Health Canada Santé Canada

GUIDANCE FOR CLINICAL TRIAL SPONSORS

Clinical Trial Applications

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

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 scientific 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 guidance, 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 guidances.

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1. PURPOSE

This is a guidance document for the administration of the *Food and Drug Regulations* Amendment (Schedule No. 1024) Clinical Trial Framework [SOR/2001-203] (also referred to as the *Regulations*). This guidance document is not an exhaustive description or explanation of Part C, Division 5 of the *Regulations*, but rather, outlines the application requirements for sponsors wishing to conduct clinical trials with drugs in humans. The format outlined in this guidance for Clinical Trial Applications (CTAs) is consistent with that used for other types of drug submissions filed in Canada, based on the format of the International Conference on Harmonization (ICH) Common Technical Document (CTD). Although the scope of ICH's CTD does not include applications at the clinical research stage of development, the modular format of the CTD is being extended to CTAs that are filed with Health Canada. This approach is intended to facilitate the preparation of drug submission information throughout the lifecycle of a drug (e.g., from Clinical Trial Application to the New Drug Submission stage).

This guidance document supercedes the *Clinical Trials Review and Approval Policy (1997)*, the *Preparation of Investigational New Drug Submissions (1991)* and the *Conduct of Clinical Investigations (1989).*

This document does not constitute part of the *Regulations* and in the event of any inconsistency or conflict, the *Regulations* take precedence over this guidance document.

2. DEFINITIONS

Most of the definitions listed below were taken from the *Food and Drug Regulations* Amendment (Schedule No. 1024) Clinical Trial Framework, Health Canada / ICH Guidance Documents *E6: Guideline for Good Clinical Practice: Consolidated Guideline* 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.
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.

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]

Comparative Bioavailability Studies

For the purpose of this document, studies comparing the pharmacokinetics of two drug formulations in healthy adult volunteers.

Drug

For the purpose of this document, a drug for human use that is to be tested in a clinical trial.

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, and the good clinical practices referred to in section C.05.010 of Division 5 of the *Food and Drug 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

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.

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

Investigator's Brochure In respect of a drug, a document containing the preclinical and clinical data on the drug that are described in section C.05.005(e) of Division 5 of the *Food and Drug Regulations*.

Phase I Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical.

Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses. Pharmacokinetic as well as drug-drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development as these are generally conducted in healthy volunteers. Phase I trials also include trials in which new drugs are used as research tools to explore biological phenomena or disease processes.

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 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 efficacy and safety that is needed for further risk/benefit assessment of the drug. In this phase, clinical trials are also conducted in special patient populations (e.g., renal failure patients), or under special conditions dictated by the nature of the drug and disease.

Phase IV All studies performed after the drug has been approved by the regulator for the market, and related to the approved indication. 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 such as 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.

3. REGULATORY OVERVIEW

The *Food and Drugs Act and Regulations* provide authority to Health Canada to regulate the sale of drugs for the purposes of use in human clinical trials. Part C, Division 5 of the *Regulations* defines specific Clinical Trial Application (CTA), and Clinical Trial Application Amendment (CTA-A), requirements for the sale and importation of drugs for use in human clinical trials in Canada.

The *Regulations* are consistent with the principles, definitions and standards found in the Health Canada / ICH Guidance Documents *E6: Good Clinical Practice: Consolidated Guideline*, *E8: General Considerations for Clinical Trials* and *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*. These guidance documents, developed through

the International Conference on Harmonisation[2] (ICH) process have been adopted by Health Canada. Together, they define parameters for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials.

A CTA must be filed prior to the initiation of a clinical trial in Canada. Health Canada must review the application and notify the sponsor within 30 days if the application is found to be deficient [C.05.006(1)].

Sponsors must file applications to conduct clinical trials in Phases I through III of drug development and comparative bioavailability trials. This includes applications to conduct clinical trials involving marketed products where the proposed use of the product is outside the parameters of the approved Notice of Compliance (NOC) or Drug Identification Number (DIN) application.

Sponsors conducting clinical trials in Canada with products that have received a Notice of Compliance with Conditions (NOC/c) are required to file a CTA. In this case, studies conducted within the parameters of the NOC/c would be subject to review and authorization.

Applications to conduct Phase IV trials are not subject to filing with Health Canada.

Health Canada targets to review applications to conduct comparative bioavailability trials and Phase I trials in healthy adult volunteers within 7 days, with the exception of applications for Phase I trials using somatic cell therapies, xenografts, gene therapies, prophylactic vaccines or reproductive and genetic technologies. **Trials which do qualify for the expedited review process can only proceed if:**

- **a No Objection Letter (NOL) is received from Health Canada prior to the 30 day default period; or**
- **within 30 days after the date of receipt of the application, a notice in respect of the drug, indicating that the sponsor may not sell or import the drug, has not been received.**

4. PRE-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.

[2] For more information on the *International Conference on Harmonisation*, consult the ICH website: www.ich.org

The pre-CTA consultation meeting provides an opportunity for the sponsor to present relevant data, discuss concerns and resolve 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.

4.1 Pre-CTA Information Package

Requests for a pre-CTA consultation meeting should be submitted in writing by the sponsor to the appropriate Directorate at the addresses identified in Section 5.1. Requests should include a cover letter proposing 4 dates and times suitable for a pre-CTA consultation meeting. A pre-CTA consultation meeting may be scheduled in advance, however the information package should be provided to the appropriate Directorate 30 days prior to the meeting date. The Directorate will acknowledge the request for consultation, indicate the number of copies of the information package to be provided and confirm the pre-CTA consultation meeting date.

The Information Package should contain:

a) a brief summary of all data including:

   i) a tabular listing of completed preclinical 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;

b) 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.]

c) 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;

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

e) **for Biologicals (Schedule D) and Radiopharmaceuticals (Schedule C):**

i) a listing of all production site(s),
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.

4.2 Pre-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.

5. CLINICAL TRIAL APPLICATIONS (CTAs)

Applications must be filed by the sponsor **prior** to the initiation of the trial [C.05.006(1)].
Sponsors must conduct all clinical trials, including Phase IV trials, in accordance with the principles of Good Clinical Practices [C.05.010].

5.1 Filing a CTA

Sponsors must file a CTA for human drug clinical trials in Phases I through III of development and comparative bioavailability trials [C.05.006]. This includes trials involving marketed drugs, where the proposed trial is outside of the parameters of the approved NOC or DIN application, 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 application. These trials are referred to as Phase IV clinical trials.

CTAs and CTA-As should be sent **directly to the applicable review Directorate as follows:**

Pharmaceutical Drugs

Therapeutic Products Directorate
Office of Clinical Trials
5th Floor, Holland Cross, Tower B
A/L 3105A
1600 Scott Sreet
Ottawa, Ontario
Canada K1A 0K9

Biological and Radiopharmaceutical Drugs

Biologics and Genetic Therapies Directorate
Regulatory Affairs Division
Health Canada Building #7, 1st Floor
A/L 0701A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0K9

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

5.2 CTA Requirements

Information for a CTA should be formatted as outlined below (refer to Appendix 3 for an outline of the CTA sections, as well as to the draft Health Canada guidance: *Preparation of New Drug Submissions in the CTD Format*, and to the ICH M4 guidance: *Organisation of the Common Technical Document*[1] for more general guidance regarding CTD- formatted submissions). Each Module should be submitted in a separate binder.

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

[1] The format described in these documents should be followed to the extent possible for CTAs and for CTA-As, if appropriate. These CTD- related guidances may undergo further changes based upon practical experience gained through the use of the CTD and with efforts to further harmonise internationally. During the transition period of implementing the CTD format, a certain level of discretionary flexibility may be exercised by Health Canada with respect to format changes.

Items marked with an asterisk (*) should be submitted in hard copy and in electronic format accepted by Health Canada (e.g., CD-ROM).

Note: Module 1 should include the cover letter.

Module 1: Administrative / Clinical Information
The Administrative / Clinical Information Module should include:

1.1 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 Application Information

1.2.1 Drug Submission Application Form (HC/SC 3011)
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 should be completed and submitted if applicable);

1.2.2 Information on Prior-related Applications
a list of ongoing clinical trials in Canada for which approval has been granted by Health Canada, if applicable;

1.2.3* Investigator's Brochure
a copy of the current Investigator's Brochure, supplemented as appropriate with up-to-date safety, pre-clinical and clinical data;

The Investigator's Brochure containing all information regarding the product to date should be prepared in accordance with the Health Canada / ICH Guidance Document *E6: Good Clinical Practice: Consolidated Guideline*, and updated annually. Sectional reports should not be submitted.

For products marketed in Canada, a copy of the Product Monograph may be submitted in lieu of the Investigator's Brochure.

For Biologicals and Radiopharmaceuticals: if the Investigator's Brochure has been updated relative to a version contained within a previously approved CTA/CTA-A, a summary of the changes should be provided.

1.2.4***For Pharmaceuticals:**

Protocol Synopsis (PCERT)

a Protocol Synopsis in the format of the Pre-clinical and Clinical Evaluation Report Template (PCERT)[4] [see Appendix 4 for further guidance]. A submission rationale and a brief summary is included in the PCERT;

For Biologicals and Radiopharmaceuticals:

Submission Rationale/Brief Summary of the Drug Product

a Submission Rationale and a Brief Summary of the Drug Product being proposed for use in the clinical trial;

1.2.5*Study Protocol(s)

a copy of the final proposed protocol(s);

1.2.6 Informed Consent Document(s)

a copy of the Informed Consent documents(s) to be used in conjunction with the clinical trial(s), including a statement regarding the risks and anticipated benefits to the clinical trial subjects as a result of their participation in the clinical trial(s);

Informed Consent document(s) to be used in conjunction with the clinical trial(s) should be prepared in accordance with the Health Canada / ICH Guidance Document *E6: Good Clinical Practice: Consolidated Guideline*.

1.2.7 Clinical Trial Site Information

a **completed** Clinical Trial Site Information Form for each proposed clinical trial site, if known at the time of the application;

Please do not provide forms until all fields are completed.

For all clinical trial site information which becomes available after the time of application, a completed Clinical Trial Site Information Form must be provided to the appropriate Directorate. The forms may be faxed or mailed to the addresses below prior to the commencement of the trial at that site.

[4] The Pre-clinical and Clinical Evaluation Report Template (PCERT) is the current standard for providing a synopsis of the proposed protocol(s).

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

Pharmaceutical Drugs

Therapeutic Products Directorate
Office of Clinical Trials
5th Floor, Holland Cross, Tower B
A/L 3105A
1600 Scott Sreet
Ottawa, Ontario
Canada K1A 0K9

Fax #: (613) 946-7996

Biological and Radiopharmaceutical Drugs

Biologics and Genetic Therapies Directorate
Regulatory Affairs Division
Health Canada Building #7, 1st Floor
A/L 0701A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0K9

Fax #: (613) 941-1708

If any changes are made to the Clinical Trial Site Information Form (e.g., change of qualified investigator) a revised form should be submitted. Receipt of the Clinical Trial Site Information Form will not be subject to an acknowledgment letter.

1.2.8 Canadian Research Ethics Board(s) Refusals
the name, address and telephone number and, if applicable, the fax number and electronic mail address of any Research Ethics Board in Canada that has previously refused to approve the clinical trial protocol, its reasons for doing so and the date on which the refusal was given, if known at the time of submitting the application;

1.2.9 Foreign Refusals
information regarding refusals by regulatory authorities outside Canada, if applicable;

1.2.10 Letters of Access
letters authorizing Health Canada to access related Master Files (e.g., Drug Master Files, Site Reference Files), if applicable;

For Pharmaceuticals: The CTA sponsor should ensure that the supporting Drug Master File has been submitted to and accepted by Health Canada prior to filing a CTA.

For Biologicals and Radiopharmaceuticals: Any supporting Master File information should be submitted or resubmitted simultaneously with the related CTA to Health Canada.

1.2.11 Other Application-related Information

including e.g., a copy of the record of the discussions and conclusions of the pre-CTA consultation meeting, if applicable.

1.3 Electronic Review Documents

Health Canada is developing a plan for the *electronic Clinical Trial Application (eCTA)* that will be consistent with the standard for the *electronic Common Technical Document (eCTD)* being developed at ICH. Applicants should consult the Health Canada website for CTD/ eCTD update Notices for guidance on the filing of electronic review documents.

Items marked with an asterisk (*) should be submitted in hard copy and in electronic format accepted by Health Canada (e.g., CD-ROM).

For Pharmaceuticals: Module 1 electronic files should be placed under this section, whereas Module 2 electronic files should be placed at the beginning of Module 2.

For Biologicals and Radiopharmaceuticals: All electronic files (i.e., Modules 1 and 2) should be placed under this section.

Module 2: Common Technical Document Summaries

For a CTA, this module reflects Quality (Chemistry and Manufacturing) Information only. The Common Technical Document Summaries Module should include:

2.1 Common Technical Document Table of Contents

a listing of the contents of Modules 2 and 3, if applicable;

2.2 CTD Introduction:

Not applicable to CTAs.

This section has been reserved for use during the preparation of drug submissions at later stages of development (e.g., New Drug Submissions) and maintained to ensure consistent numbering of subsequent sections (e.g., Section 2.3);

2.3* Quality Overall Summary

This section does not apply if the drug product to be used in the clinical trial has received a NOC and/or DIN.

Items marked with an asterisk (*) should be submitted in hard copy and in electronic format accepted by Health Canada (e.g., CD-ROM).

a)* **For Pharmaceuticals:** (refer to *Quality Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals* for additional information).

Depending on the phase of the clinical trial, the completed *applicable* "Quality Overall Summary - Chemical Entities (QOS-CE)" template, as well as additional Quality information as outlined in the template, should be submitted;

- Clinical Trial Applications - Phase I: QOS-CE (CTA - Phase I);
- Clinical Trial Applications - Phase II or III: QOS-CE (CTA - Phase II or III);

If the Quality information was previously submitted to and approved by Health Canada and **has not changed**, re-submission of the applicable Quality Summary is not required. Sponsors should, however, refer to the control number of the prior application.

Note: i) Quality for Phase II trials cannot be cross-referenced to the Quality information submitted with Phase I trials; and

ii) Quality for Phase III trials cannot be cross-referenced to the Quality information submitted with Phase II trials.

b)* **For Biologicals and Radiopharmaceuticals:** If the Quality information was previously submitted to and approved by Health Canada and **has not changed**, re-submission of the applicable Quality Summary is not required. Sponsors should, however, refer to the control number of the prior application.

The completed Quality Summary (i.e., check marked sections of an acceptable and appropriate version available, based upon the product type), should be provided. Sponsors should also refer to the applicable Health Canada Quality guidances and updated notices for additional information.

c) **For Placebo-controlled studies:** a qualitative list of the ingredients in the placebo should be submitted.

Module 3: Quality
The Quality Module should include:

3.1 Table of Contents of Module 3
a listing of the contents of Module 3 (Quality);

3.2 Body of Data
Where there is additional supporting Quality information to that provided in Module 2.3, this information should be provided separately in the appropriate Module 3 section and cross-referenced under Module 2.3. The extent of available supporting information may vary depending upon the stage of drug development (e.g., Phase I-III studies). Sponsors should also refer to the applicable Health Canada Quality guidances for additional information.

For Biologicals and Radiopharmaceuticals only:
3.2.R.1 Production Documentation
3.2.R.1.1 Executed Batch Records
Executed Batch Records should be provided if available, depending upon the stage of drug development (e.g., Phase I - III studies).

3.3 Literature References
For Biologicals and Radiopharmaceuticals only: Literature references related to Quality information should be provided here if applicable.

5.3 CTA Requirements for Institution / Investigator-initiated Clinical Trials

The regulatory requirements for CTAs outlined in Part C, Division 5 of the *Food and Drug Regulations* also apply to institution / investigator-initiated clinical trials. These include the following:

a) the use of a product not approved for marketing in Canada; and

b) a product marketed in Canada, where the use of the product in the clinical trial is outside the parameters of the NOC and/or DIN.

For such trials, the institution / investigator is considered to be the sponsor of the trial and therefore, must fulfill all the regulatory obligations of the sponsor as outlined in Part C, Division 5 of the *Food and Drug Regulations*.

CTA filing requirements for these types of trials should include the information as described in Section 5.2, with the following modifications:

a) 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 may sign in lieu of the Senior Medical or Scientific Officer (Appendices 1 and 2 should be completed and submitted if applicable);

b) For products **not** marketed in Canada, the Investigator's Brochure and data on Quality (Chemistry and Manufacturing) must be submitted [C.05.005].

If the manufacturer of that product has previously submitted information to Health Canada that meets the regulatory requirements for CTAs, a letter authorizing cross reference to their information on file may be submitted in lieu of:

- Investigator's Brochure; and/or
- Quality (Chemistry and Manufacturing) Information.

5.4 Comparative Bioavailability Trial Application Requirements

A separate guidance document "*Clinical Trial Applications for Comparative Bioavailability Studies for Pharmaceuticals"* and the "Quality Overall Summary template QOS-CE (CTA-BA)" are located on the website.

6 CTA AMENDMENTS (CTA-As)

CTA-As are applications in which a sponsor proposes information to support changes to a **previously approved** application [C.05.008]. CTA-As may involve changes to clinical trial drug supplies (e.g., the manufacturing process for the drug has changed), changes to an approved protocol (e.g., a revised dosing regimen), or both.

CTA-As must be approved by Health Canada prior to implementation of the changes [C.05.008]. Amendments submitted with a CTA or when the CTA is under review will not be accepted. This does not apply when a protocol is amended prior to the initial filing of the CTA.

Where a sponsor wishes to make changes to the CTA under review, the sponsor should withdraw the active CTA and submit a new CTA.

Amendments filed to Investigational New Drug Submission(s) submitted prior to September 1st, 2001 should be filed in accordance with the requirements of Part C, Division 5 of the *Regulations*.

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 a clinical trial subject or other person, the sponsor may immediately make the amendment without prior review by Health Canada. A corresponding CTA-A which provides the information required below, and which clearly identifies the change and the rationale for immediate implementation of the change must be filed within 15 days after the date of implementation of the amendment [C.05.008(4)]. This is subject to a 30 day review period.

6.1 CTA-As: Clinical

Sponsors must file a CTA-A when the proposed changes to the protocol:

a) affect the selection, the criteria for 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 health of a clinical trial subject;

d) affect the safety evaluation of the drug; or

e) extend the duration of the clinical trial.

6.1.1 Filing a CTA-A: Clinical

A single copy of the application should be filed directly to the appropriate Directorate, at the addresses previously identified in Section 5.1. The outer label should be clearly labelled with **"Clinical Trial Application - Amendment".**

6.1.2 CTA-A Requirements: Clinical

Items marked with an asterisk (*) should be submitted in hard copy and in electronic format accepted by Health Canada (e.g., CD-ROM).

Note: A cover letter, indicating the original CTA(s) with file number and control number(s), should be included.

Module 1: Administrative / Clinical Information

The Administrative / Clinical Information Module should include:

1.1 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 Application Information

1.2.1 Drug Submission Application Form (HC/SC 3011)

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 should be completed and submitted if applicable);

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.

1.2.5*Study Protocol(s)

a copy of the **amended or working protocol** and a clear description of the changes that are being proposed (i.e., original wording vs. revised wording);

This should include a copy of the **most recently approved protocol** and a rationale for ***each*** proposed change. Cross-referencing is not acceptable.

1.2.6 Informed Consent Document(s)

revised statements, regarding the protocol amendments being made, to be included in the Informed Consent document, if applicable;

1.2.7 Clinical Trial Site Information
a **completed** Clinical Trial Site Information Form for each clinical trial site respecting the amendment;

Please do not provide forms until all fields are completed.

For all clinical trial site information which becomes available after the time of the filing of the CTA-A, a completed Clinical Trial Site Information Form must be provided to the appropriate Directorate. The forms may be faxed or mailed to the addresses identified in Section 5.2 prior to the commencement of the trial at that site.

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

If any changes are made to the Clinical Trial Site Information Form, a revised form should be submitted.

Receipt of the Clinical Trial Site Information Form will not be subject to an acknowledgment letter.

1.2.8 Canadian Research Ethics Board(s) Refusals
the name, address and telephone number and, if applicable, the fax number and electronic mail address of any Research Ethics Board in Canada 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 CTA-A;

1.2.9 Foreign Refusals
information regarding refusals by other regulatory authorities outside Canada, if applicable.

1.3 Electronic Review Documents
Refer to section 5.2 (Module 1) for guidance.

6.2 CTA-As: Quality (Chemistry and Manufacturing)

Sponsors must file a CTA-A to a previously approved 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.

a) **For Pharmaceuticals:**

i) S.2 MANUFACTURE (Drug Substance), where new ingredients are used, including ingredients which do not appear in the final drug substance;

ii) S.3.2 IMPURITIES, where a new impurity or degradation product has been identified;

iii) S.4 CONTROL OF DRUG SUBSTANCE, where a test is removed from the specification and/or the test methods or limits are relaxed;

iv) P.3 MANUFACTURE (Drug Product), where new ingredients are used, including ingredients which do not appear in the final product;

v) P.3.3 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS, for sterile products only where the sterilization process is changed; and

vi) P.5 CONTROL OF DRUG PRODUCT where a test is removed from the specification and/or the test methods or limits are relaxed.

b) **For Biologicals and Radiopharmaceuticals:**

i) S.2 MANUFACTURE, regarding raw materials, where a new medicinal or non-medicinal ingredient is used, including ingredients not appearing in the final formulation;

ii) S.4 CONTROL OF DRUG SUBSTANCE, where a test method is altered and/or the test limits are relaxed;

iii) P.3 MANUFACTURE, where minor changes to the formulation process are proposed;

iv) P.5 CONTROL OF DRUG PRODUCT, where a test method is changed and/or test limits are relaxed;

v) P.8 STABILITY, where an extension of the shelf life for drug product is proposed, and the original expiry date granted was ≤ 18 months; and

vi) A.1 FACILITIES AND EQUIPMENT, where modifications to an existing facility are proposed.

It should be noted that for Biologicals and Radiopharmaceuticals, certain changes relating to the production of a given drug may be considered **beyond the scope** of an approved CTA. If such changes are submitted as CTA-As they will be subject to reclassification as a CTA.

These changes include, but are not limited to:

i) use of a new or alternate facility for any stage of production except those used for packaging,
ii) changes in biological source material,
iii) changes to genetic expression systems,
iv) changes to the purification process,
v) changes in drug substance and/or final product dosage form (e.g., liquid to lyophilized formulation),
vi) significant changes to product release specifications, and
vii) changes in drug substance and/or final product strength.

6.2.1 Filing a CTA-A: Quality (Chemistry and Manufacturing)

Submit one (1) copy of the following information to the appropriate Directorate at the addresses identified in Section 5.1. Clearly identify the submission on the outer label with **"Clinical Trial Application - Amendment".**

6.2.2 CTA-A Requirements: Quality (Chemistry and Manufacturing)

Items marked with an asterisk (*) should be submitted in hard copy and in electronic format accepted by Health Canada (e.g., CD-ROM).

Note: A cover letter, indicating the original CTA(s) with file number and control number(s), should be included.

All CTA-As: Quality should contain the following:

Module 1: Administrative / Clinical Information
The Administrative / Clinical Information Module should include:

1.1 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 Application Information
1.2.1 Drug Submission Application Form (HC/SC 3011)
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 should be completed and submitted if applicable);

1.2.3* Investigator's Brochure
For Biologicals and Radiopharmaceuticals only: a revised Investigator's Brochure or an Addendum to the Investigator's Brochure describing any new Quality (Chemistry and Manufacturing) information, including supporting data as required, if applicable;

1.3 Electronic Review Documents
Refer to section 5.2 (Module 1) for guidance.

Module 2: Common Technical Document Summaries
The Common Technical Document Summaries Module should include:

2.1 Common Technical Document Table of Contents
a listing of the contents of Modules 2 and 3, if applicable;

2.3* Quality Overall Summary
applicable updated Quality Summary. Revised information should be clearly identified.

Module 3: Quality (if applicable)
The Quality Module should include:

3.1 Table of Contents of Module 3
a listing of the contents of Module 3 (Quality);

3.2 Body of Data
Additional supporting Quality information to that provided in Module 2.3, if applicable and available. (Refer to section 5.2 (Module 3) for additional guidance.)

3.3 Literature References
For Biologicals and Radiopharmaceuticals only: Literature references related to Quality information should be provided here, if applicable.

7 CTA and CTA-A REVIEW PROCESS

All CTAs and CTA-As are subject to a 30-day default review period from the date of receipt in Health Canada. An acknowledgement letter will be issued to indicate the start of the review period.

Health Canada targets to review applications to conduct comparative bioavailability trials and Phase I trials in healthy adult volunteers within 7 days (for both CTA and CTA-As), with the exception of Phase I trials using somatic cell therapies, xenografts, gene therapies, prophylactic vaccines or reproductive and genetic technologies.

7.1 Screening of CTAs and CTA-As

All CTAs and CTA-As will be screened for acceptability, and deficiencies identified at screening will be addressed by:

a) Request for Clarification (Clarifax), or

b) Screening Rejection Letter.

7.1.1 Requests for Clarification

Requests for clarification that are issued during screening should be responded to within 2 calendar days [C.05.009]. A Rejection Letter will be issued if a timely response to a Clarifax has not been provided.

7.1.2 Screening Rejection Letter

A Screening Rejection Letter will be issued when significant information requirements have not been included in the CTA or CTA-A. 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 new information and material, and will be assigned a new control number as per the *Management of Drug Submissions Guidance*.[5]

7.2 Review of CTAs and CTA-As

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

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

If there have not been any deficiencies identified and the CTA or CTA-A is deemed acceptable, a No Objection Letter (NOL) will be issued within the review period**. Sponsors of trials which qualify for the expedited review process can only proceed if:**

- **a No Objection Letter (NOL) is received from Health Canada prior to the 30 day default period, or**

- **within 30 days after the receipt of the application, a notice in respect of the drug, indicating that the sponsor may not sell or import the drug, has not been received.**

7.3 Filing of Trial Commencement Information

Prior to commencement of the Clinical Trial or implementation of a Clinical Trial Amendment, sponsors are required to complete and submit a **Clinical Trial Site Information Form**. Receipt of this form will not be subject to an acknowledgement letter.

[5] *Management of Drug Submissions Guidance 2003/04/04* is located on the Health Canada website.

8 NOTIFICATION

Notifications, as described below, must be provided for changes to CTAs and CTA-As. The changes may be implemented immediately, but Health Canada must be informed in writing, within 15 calendar days after the day of the change [C.05.007]. Notification changes include the following changes to CTAs and CTA-As:

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 6;

b) information on site closure or completion of the Clinical Trial;

c) when the Clinical Trial has been discontinued in its entirety or at any clinical trial site for reasons not related to the safety of clinical trial participants (e.g., for administrative purposes, lack of recruitment, etc); and

d) changes to Quality (Chemistry and Manufacturing) information that do not affect the quality or safety of the drug, for example:

   i) for Pharmaceuticals: production scale-ups with no changes in the process,
   ii) tightening of existing test specifications,
   iii) changes in contract testing laboratories,
   iv) changes in packaging material,
   v) for Pharmaceuticals: extension of shelf life, and
   vi) for Pharmaceuticals: changes not listed under 6.2 (a).

Updated 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.

9 LABELLING REQUIREMENTS

Labelling of clinical trial drug supplies must conform with Section C.05.011 of the *Food and Drug Regulations*. Labels of CTAs should not be submitted unless requested by the appropriate Directorate.

10 CLINICAL TRIALS INVOLVING INVESTIGATIONAL MEDICAL DEVICES AND A DRUG (PHARMACEUTICAL OR BIOLOGICAL / RADIOPHARMACEUTICAL)

Applications that involve the use of a medical device with a drug must be submitted to the lead Bureau / Directorate[6] **in duplicate**.

Authorization for the CTA or CTA-A, as well as authorization for the use of the investigational medical device, must be obtained prior to the initiation of the clinical trial or implementation of the protocol amendment.

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

11 CLINICAL TRIALS INVOLVING A PHARMACEUTICAL AND A BIOLOGICAL / RADIOPHARMACEUTICAL DRUG

CTAs or CTA-As that involve the use of pharmaceuticals **and** biologicals or radiopharmaceuticals must be submitted to the appropriate lead Directorate[6] **in duplicate**.

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

12 CONTINUOUS ASSESSMENT

12.1 Research Ethics Board Refusals

Following regulatory approval of a CTA or CTA-A, information regarding refusals by other regulatory authorities or Research Ethics Board(s), 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.

12.2 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 [C.05.015(1)].

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[6] The lead Bureau / Directorate is that defined as the Bureau / Directorate responsible for the review of the product filed by the sponsor of the CTA or CTA-A.

This notification should include:

a) detailed rationale for this action;

b) description of the impact on the proposed or ongoing trials, in respect of the drug, 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 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 [C.05.015(2)]:

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;

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

This information will be subject to review, and should be submitted as a CTA-A (see Section 6), in conjunction with the information submitted at the time of notification of trial suspension. Sponsors may only resume a trial when a No Objection letter (NOL) has been issued from the appropriate Directorate within 30 days of the submission of information.

12.3 Adverse Drug Reactions (ADRs)

Only adverse drug reactions that are ***both*** serious and unexpected are subject to expedited reporting to Health Canada. Expedited reporting of reactions which are serious but expected is not required. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered unrelated to the study product, whether or not the event is expected.

During a clinical trial the sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction 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, immediately where possible and, in any event, within 7 days after becoming aware of the information; and

c) within 8 days after having informed Health Canada of the ADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings.

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.*

Further definitions and standards for expedited reporting of adverse drug reactions are described in the Health Canada / ICH Guidance Document *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*. 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 addressed in a cover letter.

Final 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.

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.

A completed *ADR Expedited Reporting Summary Form* should be attached to the front of the report and reports should be submitted, by fax to:

Therapeutic Products Directorate
Pharmaceuticals **(613) 941-2121**

Biologics and Genetic Therapies Directorate
Biologics and Radiopharmaceuticals **(613) 957-0364**

Ongoing safety information respecting a drug should be conveyed to Investigator(s) and their Research Ethics Board(s). For further information refer to the Health Canada / ICH Guidance Documents *E6: Guideline for Good Clinical Practice* and *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

12.4 Updated Investigator's Brochure

Updated Investigator's Brochures, including all safety information and global status should be submitted annually. **Additional information and any changes that have been incorporated in the updated Investigator's Brochure should be highlighted for ease of review and evaluation.** If an Investigator's Brochure is updated more frequently, it should be submitted as required.

13 RECORDS RELATED TO CTAs AND 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 good clinical practices and these *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 Investigator's Brochure for the drug;

   ii) records respecting each change made to the Investigator's Brochure, 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 good clinical practices, 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 Research Ethics Board 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, informed consent form and any amendment to the protocol or informed consent form that have been approved by the Research Ethics Board for that clinical trial site; and

viii) for each clinical trial site, an attestation, signed and dated by the Research Ethics Board for that clinical trial site, stating that it has reviewed and approved the protocol and informed consent form and that the board carries out its functions in a manner consistent with good clinical practices.

d) The sponsor shall maintain all records referred to in this Division 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].

14 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 informed consent must be reviewed and approved by a Research Ethics Board (REB) as defined in the *Regulations.*

As described previously, 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 Research Ethics Board Attestation, signed by the REB that approved the protocol or protocol amendment at each site, that it carries out its functions in a manner consistent with Good Clinical Practices. Research Ethics Board(s) may wish to use the Research Ethics Board Attestation(s) or develop similar documentation that meets the requirements of Part C, Division 5 of the *Food and Drug Regulations*; and

c) submit information pertaining to the refusal of the protocol for any reason by an REB.

Please note that the Research Ethics Board Attestation should not be submitted unless requested by Health Canada.

The information required on the Qualified Investigator Undertaking, Research Ethics Board Attestation, HC/SC 3011, and Clinical Trial Site Information Form, is necessary due to differences in signing authority and attestation.

15 QUALIFIED INVESTIGATORS

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

Qualified Investigator(s) may wish to use the Qualified Investigator Undertaking(s) or develop similar documentation that meets the requirements of Part C, Division 5 of the *Food and Drug Regulations*.

Please note that the Qualified Investigator Undertaking(s) should not be submitted unless requested by Health Canada.

The information required on the Qualified Investigator Undertaking, Research Ethics Board Attestation, HC/SC 3011, and Clinical Trial Site Information Form, is necessary due to differences in signing authority and attestation.

16 INDEX OF APPENDICES

Appendix 1: List of Abbreviations;

Appendix 2: Useful Internet Website Addresses;

Appendix 3: Outline of a Clinical Trial Application;

Appendix 4: Guidance Notes for Protocol Synopsis (PCERT).

Appendix 1: List of Abbreviations

Adverse Drug Reaction.....ADR
Clinical Trial Application.....CTA
Clinical Trial Application Amendment.....CTA-A
Common Technical Document.....CTD
Drug Identification Number.....DIN
Good Clinical Practice.....GCP
International Conference on Harmonization.....ICH
Notice of Compliance.....NOC
No Objection Letter.....NOL
Not Satisfactory Notice.....NSN
Pre-clinical and Clinical Evaluation Report Template.....PCERT
Quality Overall Summary-Chemical Entities (Clinical Trial Applications).....QOS-CE(CTA)
Research Ethics Board.....REB

Appendix 2: Useful Internet Website Addresses

Biologics and Genetic Therapies Directorate . . . ***www.hc-sc.gc.ca/dhp-mps/brgtherap/index_e.html***

Canadian Institutes of Health Research . . . . . ***www.cihr.ca***

Health Canada . . . . . ***www.hc-sc.gc.ca***

Health Products and Food Branch . . . . . ***www.hc-sc.gc.ca/hpfb-dgpsa***

International Conference on Harmonization . . . . . ***www.ich.org***

National Council on Ethics in Human Research . . . . . ***www.ncehr-cnerh.org***

Therapeutic Products Directorate . . . . . ***www.hc-sc.gc.ca/dhp-mps/prodpharma/index_e.html***

Appendix 3: Outline of a CTA / CTA-A

Module	Pharmaceuticals	Biologicals and Radiopharmaceuticals
1	**Administrative / Clinical Information**	
1.1	Table of Contents (Modules 1-3)	
1.2	Application Information	
1.2.1	Drug Submission Application Form (HC/SC 3011)	
1.2.2	Information on Prior-related Applications	
1.2.3*	Investigator's Brochure	
1.2.4*	Protocol Synopsis (PCERT)	Submission Rationale / Brief Summary of the Drug Product
1.2.5*	Study Protocol(s)	
1.2.6	Informed Consent Document(s)	
1.2.7	Clinical Trial Site Information	
1.2.8	Canadian Research Ethics Board(s) Refusals	
1.2.9	Foreign Refusals	
1.2.10	Letters of Access	
1.2.11	Other Application-related Information	
1.3	Electronic Review Documents	
2	**Common Technical Document Summaries**	
2.1	Common Technical Document Table of Contents	
2.2	----	
2.3[7]*	Quality Overall Summary	
3	**Quality** (if submitted)	
3.1	Table of Contents of Module 3	
3.2	Body of Data	
3.2.R.1	----	Production Documentation
3.2.R.1.1	----	Executed Batch Records
3.3	----	Literature References

* These items should be submitted in hard copy and in electronic format accepted by Health Canada (e.g., CD-ROM).

[7] Refer to related Quality guidances for drug submissions in the CTD format for additional, specific information on the other available options under Module 2.3

Appendix 4: Guidance Notes for Protocol Synopsis (PCERT)

GUIDANCE NOTES: "PROTOCOL SYNOPSIS"
The following information should be included in the Protocol Synopsis (PCERT):

Trial Title and Number

Background / Rationale

Background: A brief, concise introduction into the clinical problem and previous treatments and developments, i.e., pertinent data from previous preclinical/clinical pharmacology studies and therapeutic exploratory studies taking into account relevant scientific literature *(citations by consecutive numbering, with list at end of this section; important or not readily available references may be included with the paper submission, if appropriate).* This section should also contain information on the new drug

Rationale: Reasoning and justification for the proposed new approach/ therapy.

Trial Objectives

Statement of the precise goal(s) of the trial (may be subdivided into primary and secondary objectives) which may including testing of the null hypothesis (H_o), i.e., testing a new drug population/ indication etc., as applicable.

Study Design & Duration

1. The statement of study design should include the method of randomization, blinding and the comparative agent, if applicable.
2. A "Brief outline of the study conduct" should be included, if applicable.
3. The design of the study should be able to support any claims related to the proposed study.
4. Total study duration (anticipated starting/ finishing dates).
5. Duration for each subject including post treatment period etc.

Number of Centres

Total number of trial sites with list of countries/geographical areas and number of sites in Canada.

List of Investigators

Principal Investigators at each Canadian site.

Sample Size

Rationale and calculation for sample size requirement, anticipated drop-out rate etc. The sample determination may include H_0 testing and desired power of the study.

Patient Population (*Target population)*
Description of specific characteristics of trial participants re. disease/ stage/ indication/ conditions/ treatment etc., as applicable. Description of diagnostic criteria and assessment.

Inclusion Criteria
Enumeration of conditions determining participation in the proposed clinical trial.

Exclusion Criteria
Enumeration of conditions determining exclusion from the proposed trial.

Drug Formulation
Brief description of the study drug(s) and formulation to be used in the clinical trial. The relationship to the formulations used in the preclinical and/or other clinical trials should be delineated, as applicable. This may also include disclosure of the formulation intended to be marketed and/or any bridging studies which may be necessary, planned, initiated and/or already performed if different formulations have been used during clinical development.

Instructions for safe handling.

Dosage Regimen
Rationale for dose selection.
Description of the schedule(s) for using the study drug(s) including escalations/ maintenance / reductions / discontinuation, as applicable.
Description of other supportive measures and dose modifications for specific adverse events (anticipated toxicities), as applicable.

Washout Period
Description for pre-, during- and post-trial, as applicable.

Pre-study Screening and Baseline Evaluation
Description of the process of clinical validation for participation in the clinical trial, including methodology / schedule of events.

Treatment Visit
Schedule of all events / visits / procedures during the clinical trial.

Premature Withdrawal/Discontinuation Criteria
Enumeration of all conditions / criteria and management for drug/ patient's withdrawal or (premature) discontinuation, including voluntary withdrawal by subject without prejudice to future treatment by the physician.
Early stopping rules for the trial.

Rescue Medication and Risk Management

Description of antidotes/ medications/ dosages / procedures used to help reverse untoward effects or lack of efficacy resulting from any applications of drug(s)/ procedures in connection with the clinical trial. This section should include any risks, for example, dose dumping from slow release formulations.

Concomitant Medication

Enumeration and description of all dis-/allowed drug/ medications, in addition to the study drugs.

Efficacy Variables & Analysis

Description and validation of primary endpoint(s), ie. responses/changes from baseline over time in relation to clinical trial events. Description and validation of related secondary changes (secondary endpoints) following from clinical trial events.

Safety Variables & Analysis

Monitoring/ assessing adverse drug reactions/ adverse events/ toxicities/ clinical laboratory parameters etc. in relation to clinical trial events.

Statistical Analysis

(The following points are presented for consideration while completing this section)

1. Analysis of trial parameters (primary/ secondary endpoints), population, demographics, as applicable.
2. Efficacy analysis methods and results of efficacy end-point analysis.
3. Safety analysis methods and results of safety end-point analysis.
4. Exploratory end-point analysis: evaluation effect(s) (or lack of effects) of relevant biochemical/ pharmacological etc parameters, as applicable.
5. Pharmacokinetic endpoint analysis, as applicable.
6. Interim analysis and role of Data Safety Monitoring Board, as applicable.