membership of the REB complies with the membership requirements for REBs defined in the *Regulations*;

- The REB carries out its functions in a manner consistent with GCPs; and
- The REB has reviewed and approved the clinical trial protocol and ICD for the trial which is to be conducted by the qualified investigator named on the attestation for the specified clinical trial site. The approval and the views of the REB have been documented in writing.

The REB letter does not need to include all the elements contained in PART 1, PART 2 and PART 3 of the Health Canada REB Attestation Form.

If the REB is approving the clinical trial for multiple sites, the sites may be identified by duplicating Part 3 of the REB Attestation as many times as necessary to capture all site addresses approved by the same REB. Only the final page of the REB Attestation would contain the REB representative signature. The additional pages listing multiple clinical trial sites are attached to Parts 1 and 2, and the complete document should be paginated (e.g., 1 of 5, 2 of 5, etc.).

The REB Attestation should not be submitted unless requested by Health Canada but must be available at each clinical trial site as per C.05.012.

2.7.1.1 Refusals

Following regulatory authorization of a CTA or CTA-A, information regarding refusals by other regulatory authorities or REBs should be submitted as a notification. This information will be added to the file, but will not be subject to an acknowledgement letter, nor will a No Objection Letter (NOL) be issued.

2.7.2 Qualified Investigators

There must be no more than one (1) qualified investigator at each site. These restrictions do not apply to co-investigators.

Qualified Investigators must complete the Qualified Investigator Undertaking (QIU) or develop similar documentation that meets the requirements of the *Regulations*.

When the Qualified Investigator is conducting the trial at multiple sites, these sites may be identified by duplicating Part 3 of the QIU form as many times as necessary to capture all site addresses under the responsibility of the same QI. Only the final page of the QIU would contain the QI's signature. The additional pages listing multiple clinical trial sites are attached to Parts 1 and 2, and the complete document should be paginated (e.g., 1 of 5, 2 of 5, etc.).

If there is a change in the Qualified Investigator at a site, a new Clinical Trial Site Information Form must be submitted to Health Canada, and a new QIU form must be kept at the site.

Please note that the QIU form should not be submitted unless requested by Health Canada but must be kept at each clinical trial site as per C.05.012.

2.7.3 Filing of Trial Commencement Information

Prior to commencement of the clinical trial or implementation of a CTA-A, sponsors are required to complete and submit a **Clinical Trial Site Information (CTSI) form** for each clinical trial site.

A clinical trial site is the location where trial-related activities are conducted, such as the location where the drug is administered or dispensed (directly or by prescription) to the subject and where the subject returns for subsequent assessment. Locations where ancillary medical procedures such as X-rays, magnetic resonance images (MRIs), or blood collections are conducted do not require CTSI forms.

When the Qualified Investigator will be conducting the clinical trial at multiple sites overseen by the same REB, all sites may be identified by duplicating Part 3 of the CTSI form as many times as necessary. The additional pages listing multiple clinical trial sites should be attached to Parts 1 and 2, and the complete document should be paginated (e.g., 1 of 5, 2 of 5, etc.).

Health Canada recognizes that all information requested in the CTSI form (e.g. dates for Boxes 35 and 47) may not be available at the time of submission. In that case, sponsors should provide a commitment to submit the CTSI form prior to the commencement of the trial at a site. The forms may be faxed or mailed to the addresses in Appendix 1.

For Pharmaceuticals, the forms may be sent electronically in Microsoft Word, WordPerfect or unlocked PDF format to: clinical.trials.site@hc-sc.gc.ca.

If any changes are made to the CTSI form, a revised form should be submitted.

2.7.4 Lot Release Information (for Biologics)

All investigational biologic drug product lots to be used in a clinical trial are subject to the Lot Release requirements drugs as outlined in *Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs.*

With the exception of prophylatic vaccines, the BGTD will require that the CTA sponsor/manufacturer provide the Directorate, before its use in the trial, with the following information via the "Fax-back" process on the final product and bulk product of their material:

a. Lot numbers of materials being used during the trial and any Batch Identification Numbers that are assigned to lots received from elsewhere [that is (i.e.) all numbers associated with a particular lot]; and
b. The lot number(s) and manufacturing source of any associated human-derived excipient (e.g. human albumin).

The sponsor/manufacturer is required to sign a certification stating that all testing, on the drug substance as well as any human-derived excipients, is complete and within specification. A completed "Fax-Back" form, including the required certification, should be sent to the BGTD. This will be faxed back to the sponsor/manufacturer within 48 hours, providing the CTA has received prior BGTD authorization. If the CTA has not been cleared by the BGTD, the Fax-Back will be held until such time as authorization for the CTA has been given. Upon receipt of the faxed-back form, the sponsor/manufacturer may implement the use of the particular lot(s).

If the sponsor/manufacturer wishes to use a lot that has failed one or more specifications, they must provide the testing protocol, an explanation, and the rationale for its use along with the completed Fax-Back form. The lot must not be used until such time as it has been released by the BGTD.

For investigational prophylatic vaccines lot release for use in an authorized CTA, the BGTD will require the submission of testing protocols and/or Certificates of Analysis before its use in the trial. The BGTD issues a formal release letter for use of a prophylatic vaccine lot in a clinical trial. The lot must not be used until such time as it has been released by the BGTD.

2.7.5 Importation of Clinical Trial Drugs

For sponsors of Canadian clinical trials who wish to import a drug into Canada for the purpose of a clinical trial, a No Objection Letter should be provided at the time of importation to facilitate shipment and to demonstrate compliance with section C.05.006 or section C.05.008 of the *Food and Drug Regulations*. We ask that a copy of this authorization be provided at the port of entry.

Any delegation of importation duties to third parties should be clearly articulated through written agreement. Systems must be in place for the monitoring, storage conditions, transportation and disposition of the drug to be imported. Regardless of the agreements

in place for the importation of the product, the sponsor ultimately bears responsibility for the correct manufacture, handling and storage of the product to be used in the clinical trial.

Sponsors who are located outside of Canada must have an authorized Canadian agent (the sponsor, in terms of regulatory responsibility in Canada) responsible for the importation of all clinical trial drugs. This information must be included in Appendix 1 of the HC/SC 3011 form and should be provided at the time of application. If the drugs will be shipped to individual clinical trial sites, Appendix 1 may be replicated as many times as necessary to capture all sites.

In the event that additional drugs which are not specifically the subject of the CTA (e.g. comparator, concomitant and rescue medications) are being imported for the purpose of the clinical trial, we ask that a list of these drugs be specified in Section 1.2.9 of the Clinical Trial Application. For each associated drug listed in this section, the following information should be provided by the clinical trial sponsor at the time of application:

- Name of the country where the investigational drug is marketed;
- Name of the company as stated on the market label;
- Name of the drug as stated on the label;
- Common name of the active ingredient;
- Dosage form;
- Strength;
- Attestation that the drug has undergone review from, and is market authorized in, an ICH or equivalent region (e.g. Australia, Japan, Europe, United States), and that it will be used in the proposed clinical trial under the indication and conditions of use for which the authorization was granted

If this information is not known at the time of application, or changes between the time of application and the actual import of the clinical trial drugs, sponsors may submit that information to the appropriate review directorate when it becomes available as a CTA-Notification.

This information is collected to facilitate the assessment of a clinical trial shipments' admissibility into Canada.

To that end, a copy of Appendix 1 of the HC/SC 3011 form as well as the Summary of Additional Drugs should be included with the shipment.

2.8 Post-Authorization Requirements

2.8.1 Premature Discontinuation of a Trial

In the event of the premature discontinuation of a trial in its entirety or at a clinical trial site for which a CTA or CTA-A has been filed in Canada, the responsible Directorate must be notified as soon as possible, but no later than 15 calendar days after the date of discontinuance.

This notification should include:

a) Detailed reason(s) for this action;

b) Description of the impact on the proposed or ongoing trials conducted in Canada;

c) Confirmation that all qualified investigators have been notified of the discontinuation and the reasons for the discontinuance and have been advised in writing of any potential risks to the health of clinical trial subjects or other persons;

d) Confirmation that the sale or importation of the drug to all sites involved has been stopped; and

e) Confirmation that reasonable measures to ensure the return of all unused quantities of the drug will be taken.

Note: Notification of a premature discontinuation of a clinical trial outside Canada, for which there are ongoing trials with the drug in Canada, should also be submitted to the appropriate Directorate.

The sponsor may resume the trial in its entirety or at a site that was previously discontinued if the sponsor submits the following information:

a) The name, address and telephone number, and if applicable, the fax number and electronic mail address of the qualified investigator for each site and of the REB that approved the re-initiation of the trial at each site;

b) The name, address and telephone number and, if applicable, the fax number and electronic mail address of any REB that has previously refused to approve the re-initiation of the trial, if applicable; and

c) The proposed date of re-initiation of the clinical trial at each clinical trial site.

The above information may be submitted as a CTA-Notification if there are no changes to the study protocol or to the Chemistry and Manufacturing, and the trial may resume accordingly. When there has been a change to the study protocol or to the Chemistry and Manufacturing, the information should be submitted with a CTA-A (see Section 2.4). The sponsors may only resume the trial when a No Objection Letter (NOL) has been issued from the appropriate Directorate within 30 days of the submission of a CTA-A.

2.8.2 Safety Reporting Post- No Objection Letter (NOL)

2.8.2.1 Adverse Drug Reactions (ADRs)

During a clinical trial the sponsor is required to inform Health Canada, in an expedited manner, of any serious unexpected adverse drug reaction, in respect of the drug that has occurred inside or outside Canada:

a) Where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;

b) Where it is fatal or life-threatening, within 7 days after becoming aware of the information. Within 8 days after having initially informed Health Canada of the fatal or life-threatening ADR, submit as complete a report as possible. Follow-up reports of fatal or life-threatening reactions **must** include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

2.8.2.2 Adverse Drug Reactions (ADRs) Reporting criteria

Each ADR which is subject to expedited reporting should be reported individually in accordance with the data element(s) specified in the Health Canada/ICH Guidance Document E2A: "*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*". Expedited reports are required for events that meet all of these three criteria: serious, unexpected and a suspected causal relationship.

1) Serious:
Any untoward medical occurrence that at any dose:

- *results in death,*
- *is life-threatening,*
- *requires inpatient hospitalisation or prolongation of existing hospitalisation,*

- *results in persistent or significant disability/incapacity, or*
- *is a congenital anomaly/birth defect.*

2) Expectedness:

An "unexpected" adverse reaction is one in which the nature or severity is not consistent with information in the relevant source document(s), such as the IB or Product Monograph. Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the IB would be considered "unexpected" and should be reported (i.e., hepatitis with a first report of fulminant hepatitis).

3) Causality:

Causality assessment is required for clinical investigation cases:

- All cases judged by **either** the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs and should be reported.

- Concomitantly, adverse reactions that are considered to be unrelated to the study drug by both the investigator and the sponsor should not be reported. However, in situations when causality assessment and determination of expectedness is not straightforward, the report should be submitted in the expedited manner and the relevant issues **should be** addressed in a cover letter.

2.8.2.3 How to Report

When submitting an ADR report to Health Canada, a complete ADR Expedited Reporting Summary Form (Form 01-03) and the CIOMS Form should be attached and as applicable be mailed or faxed to:

Biologics and Genetic Therapies Directorate
Biologics and Radiopharmaceuticals **Fax: 613-957-0364**

Therapeutic Products Directorate
Pharmaceuticals **Fax: 613-941-2121**

2.8.2.4 Submission of Safety Information

Health Canada may request a sponsor, at any time during an ongoing clinical trial, to submit information or records kept under C.05.012 in order to assess the safety of the drug. The safety report could include a line listing of **all serious** events and/or other expected ADRs.

2.8.2.5 Study Endpoints

When a fatal or other serious outcome is the **primary efficacy endpoint** in a clinical investigation, it may be appropriate to reach agreement with Health Canada in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

2.8.2.6 Additional Safety Information

There are situations in addition to the above that may necessitate rapid communication to Health Canada, and appropriate scientific and medical judgment should be applied to each situation. For example, information that might influence the risk-benefit assessment of a drug, or that would be sufficient to consider changes in drug administration, or in the overall conduct of a clinical trial, represent such situations; including:

a) For an "expected" serious ADR, an increase in the rate of occurrence which is judged clinically important;

b) A significant hazard to the patient population, such as lack of efficacy with a drug used in treating a life-threatening disease; and

c) A major safety finding from a newly completed animal study.

This information should be submitted where applicable to either:

Biologics and Genetic Therapies Directorate
Biologics and Radiopharmaceuticals **Fax: 613-957-0364**

Office of Clinical Trials, Therapeutic Products Directorate
Pharmaceuticals **Fax: 613-954-4474**

Sponsors should refer to ICH Guidance Documents *E6: Guideline for Good Clinical Practice* and *E2A:* Clinical Safety Data Management for safety reporting requirements to Qualified Investigator(s) and their Research Ethics Board(s).

2.8.3 Other Communications

The sponsor is requested to notify the relevant Directorate(s) when a clinical trial is completed.

2.8.4 Updated Investigator's Brochure

In accordance with ICH GCP, the IB, including all safety information and global status, should be reviewed at least annually and revised as necessary. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. If the sponsor is planning to submit a CTA, or planning or required to submit a CTA-A or CTA-N, the updated IB should be submitted with the application. Otherwise, the updated IB should be submitted separately as a CTA-N, and include a statement confirming that the protocol and/or ICF of all ongoing trials do not require changes as a result of the updated IB. In all cases, the updated IB should be accompanied by a list of changes that clearly describes the sections that have changed, including a rationale for each change.

2.8.5 Records related to Clinical Trial Applications (CTAs) and Clinical Trial Application-Amendments (CTA-As)

As required in Part C, Division 5 of the *Food and Drug Regulations* [C.05.012]:

a) The sponsor shall record, handle and store all information in respect of a clinical trial in a way that allows its complete and accurate reporting as well as its interpretation and verification.

b) The sponsor shall maintain complete and accurate records to establish that the clinical trial is conducted in accordance with GCPs and the *Regulations*.

c) The sponsor shall maintain complete and accurate records in respect of the use of a drug in a clinical trial, including:
   i) a copy of all versions of the IB for the drug;

   ii) records respecting each change made to the IB, including the rationale for each change and documentation that supports each change;

   iii) records respecting all adverse events in respect of the drug that have occurred inside or outside Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;

iv) records respecting the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the sale of the drug may endanger the health of the clinical trial subjects or other persons;

v) records respecting the shipment, receipt, disposition, return and destruction of the drug;

vi) for each clinical trial site, an undertaking from the qualified investigator that is signed and dated by the qualified investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that:

- the qualified investigator will conduct the clinical trial in accordance with GCPs, and
- the qualified investigator will immediately, on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the REB of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial subjects or other persons;

vii) for each clinical trial site, a copy of the protocol, ICD and any amendment to the protocol or ICD that have been approved by the REB for that clinical trial site; and

viii) for each clinical trial site, an attestation, signed and dated by the REB for that clinical trial site, stating that it has reviewed and approved the protocol and ICD and that the board carries out its functions in a manner consistent with GCPs.

d) The sponsor shall maintain all records referred to in the applicable *Regulations* for a period of 25 years.

Records must be made available to the relevant Directorate within 2 days if there is a concern regarding the use of the drug for the purposes of a clinical trial and a risk to health of the subjects involved in that trial. In any other case, records must be provided within 7 days of a request [C.05.013].

3 INDEX OF APPENDICES

APPENDIX 1: RELEVANT ADDRESSES

Pharmaceutical Drugs	**Biologic and Radiopharmaceutical Drugs**
CTAs and CTAAs	
Office of Clinical Trials	Regulatory Affairs Division
Therapeutic Products Directorate	Biologics and Genetic Therapies Directorate
5th Floor, Holland Cross, Tower B	Health Protection Building, 1st Floor
Address Locator 3105A	Address Locator 0701A
1600 Scott Street	200 Tunney's Pasture Driveway
Ottawa, Ontario	Ottawa, Ontario
Canada	Canada
K1A 0K9	K1A 0K9
Clinical Trial Site Information Forms	
Fax #: 613-946-7996	Fax #: 613-941-1708

The forms may also be sent electronically in WordPerfect or unlocked PDF format to:
clinical.trials.site@hc-sc.gc.ca

APPENDIX 2: USEFUL INTERNET WEBSITES

Bioavailability and Bioequivalence (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/index-eng.php)

Biologics and Genetic Therapies Directorate (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-eng.php)

Clinical Trials for Natural Health Products (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/clini_trials-essais_nhp-psn-eng.php)

Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ct_regrev_ce_exareg-eng.php)

Good Clinical Practices (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/index-eng.php)

Health Canada (http://www.hc-sc.gc.ca/index-eng.php)

Health Products and Food Branch (http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/index-eng.php)

International Conference on Harmonisation (http://www.ich.org/)

Medical Devices Guidance Documents (http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php#guidance_devices)

Review of the 2001 Clinical Trials Regulatory Framework: Part C, Division 5 of the Food and Drug Regulations (Drugs for Clinical Trials Involving Human Subjects) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ctrf_dd_eccr_dt_2007-03-26-eng.php)

Therapeutic Products Directorate (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index-eng.php)

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2nd edition) (http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/)

The following documents may be useful in the preparation of the application:

Notice - Release of Draft Electronic Specifications for Clinical Trial Applications and Amendments filed in accordance with Guidance for Clinical Trial Sponsors: Clinical Trial Applications (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/notice_cta_avis_dec-eng.php)

Notice: Revised Quality Guidances on the Implementation of the Common Technical Document for Biological Products (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_bgtd-dpbgt_notice-avis-eng.php)

ADR Expedited Reporting Summary for ADRs Occurring During Clinical Trials (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctadr_dceim-eng.php)

CIOMS Form I (http://www.cioms.ch/form/frame_form.htm)

Clinical Trial Site Information Form (http://www.cioms.ch/form/frame_form.htm)

Health Canada 3011: Drug Submission Application Form for Human, Veterinary, Disinfectant Drugs and Clinical Trial Application/Attestation (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/hc3011_sc3011-eng.php)

Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/qual_cta_dec-eng.php)

Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/glp_bpl-eng.php)

Guidance for Records Related to Clinical Trials (GUIDE-0068) (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_68-eng.php)

Revised Draft Guidance Document: Preparation of Drug Submissions and Applications in the Common Technical Document (CTD) Format (http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/ctd_prep_draft_rev_ebauche_nds_2011-eng.php)

For Biologics - Guidance Documents:
Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotechnological/ Biological (Biotech) Products, Date: 2004-05-25 (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_biotech-eng.php)

Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Blood Products, Date: 2004-05-25 (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_blood-sang_prods-eng.php)

Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products, Date: 2004-05-25 (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_convbio-eng.php)

Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Vaccines, Date: 2004-05-25 (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_vacc-eng.php)

Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs, Date: 2005-06-01 (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/lot/gui_sponsors-dir_promoteurs_lot_program-eng.php)

For Radiopharmaceuticals/Generators - Guidance Document:

The Draft Guidance for Industry, Preparation of the Quality Information for Radiopharmaceuticals (Schedule C Drugs) using the Quality Information Summary-Radiopharmaceuticals (QIS-R) and Certified Product Information Document-Radiopharmaceuticals (CPID-R) Templates (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/radiopharm/qisr-sdqr_guide-eng.php)

For Radiopharmaceuticals - Templates:

Blank QIS-R template (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/templates-modeles/radiopharm/blnkqisr-eng.php)

Blank QIS-PER template [not yet posted externally as of January 2011]

Health Canada Santé Canada

Summary of Additional Drugs to be Imported for a Clinical Trial

Please note that this form is only to be completed for products not explicitly authorized under the No Objection Letter. The completed form will be sent to the sponsor at the time of issuance of a No Objection Letter.

Clinical Trial Protocol Number (must be assigned)	Clinical Trial Protocol Title

Name of the country where the product is marketed	
Name of the company as stated on the marketed label	
Name of the drug product as stated on the marketed label	
Common name of the active ingredient	
Dosage form	
Strength	
Attestation that the product has undergone review from an International Conference on Harmonisation (ICH) or equivalent jurisdiction (Japan, United States, Europe, Australia)	

This table may be replicated as many times as necessary to cover all additional medicinal products to be imported.

I, the undersigned, certify that the information and material included in this appendix is accurate and complete.

Name of Authorized Signing Official	Signature	Date		
		YYYY MM		DD
Title	Telephone:	Fax:		
Name of Company to which the Authorized Signing Official Belongs				

FOR HEALTH CANADA USE ONLY

Date Received			Drug Submission Tracking System (DSTS) Control Number		
YYYY M	M	DD			
Name of Signing Official			Telephone:	Signature	
Title: Fax			:	Date Sent:	
				YYYY M M	DD

Canada