Draft guidance on clinical trial applications for clinical trial sponsors

This guidance document is being distributed for comment purposes only.

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Health Canada Santé Canada

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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 drug or clinical trial. 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, the Clinical Trials Regulations (regulations) under section 30 of the *Food and Drugs Act* (FDA) and the relevant sections of other applicable guidance documents.

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1. Introduction

1.1 Purpose and scope

This guidance document is for sponsors conducting or who intend to conduct clinical trials (CTs) involving the use of drugs (pharmaceuticals and/or biologics and radiopharmaceuticals). Under the FDA, a clinical trial is a study, involving human subjects, conducted to discover or verify the effects of a drug, device or food for a special dietary purpose.

This guidance document applies to all sponsors (for example, industry, academic, contract research organization) conducting the following types of trials:

- clinical trials involving the use of drugs that are not authorized for sale in Canada, including clinical trials for Phases I through III of drug development and comparative bioavailability studies
    - may also include drugs authorized for sale
- clinical trials involving the use of authorized drugs where their proposed use is outside the parameters of the purpose and conditions of use that were approved by Health Canada as part of the marketing authorization (Canadian notice of compliance (NOC) and/or a drug identification number (DIN)
- clinical trial application amendments (CTA-A) and notifications (CTA-N) for the CTAs mentioned
- Phase IV clinical trials where no authorization is required from Health Canada to conduct the trial
    - for example, CTs that only involve 1 or more drugs that have been issued an NOC and/or a DIN, if the use of all of the drugs in the trial are in accordance with the approved purpose and conditions of use
    - sponsors of these trials are subject to some regulatory requirements, such as good clinical practice (GCP) and record-keeping

Refer to section 2.2 of this guidance document for more information on Phase IV CTs.

This guidance document describes the requirements under the Clinical Trial Regulations. It supersedes the *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications* (May 29, 2013), which related to Division 5 of Part C of the Food and Drug Regulations (FDR), before Division 5 was repealed.

1.2 Policy objectives

This document gives guidance to sponsors seeking to conduct a clinical trial in Canada, as well as investigators and service providers. As such, it supports the protection of clinical trial participants and contributes to the high standards of excellence in research and development in Canada.

This document also clarifies the application and post-authorization requirements and outlines procedures for obtaining authorization.

1.3 Policy statements

Except for studies that only involve approved drugs used according to the authorized purpose and conditions of use (such as Phase IV studies), clinical trial sponsors must submit a clinical trial application (CTA) to Health Canada for authorization to conduct a trial, as well as to sell or import the drugs for the purpose of a clinical trial. All clinical trials must be conducted according to generally accepted principles of GCP, which are designed to ensure the protection of the rights, safety and well-being of clinical trial participants and other persons, and the reliability of results.

Research ethics boards (REBs) have an important role in the oversight of the conduct of clinical trials. All sponsors are required by the regulations to obtain REB approval for each clinical trial site before commencing the trial at that site. Alternatively, sponsors may obtain approval of their proposed protocol and informed consent statement by a national REB that is on the Canadian List of National Research Ethics Boards. Sponsors who have obtained national REB approval are not required by the regulations to obtain a separate REB approval for each clinical trial site.

The regulations are generally consistent with the principles, definitions and standards found in the International Conference on Harmonization (ICH) guidance documents on clinical trials. Where inconsistencies exist between the regulations and ICH guidelines, the regulations will take precedence.

The format for CTAs 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. This is to facilitate the preparation of drug submission information throughout the lifecycle of a drug.

1.4 Overview of new regulatory features

The regulations would include the following features that are not present under Part C, Division 5 of the current FDR.

A shift to regulating the conduct of a trial: The regulations would shift Health Canada's oversight from only regulating the importation and sale of a drug to be used in a clinical trial. Oversight would shift to directly regulating the conduct of a clinical trial (which encompasses a range of activities such as obtaining informed consent, distributing the drug to the participants, monitoring visits with the participants). This would provide the necessary flexibility to better enable oversight during the entire lifecycle of a trial, at a level where oversight is proportional to risk.

Issuance of authorization: Clinical trials requiring submission of an application to the Minister will no longer be deemed authorized by operation of the regulations, as was previously the case under Part C, Division 5 of the FDR. Instead, Health Canada will issue formal letters of authorization for clinical trials. Within the first 7 days, Health Canada will issue an acknowledgement letter and a "contingent authorization". Unless, following its review, Health Canada objects to the trial, this contingent authorization becomes a full authorization to conduct the trial. This would occur either after the 30-day review period has elapsed or once Health Canada has issued a "notice of no objection", whichever comes first.

During this period, Health Canada will conduct a thorough assessment of each application to determine whether the sponsor should be authorized to conduct the clinical trial. A "contingent authorization" does **not** authorize importation of a drug or any other regulated activity for the clinical trial while the application is still under review (subsection 14(2) of the regulations).

Risk-based approach: Regulatory requirements for a trial would be proportionately tailored to the level of risk of the drugs used in the trial. Health Canada would have the ability to impose terms and conditions on a clinical trial authorization at any point over the lifecycle of the trial to mitigate risks or address uncertainties.

Extended review timelines for some CTAs: In certain cases, the review periods may be extended from 30 to 60 days. This could apply to:

- accommodate the evaluation of complex clinical trials and evolving innovations in technology, science or medicine **or**
- thoroughly assess protocols involving vulnerable participant populations, ensuring appropriate protections are in place

Modified requirements: The regulations introduce some modified regulatory requirements to support an agile, lifecycle approach to oversight and enable appropriate oversight of innovative new designs for clinical trials. Examples include:

- master protocol trials (trials involving multiple drugs and/or disease populations in multiple sub-studies) **and**
- decentralized clinical trials (a trial where some or all of the activities are conducted at locations remote from the main location of a clinical trial site)

Other flexibilities include:

- the ability to suspend or revoke a part of an authorization in a more flexible way (for example, 1 or more arms of a trial or the use of a product within a trial)
    - This would allow risks to be managed without having to suspend or revoke an entire trial or site.
- an expanded ability to request an assessment of safety information
- to facilitate decentralized clinical trials, there would be greater flexibility with respect to the types of regulated health professionals that can conduct a trial as an investigator and greater clarity on the meaning of a trial site and how it is referenced in regulations (to capture the main location and remote locations)
- flexibilities on the timing of the provision of informed consent for clinical trials involving medical emergencies
- possibility to take a selective approach to keeping records of adverse events for trials involving drugs for which there is a well-understood and documented safety profile, as per the authorized protocol

Post-trial obligations: New post-trial reporting provisions enable the Minister to impose certain post-trial reporting requirements on a case-by-case basis. An example of this could include reporting serious unexpected adverse drug reactions for a period of up to 15 years post-trial for drugs that have not been approved in Canada for any indication. However, this obligation would only apply if Health Canada has reasonable grounds to believe that there could be a risk of long-term health consequences for participants.

Oversight of service providers: The oversight of additional parties involved in the conduct of a trial who carry out activities related to a clinical trial on behalf of the sponsor or investigator would now be explicit in regulations.

2. Exempt Phase IV clinical trials (no authorization from Health Canada required)

2.1 Regulatory requirements for exempt Phase IV clinical trials

Sponsors are not required to file a CTA or receive authorization for the conduct of clinical trials only involving authorized drugs where the investigation is to be conducted within the parameters of the approved NOC or DIN. These types of Phase IV trials are exempt from section 3.1 of the FDA.

Additionally, investigators, service providers and any other persons involved in the conduct of a clinical trial are also exempt from section 3.1 of the FDA, if they are conducting on behalf of a sponsor who is exempt. Although the sponsors and their employees as well as service providers and investigators of these types of trials may be exempt from section 3.1 of the FDA, they must nonetheless conduct their trials according to GCP, which includes the obligation to obtain REB approval prior to commencing their trial and to adhere to some record keeping requirements.

For more guidance on Phase IV trials, consult:

- Guidance document: Part C, Division 5 of the Food and Drug Regulations “drugs for clinical trials involving human subjects” (GUI-0100)

Despite not requiring an authorization from Health Canada to conduct such a trial, Health Canada has certain authorities with respect to these trials. For example, Health Canada has the ability to request information and samples, and the power to order a sponsor to cease conduct.

Refer to section 13 of this guidance document for further details on these authorities.

Furthermore, investigators of clinical trials involving controlled substances must apply to Health Canada for an exemption from the Controlled Drugs and Substances Act (CDSA).

Find additional information on the use of controlled substances for scientific purposes, including the application form.

Refer to section 10.5.2 of this guidance document for further details on clinical trials involving controlled substances.

2.2 Importation of Phase IV clinical trial drugs

In accordance with section 6(1) and section 8(2) of the regulations, the sponsor of a Phase IV clinical trial does not have to file a clinical trial application (CTA) for importation and/or sale of the study drug. However, certain regulations for selling and/or importing the trial drug apply.

For more information, consult:

- Importing and exporting health products for commercial use (GUI-0117)

2.3 Adverse drug reactions for Phase IV clinical trials

For more information on the requirements for reporting adverse drug reactions (ADRs) for Phase IV clinical trials, consult:

- Overview of the reporting adverse reactions to marketed health products - Guidance document for industry

Note: Sections C.01.016 to C.01.019 of the FDR, which also refer to serious ADR reporting, continue to apply to authorized drugs used in a clinical trial according to their approved purpose and conditions of use.

2.4 Inspection of Phase IV clinical trials

Phase IV studies are subject to the regulations and must be conducted in accordance with GCP.

Refer to section 13 of this guidance document (Authorities for a clinical trial for which the sponsor is exempt from section 3.1 of the FDA).

For more information, refer to:

- Guidance document: Part C, Division 5 of the Food and Drug Regulations “drugs for clinical trials involving human subjects” (GUI-0100)

3. Pre-clinical trial application (CTA) consultation meeting

Potential sponsors may request a pre-CTA consultation meeting. Such consultations may be particularly useful for a new drug type or applications with complex considerations.

The pre-CTA consultation meeting provides an opportunity for the sponsor to pose specific questions to Health Canada, present relevant background and characterization data, and discuss concerns and issues regarding drug development.

It gives Health Canada an opportunity to provide guidance on the proposed trial. Sponsors are also able to proactively identify any unique conditions or data related to complex clinical trial designs (for example, master protocol trial with multiple sub-studies or clinical trial with multiple trial locations). This supports Health Canada's review process and helps reduce follow-up.

Examples of other elements of complexity:

- The drug represents an emerging or innovative technological, scientific or medical development.
- The manufacturing of the drug or its quality control involves a process that is emerging or innovative.
- The participant population, or any part of it, has a particular vulnerability that could require special consideration and protections during the conduct of the trial.

Sponsors may invite to the meeting the investigators who will be involved in the proposed trial in Canada. The purpose of the pre-CTA meeting is to provide advice for CTA filing based on the sponsor's specific questions posed to Health Canada. Any advice provided is not intended to represent or replace the formal review of a CTA submission.

3.1 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 C.

Requests should be submitted in the form of a cover letter proposing 4 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 specific preliminary questions to be addressed by the Directorate during the meeting
- 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 and the sponsor's resources.

The directorate will acknowledge the request for consultation in a timely manner. If the directorate agrees with the request, the sponsor will be notified of the pre-CTA consultation meeting date, time and timeline to provide the pre-CTA information package. This is usually 6 weeks before the confirmed meeting.

3.2 Pre-submission meeting: Clinical trial application (CTA) information package

The information package should be submitted in accordance with current electronic specifications.

Refer to Appendix D.

It could contain:

- the proposed agenda, any prepared slides including a finalized list of questions and a complete list of attendees
    - recognizing that the slides may change before the meeting

- a rationale for the purpose of the study
- a brief summary of all relevant data including, as applicable:
    - a tabular listing for any planned, ongoing and completed non-clinical and clinical studies
    - results from pharmacokinetic (PK), pharmacodynamic (PD) and proof of concept studies, as available and relevant to the proposed pre-submission meeting
    - results from studies characterizing the toxicity endpoints, adverse events in animals and/or toxicological manifestations in humans, as available and reflective of the phase of development, with a discussion of potential (and any known) safety signals, and relevance to the use of the drug and its risk mitigation in humans
- a proposed global clinical plan for the current stage of drug development including regulatory status in other countries, or any impositions of any terms and conditions on an authorization to conduct the clinical trial by a foreign regulatory authority
    - recognizing that this plan is subjects to change as new information becomes available
- details of the proposed clinical trial to be conducted in Canada, including, as appropriate, a general or detailed description of the trial design, for example:
    - study objectives and endpoints, risk mitigation plans and other elements of the study design relevant to the sponsor's questions
    - details on a drug that is considered an "emerging, innovative or technological, scientific or medical development"
    - information on the manufacturing of the drug or its quality control, if it involves a process that is emerging or innovative
    - information on any particular vulnerabilities of the proposed participant populations
    - any complexities, for example, linked to master protocol trials containing multiple sub-studies within the overall organization of the trial
    - parameters, values, ranges or limits for dosage forms, dosage regimens and formulations

    - proposed procedures and/or criteria for patient monitoring, clinical efficacy and safety assessments, alternative treatments, premature patient discontinuation and other considerations, as appropriate
- a summary of significant quality (chemistry and manufacturing) aspects of the drug, if applicable:
    - a summary of the method of manufacture for both drug substance (medicinal ingredient) and dosage form
    - relevant flow charts
    - a listing of quality control procedures and specifications
    - parameters, values, ranges or limits for indications and clinical uses, patient study populations and routes of administration
    - a summary of product characteristics
    - a listing of all production sites (only for biologics and radiopharmaceuticals)
        - If a drug to be used in the clinical trial contains a novel excipient, full details of manufacture, characterization and controls in respect of the excipient, with supporting safety data will be needed in the CTA package.
- research ethics board status
- details about any proposal for the selective retention of records of adverse events

Should the pre-CTA package be considered insufficient (for example, the information does not provide enough context for the pre-CTA questions to be adequately addressed), the sponsor may be asked to cancel the meeting. Doing so will allow the sponsor to assemble a more thorough package.

Notes: The directorate may request that the proposed agenda be modified to allow enough time to achieve the stated goals of the meeting.

3.3 Pre-clinical trial application (CTA) consultation meeting record

The sponsor should prepare and send to the appropriate directorate a written summary of the discussions and conclusions of the consultation meeting within 14 days of the

consultation date. The directorate may make clarifications to the written summary, including adding “post-meeting clarification notes”. The sponsor may wish to include their own post-meeting clarification notes. All records of this consultation will be added to the dossier for the pre-CTA meeting.

A copy of the record of discussions and conclusions approved by all parties in attendance at the meeting should be included in the subsequent CTA.

4. Clinical trial applications (CTAs)

Unless the sponsor is exempt, the sponsor must file a CTA and receive an authorization to conduct the trial before its initiation.

Refer to section 2.

CTAs are required for clinical trials using drugs not authorized for sale in Canada, including clinical trials in Phases I through III of drug development and comparative bioavailability studies. This also applies to trials involving authorized drugs, where the proposed use of the drug is outside the parameters of the NOC or DIN (for example, when one or more of the following is different:

- indication and clinical use
- target patient population
- route of administration **or**
- dosage regimen

The CTA should contain sufficient scientific evidence to demonstrate that the drug being investigated in the clinical trial has the potential to contribute to scientific understanding or advance medical knowledge. It must also provide sufficient information to enable Health Canada to determine whether to authorize the sponsor to conduct the trial. This would include information that the:

- conduct of the clinical trial, including the use of any drug for the purposes of the trial, is unlikely to result in unacceptable risks to the health of clinical trial participants or other persons
- clinical trial is not contrary to the best interests of clinical trial participants **and**
- objectives of the clinical trial are achievable

The CTA must be signed and dated by the sponsor's senior medical or scientific officer in Canada, and the senior executive officer. The CTA must include a signed attestation that confirms:

- the sponsor takes responsibility for the overall conduct of the clinical trial
- the clinical trial will be conducted in accordance with good clinical practices and the regulations **and**
- all information and material contained in or referred to by the application is complete and is not false or misleading

4.1 Good clinical practice (GCP)

Sponsors of all clinical trials, including Phase IV trials, must obtain REB approval and conduct the trial in accordance with the principles of GCP. The sponsor is the individual or corporate person who has overall responsibility for the conduct of the clinical trial, whether they conduct all trial activities or another person conducts some or all trial activities on the sponsor's behalf.

Health Canada considers the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guideline on Good Clinical Practice (GCP) as the standard to follow on GCP.

For more information, consult:

- Guidance document: Part C, Division 5 of the Food and Drug Regulations "drugs for clinical trials involving human subjects" (GUI-0100)

Health Canada has fully adopted the ICH E6 GCP guideline. It is the sponsor's responsibility to take all reasonable measures to ensure that people conducting activities on their behalf do so in accordance with good clinical practices, the clinical trial protocol and the regulations. The sponsor must also put in place measures to ensure the protection of participants and the reliability of the trial results.

All persons conducting clinical trial-related activities must do so in accordance with good clinical practices that are relevant to their respective activities.

GCP also includes the following requirements:

- The clinical trial must be scientifically sound and clearly described in a detailed protocol, including a description of the population to be studied in the clinical trial which must be consistent with the study's objectives

    - For more information on suggested recommendations: Sex Gender Based Analysis (SGBA) Plus Demographics Action Plan in Clinical Trial Applications.
- A clinical trial for which an authorization has been issued must also be conducted in accordance with the authorization and any terms and conditions imposed on the authorization.
- Systems and procedures that are implemented must be:
    - designed to ensure the protection of the health of participants and other persons
    - proportionate to the risks to the health of participants and other persons
    - designed to ensure the quality of every aspect of the clinical trial and the reliability of its results
- Approval of an REB must be obtained before the clinical trial begins for each site.
- For each clinical trial site (whether limited to 1 location, virtual, various geographic locations within Canada or decentralized), there is no more than 1 investigator.
- For each clinical trial site, medical care and medical decisions for the clinical trial must be under the supervision of:
    - in the case of a clinical trial respecting a drug to be tested for dental purposes only, a person who is entitled to practise medicine or dentistry under the laws of the province where the main location of the clinical trial site is situated and
    - in any other case, a person who is entitled to practise medicine (in other words, a physician) under the laws of the province where the main location of the clinical trial site is situated
- Each person who is involved in the conduct of the clinical trial must be qualified by education, training and experience to perform their respective tasks.
- Except for some limited circumstances, documented informed consent, given in accordance with the applicable laws governing consent, must be obtained from every prospective participant **prior** to their participation in the clinical trial, but only after they have been informed of:
    - the risks and anticipated benefits to their health arising from participation in the clinical trial
    - all other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial

A description of the limited circumstances is found in section 4.3.

Informed consent does not always need to be provided in written format (for example, a wet signature on paper). Depending on the context, electronic signatures, and documentation of oral consent, whether given in person or virtually, live or recorded, may be acceptable. E-consent methods can be particularly valuable in fully virtual or hybrid decentralized clinical trials that incorporate technological innovations, supporting broader and more diverse participant recruitment.

Also, each drug used in the clinical trial must be fabricated, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 of Part C of the FDR, with the exception of sections C.02.019 (finished product testing), C.02.025 (the duration of sample retention), C.02.026 (the quantity of sample retention) of those regulations.

Note: Authorized drugs used in a clinical trial in accordance with the conditions of their NOC/DIN would not be subject to exemptions from sections C.02.019, C.02.025, C.02.026 of the FDR.

4.2 Clinical trial transparency

Health Canada does not maintain a registry for clinical trials. Sponsors should register their clinical trial in an international registry that complies with the World Health Organization (WHO) standards, such as:

- ClinicalTrials.gov **or**
- ISRCTN Registry

Sponsors should report summary results in the same registry.

These publicly accessible registries can be searched free of charge. They can be used to collect and display the WHO Trial Registration Data Set and accept prospective registration of clinical trials taking place in all countries, including Canada.

4.3 Exception to prior informed consent requirements in trials involving medical emergencies

4.3.1 General principles

In accordance with good clinical practice, informed consent must ordinarily be obtained from all prospective trial participants by an investigator or delegated personnel prior to participation.

Consent must be based on a thorough explanation of potential risks, anticipated benefits and other relevant information necessary for an informed decision. However, section 47 of the regulations provides a framework for allowing an exception to certain clinical trials from the requirement to obtain prior documented informed consent. The exception applies to emergency medical situations described in the protocol where such consent is impossible.

4.3.2 Criteria for exception to prior informed consent

Sponsors may seek an exception from the prior informed consent requirement when conducting clinical trials involving medical emergencies, provided all the following conditions are met:

Nature of emergency:

- The prospective participant is experiencing severe suffering or is at imminent risk of serious bodily harm and requires immediate intervention.
- The participant is unconscious or otherwise unable to provide informed consent.
- A delay in treatment risks compromising the effectiveness of the investigational product or missing the therapeutic window.
- Informed consent cannot be obtained from a substitute decision-maker in a timely manner.

Trial protocol requirements:

- The clinical trial objectives specifically target individuals in emergency medical situations.

The protocol explicitly states that informed consent cannot be obtained prior to participation under certain circumstances, as defined in the protocol. As per a risk-benefit assessment, there are reasonable grounds to believe either:

- no standard of care exists **or**
- participation in the trial presents a greater prospect of direct benefit than the available standard of care

In addition, there are reasonable grounds to believe that the risks associated with trial participation are either:

- no greater than those posed by the standard of care **or**
- justified by the potential direct health benefit to the participant

Ethics oversight:

At the earliest feasible opportunity following enrollment, sponsors are required to obtain documented informed consent from participants in accordance with applicable laws. Post-enrollment consent must include:

- clear communication of any risks and anticipated benefits associated with continued participation
- comprehensive details of the clinical trial necessary for informed decision-making

4.4 Labelling

All drugs involved in the conduct of a clinical trial are required to have a label. “Label” is defined in the FDA as “any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package.”

The information on the label must be expressed in a legible, permanent and prominent manner, in terms that are easily understood by the intended user.

Unless the drug is labelled in accordance with the FDR, the label must include the following information, in both English and French, as per section 67(2) of the regulations:

(a) a statement indicating that the drug is for use only in a clinical trial by an investigator (or other statements that convey that meaning)
(b) the brand name, code, or chemical name of the drug or a number or identifying mark assigned to the drug for the purposes of the clinical trial
(c) the expiration date of the drug, if any
(d) the recommended storage conditions for the drug
(e) the lot or batch number of the drug (refer to subsection 67(3) of the regulations)
(f) the sponsor's name and information that enables a person in Canada to contact the sponsor and
(g) the protocol code

This information must be displayed on the label in a legible and prominent manner and expressed in plain language. In addition, the format of the label, including the manner in which its text and any graphics are displayed on it, must not impede comprehension of the labelling information.

Also, as per section 67 (5) of the regulations, if the drug is a radiopharmaceutical as defined in section C.03.201 of the FDR, the label must display the symbol and the words referred to in subparagraph C.03.202(1)(b)(vi). The label reads: "the radiation warning symbol set out in Schedule 3 to the Radiation Protection Regulations and the words "RAYONNEMENT — DANGER — RADIATION".

Sponsors of trials involving drugs that already have an NOC or a DIN may choose to use the drug's approved labelling if the drug is labelled in accordance with the FDR. However, sponsors in this situation may choose to re-label a drug as per section 67 (2) of the regulations. This means that for authorized drugs, sponsors have the option to use either a label that meets the requirements of the FDR or a new label that meets the requirements of the regulations.

4.5 Filing a clinical trial application (CTA)

Brief CTA review process and timelines:

Once a sponsor has submitted all required information for a CTA to Health Canada, the application is considered "complete" from a screening perspective. From that point:

- Within the first 7 days, Health Canada will issue the sponsor an acknowledgement letter noting the date of receipt of a complete submission and a "contingent authorization" that becomes an authorization to conduct the trial after 30 days* has expired from the date of receipt of a **complete** submission.
- A CTA is considered authorized either when the 30-day* period has expired or when the sponsor receives a notice of no objection (NNO) from Health Canada in advance of the expiry date.

* Health Canada may, at any point within 30 days of receiving a complete clinical trial application (CTA), notify the sponsor (who received the contingent authorization) that an additional 30 days is required to complete the review. This extended 60-day review period may be triggered based on 1 or more of the following factors:

- Health Canada may need to impose terms and conditions on the authorization to address a complexity of the trial.
    - Refer to section 8.
- The trial design is complex.
    - Refer to section 6 and section 7 for examples of complexity in trials, as well as for details on the review process and review timelines.
        - for example, the case of master protocol trials involving 1 or more sub-studies
        - Refer to Appendix E.
- The drug involved represents an emerging or innovative technological, scientific or medical development.
- The drug's manufacturing or quality control process involves emerging or innovative methods.
- Additional assessment is needed to address specific vulnerabilities within the participant population.

CTAs should be sent directly to the appropriate review directorate. If the sponsor is unsure which of the two directorates should review their CTA, they may email either directorate. That directorate will confirm the correct one, and the sponsor should then send the CTA to that directorate.

4.5.1 Joint reviews

CTAs or CTA-As must be submitted to the appropriate lead directorates when they involve the use of:

- pharmaceuticals and biologics or radiopharmaceuticals, if they are being used outside the conditions of use approved by Health Canada or are not approved for sale in Canada
- a combination product (for example, medical device and drug) that is classified as a drug **or**
- a natural health product (NHP) and a drug
    - The sponsor will be contacted if further information is needed to complete the application pursuant to section 66 of the Natural Health Products Regulations.

Authorization for the conduct of a clinical trial, as well as the sale and importation of all products, must be obtained prior to the initiation of the clinical trial or implementation of the protocol amendment. The lead directorate will be responsible for communicating the regulatory decision to the sponsor.

For clinical trials that involve a drug and the use of a Class II, III or IV medical device that is not a combination product, an investigational testing application (ITA) must be filed to the Medical Devices Directorate in addition to the CTA. Both must be authorized before the trial can commence.

For more information, consult: Applications for Medical Device Investigational Testing Authorizations Guidance Document - Summary - Canada.ca

For clinical trials that involve a drug and an unlicensed NHP (or an NHP that is used outside of its NHP licence), an application must be submitted to the PDD **or** BRDD, as appropriate, **and** the Natural and Non-Prescription Health Products Directorate (NNHPD).

For clinical trials that involve a drug and a licensed NHP (used in accordance with its NHP licence), the CTA should be submitted solely to the PDD or BRDD, as appropriate.

On the other hand, the CTA should be submitted solely to the NNHPD if a drug involved in the trial is approved for sale in Canada and is being used within its approved purpose

and conditions of use. Examples of CTs in these circumstances could include an NHP to treat the side effects or to increase the efficacy of a conventional pharmaceutical drug.

4.6 Clinical trial application (CTA) format

The CTA is composed of 3 parts (modules) in accordance with the CTD format:

1. Module 1: contains administrative and clinical information about the proposed trial
2. Module 2: contains quality (chemistry and manufacturing) summaries about the drug products to be used in the proposed trial
3. Module 3: contains additional supporting quality information

While providing CTA regulatory activities (RAs) in eCTD format is preferred, sponsors may choose to file in non-eCTD format.

For more details on filing submissions electronically, visit:

- Filing submissions electronically

For eCTD format, before filing an initial CTA via the Common Electronic Submissions Gateway (CESG), each company must file a sample transaction to Health Canada. This is to be done in accordance with the eCTD guidance document.

For guidance on the eCTD format for their clinical trial regulatory activities, to request a dossier ID in advance of filing or questions related to eCTD modules or file structure, sponsors should send an email to ereview@hc-sc.gc.ca.

If the sponsor chooses to file in non-eCTD format, the CTA can be submitted via email to the respective directorate:

- For pharmaceutical drugs: oct.smd-dgp.bec@hc-sc.gc.ca
- For biologic and radiopharmaceutical drugs: brdd.cta-dec.dmbr@hc-sc.gc.ca

Note the following email restrictions:

- The regulatory transaction must be provided as a zipped file.

    - Consult Guidance document: Preparation of regulatory activities in the "non-eCTD electronic-only" format.
- The submissions should not be password-protected.
- The subject line of the email should state: "CTA(-A), [Product Name], [Protocol Number]".
- Emails received after 3:00 pm EST will be considered received the following business day.
- Individual files larger than 10 MB may be rejected by the mail server (files larger than 10 MB should be split into 2 or more individual files).
- The maximum email size accepted by the corporate mail server is 20 MB.
    - If your CTA(-A) is larger than 20 MB, the CTA(-A) may be split and sent under separate emails (for example, 1 email for Module 1 and 1 email for Module 2 and 3). The subject line of the emails should clearly link to one another (for example, "Email 1 of 2: CTA(-A), [Product Name], [Protocol Number]").

Alternatively, sponsors can mail their CTA package to the respective directorate. The CTA should be submitted on electronic media, accompanied by a hard copy cover letter, and be organized in accordance with the current electronic specifications:

- Guidance document: Preparation of drug regulatory activities in the "non-eCTD electronic-only" format

If a submission is submitted via email, a couriered copy should **not** be sent in duplicate.

Refer to Table 1 for guidance on submissions or the Organization and document placement for Canadian Module 1, which is updated with the latest information for preparing a submission.

Also refer to Appendix D for guidance in preparing the application.

614 **Table 1: Contents of submission package in accordance with CTD format**

Module 1: Administrative and product information

- **1.0 Correspondence**
- **1.0.1 Cover letter**
  - **CTA/CTA-A:** For CTA-As, a cover letter indicating the original CTA(s) and relevant CTA-As with file number (Dossier ID), protocol number and control numbers. For CTA or CTA-As with a pre-CTA(-A) meeting or a refiled CTA(-A), reference to the previous control numbers should be included.
  - **CTA-A (quality) for biologics and radiopharmaceuticals only:** Include a list of all proposed quality changes from the authorized application. Refer to section 2.4.2a of Module 1.
- **1.0.2 Lifecycle management table**
  - **CTA-A:** Listing of related control numbers for the same protocol ID. Refer to the Organization and document placement for Canadian module 1 for details on the organization and placement of documents within the Canadian Regional Module 1 section of the CTD structure. It lists the Module 1 sections/subfolders, along with a list of the possible documents that must be placed in these sections/subfolders when provided as part of a regulatory transaction to Health Canada.
- **1.0.5 Meeting information**
  - **CTA/CTA-A:** Include, for example, 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.
- **1.0.7 General note to reviewer**
- **1.1 Table of contents**
  - **CTA/CTA-A**: 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 Application forms**
  - **CTA/CTA-A**: A completed and signed Drug submission application 3011 Form including Appendix 3, (Appendices 1 and 2 of the 3011 Form should be completed and submitted if applicable). Note that a new 3011

Form needs to be submitted for each CTA-A as well, not just the initial CTA. Refer to Appendix D for the relevant URL address.

When completing the forms, the following information is included in the application:

- the name and contact information of the sponsor and, in the case of a foreign sponsor, the name and contact information of the sponsor's representative in Canada
- an attestation confirming that (1) the sponsor takes responsibility for the overall conduct of the trial, (2) the clinical trial will be conducted in accordance with good clinical practices and the Regulations, and (3) all information contained in, or referenced by, the application is complete and is not false or misleading. This attestation must be made by the person who signs and dates the CTA (if the drug is to be imported, the name and contact information of the sponsor's representatives in Canada who is responsible for the importation and sale of the drug)
- if a service provider is to conduct clinical trial activities, the name and contact information of each service provider being used to conduct clinical trial activities on behalf of the sponsor, if known at the time of filing the application

- **1.2.3 Certification and attestation forms**
  - **CTA/CTA-A:** Include the Summary of Additional Drugs Form if applicable (refer to Appendix F)
- **1.2.5 Compliance and site information**
  - **1.2.5.1 Clinical trial site information form**
    - **CTA/CTA-A:** The Clinical Trial Site Information (CTSI) Form should be provided for each new proposed clinical trial site. Health Canada recognizes that not all information required in the CTSI form may be available at the time of filing a CTA. Sponsors are reminded that even if this information is not available when filing the CTA, it is required prior to commencement of the trial as per the regulations. Refer to section 10.3 of this guidance document for additional information. For instructions on how to complete the CTSI and how to submit the form, visit: Instructions for completing the Clinical Trial Site Information Form.

- The following information must be included in the CTSI form, if known at the time that the CTA is submitted:
  - the name and contact information of the investigator, and where the contact information of the investigator differs from the address of the clinical trial site's main location, the address of the clinical trial site main location
  - the name and contact information of the research ethics board (REB) that approved the protocol and the informed consent form (ICF) (Health Canada recognizes that, in some cases, a single national REB approval may cover multiple trial sites)
  - the proposed date for the commencement of the clinical trial at the clinical trial site

If any changes are made to the information submitted in a CTSI form (for example, change of investigator) a revised CTSI form should be submitted.

- **1.2.6 Authorization for sharing information**
  - **CTA/CTA-A:** Letters authorizing Health Canada to access related files (in other words, a previously authorized CTA, master 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 an 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 master file (MF):**
      - A letter written by the MF holder permitting Health Canada to reference information in the MF in support of the sponsor's CTA should be submitted.
      - The CTA sponsor should ensure that the supporting MF (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 by a different sponsor and authorized by Health Canada:**
      - A letter written by the third-party sponsor of the referenced application authorizing Health Canada to access the information in support of the CTA should be included in the submission.

        - The third-party granting authorization should not provide a copy of this letter to Health Canada separately.
        - The referenced information should meet the regulatory requirements for CTAs.
        - The letter of access should include the file number (Dossier ID) and control number(s) of the referenced submission(s).
        - 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 International information**
    - **CTA/CTA-A (clinical)**: If applicable and known at the time of submission of the application or any time before a decision is made by Health Canada about the authorization of the clinical trial, a description of the following decisions or measures, including the reasons, taken by a foreign regulatory authority:
        - refusal to authorize the conduct of the trial
        - refusal to authorize amendments to an authorization to conduct the trial
        - any suspension or revocation of clinical trial authorization, in whole or in part
        - imposition of any terms and conditions (and if applicable, their amendment) on an authorization to conduct the trial, including the text of those terms and conditions
        - any refusal by a foreign research ethics board to approve the protocol or any other protocol prepared for the clinical trial
- **1.2.9 Other administrative information**
    - **CTA/CTA-A:** 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.
    - If a service provider is to conduct clinical trial activities, the name and contact information of each service provider being used to conduct clinical trial activities on behalf of the sponsor, if known at the time of filing the application, as per the 3011 Form.

- **1.3 Product information**
    - **1.3.4 Investigator's brochure or equivalent document**
        - **CTA:** Sponsors must provide comprehensive drug information to Health Canada for all drugs involved in the clinical trial, except for those that have received an NOC and/or DIN and are used within their approved purpose and conditions of use. This information must be provided in a document such as an Investigator's Brochure (IB), that contains all of the following:
            - the physical, chemical and pharmaceutical properties of the drug
            - any non-clinical and clinical information, including risk information, that is necessary to support the use of the drug in the clinical trial and
            - if the drug is a radiopharmaceutical, directions for its preparation as well as the radiation dosimetry of, and storage requirements for, the prepared radiopharmaceutical
        - Alternatively, for products authorized in Canada, the sponsor may provide a copy of the most recent Canadian product monograph (PM) where appropriate. This said, additional information beyond the PM may be required to support the application (for example, for drugs exploring a new indication, population, or route of administration), and the sponsor may be requested to produce an IB accordingly.
        - In certain circumstances, foreign PMs for products sourced from an ICH region could be accepted by Health Canada.
        - **CTA-A (clinical):** If the CTA-A proposes to extend the duration of the treatment, an updated IB or equivalent information 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.
- **1.7 Clinical trial information**

- **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 versus 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.
  - If the sponsor proposes a selective approach to maintaining records of adverse events for a drug to be used in the trial, other than records of serious unexpected adverse drug reactions, the protocol must include sufficient information to support the proposed approach as per section 11.7.2.
  - If the protocol provides for the enrolment of participants in the clinical trial without their prior documented informed consent, it must include sufficient information to establish that the conditions for the exception are met. Refer to section 4.3.
- **1.7.2 Informed consent forms**
  - **CTA:** A copy of the statement regarding the risks and anticipated benefits to the clinical trial subjects as a result of their participation in the clinical trial that will be included in the informed consent forms (ICFs) to be used in conjunction with the clinical trial. ICFs 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 ICF.
  - **CTA-A (clinical):** The revised statement from the ICFs must be submitted if the changes to the study protocol(s) or other supporting documentation (non-clinical study results, adverse events, revisions to the IB) affect the information in the ICF. The ICF with changes clearly indicated (annotated) should be provided.
- **1.7.3 Canadian research ethics board (REB) refusals**

        - **CTA/CTA-A (clinical)**: The name and contact information 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 or at any time before a determination is made with respect to the issuance of the authorization. Refer to bullet **2.7 International information** for additional information.
- **7.4 Information on prior-related applications**
    - **CTA/CTA-A**: A list of previous submissions (for example, pre-CTA, the parent CTA and any previous CTA-amendments).
    - **CTA-A involving master protocol trials**: Refer to Appendix E.

Module 2 Common technical document summaries

This module contains quality (chemistry, manufacturing, and controls [CMC]) information only. This section does not apply if the drug product to be used in the clinical trial has received an NOC and/or DIN and has not been modified for the purposes of the clinical trial.

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 and include the necessary letter of access in the submission if applicable.

The Common Technical Document Summaries Module should include:

- **CTA-A (quality)**: An applicable updated quality overall summary (QOS) or quality information summary (QIS) containing only the revised sections. The rationale for each proposed change should be submitted, and the revised information should be clearly identified. Alternatively, the changes may be listed in a separate document or in a marked up annotated version of the QOS, QIS-R or QIS-PER, as applicable.

For pharmaceutical drugs:

- Sponsors may provide an Investigational Medicinal Product Dossier (IMPD) in lieu of a QOS to fulfil the CMC requirements for a CTA(-A) submission. If an IMPD is provided, it is expected that it would contain all the required CMC

information in accordance with the requirements outlined per the study phase. To facilitate review, sponsors should still complete and submit the QOS introduction and include it within the CTA package) in lieu of a QOS to fulfil the CMC requirements for a CTA(-A) submission. If an IMPD is provided, it is expected that it would contain all the required CMC information in accordance with the requirements outlined per the study phase. To facilitate review, sponsors should still complete and submit the QOS introduction and include it within the CTA package.)
    - For information on CMC requirements, consult Quality (chemistry and manufacturing) guidance: Clinical trial applications (CTAs) for pharmaceuticals.
- For products sourced from an acceptable foreign jurisdiction's (for instance, ICH members) authorized supply, Module 2 may be omitted, provided the sponsor includes the following information:
    - proprietary (brand) name of drug product
    - non-proprietary or common name of drug substance (medicinal ingredient)
    - manufacturer name
    - dosage form
    - strength
    - country from which product is sourced or authorized
    - Sponsors may provide this information within the cover letter of their submission.
- **2.1 Table of contents**
    - **CTA/CTA-A (quality)**: A listing of the contents of Modules 2 and 3, if applicable.
- **2.3 Quality overall summary (QOS)**
    - **CTA**
        - Details on each unapproved drug used in the clinical trial must be provided to Health Canada. This information is required irrespective of the purpose of the drug in the trial (for example, investigational or comparator). A document (such as an IB or PM) containing the following information should be submitted to Health Canada:
            - brand name, chemical name or code for the drug
            - therapeutic and pharmacological classifications of the drug

        - medicinal ingredients of the drug
        - non-medicinal ingredients of the drug
        - dosage form of the drug
    - If the drug contains a human-sourced excipient, including any used in the placebo:
        - information that indicates if the human-sourced excipient has been assigned (and not cancelled) a DIN under subsection C.01.014.2(1) of the FDR or, in the case of a new drug, is issued an NOC under section C.08.004 and C.08.004.01 of the FDR, as the case may be, or
        - in any other case, full details of manufacture, characterization, and controls, with supporting safety data (non-clinical and/or clinical)
    - if the drug contains a novel excipient, full details of manufacture, characterization and controls, with supporting safety data (non-clinical and/or clinical)
    - if the drug has not been assigned a DIN under subsection C.01.014.2(1) of the FDR or, in the case of a new drug, an NOC has not been issued under section C.08.004 or C.08.004.01 of the FDR, the chemistry and manufacturing information in respect of the drug, including its site of manufacture

For pharmaceuticals: A QOS is required [QOS-CE (CTA - Phase I), QOS-CE (CTA - Phase II), QOS-CE (CTA - Phase III)]. For placebo-controlled studies**,** a qualitative list of the ingredients in the placebo should be submitted.

For biologics and radiopharmaceuticals:

There are 4 QOS guidance documents to be used as direction for the completion of the quality section for biologic drug submissions (refer to Appendix D) and 2 QIS (quality information summary) templates for radiopharmaceutical drug submission applications (QIS-R and QIS-PER 9). The applicant should submit a completed QOS/QIS with, as a minimum, those subsections or parts which have a check mark beside the guidance document or heading, including the facility information. Note that these guidance documents 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.

For placebo-controlled studies, information on the placebo is also required including a description of the manufacturing process, a qualitative and quantitative list of ingredients, specifications, batches, stability, and facility information.

Module 3 Quality (if submitted)

- **3.1 Table of contents of Module 3**
  - **CTA/CTA-A (quality)**: A listing of the contents of Module 3.
- **3.2 Body of data**
  - **CTA/CTA-A (quality)**: Where there is additional supporting quality information 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 Literature references**
  - **CTA/CTA-A (quality)**: Literature references related to quality information should be provided here if applicable.

4.7 Comparative bioavailability trial application requirements (7-day administrative review)

Health Canada's administrative 7 days review target is intended for administrative purposes only, while it strives to adhere to this timeline, the default effective period for authorization will be 30 days if no decision is made prior to its expiration. The review target applies to applications involving comparative bioavailability studies for pharmaceuticals only where the:

- studies are single-dose studies to be performed on healthy adult volunteers
- reference drug product is authorized in Canada, the United States, the European Union, Australia, Switzerland or Japan **and**
- maximum dose of the study drug does not exceed that specified in the labelling of the reference 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 other comparative bioavailability studies, such as those conducted during drug development of new active substances to assess the impact of changes to dosage forms or manufacturing processes or studies comparing different routes of administration.

Refer to section 4.5 for CTA filing requirements and section 6 and section 7 for review process and timelines.

CTAs for comparative bioavailability studies should be filed directly to the Pharmaceutical Drugs 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 4.5) also apply to the comparative bioavailability studies that meet the criteria provided above, with some exceptions as follows:

- the cover letter to the application, which should include a rationale for the study
- 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 section 5.2 and section 5.3) also apply to comparative bioavailability studies.

5. Clinical trial application-amendments (CTA-As)

CTA-As are applications in which a sponsor proposes information to support changes to a previously authorized application (section 20 of the regulations). CTA-As are required for the changes listed in section 5.1.

CTA-As must be authorized by Health Canada prior to implementation of the changes, as per the regulations.

Amendments submitted when the initial 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 CTA and submit the amendment as a new CTA.

Since the original CTA and any prior amendments remain authorized during the review of a CTA-A, clinical trial sites may continue their activities in accordance with the most recent authorization uninterrupted until they receive an authorization for the new CTA-A.

Immediate changes to a clinical trial

As per the regulations, sponsors must generally wait for Health Canada to authorize any amendment (CTA-A) to the authorization before implementing the changes. However, if an change that would typically require an amendment needs to be made right away because the clinical trial would otherwise endanger the health of trial participants or other persons, sponsors may go ahead and make the change prior to filing a CTA-A.

Even if the change is implemented immediately, a CTA-A must be filed. The amendment should clearly describe the change and provide a rationale for its immediate implementation, including any risks to the health of participants or other persons.

If the sponsor does not submit a CTA-A within 7 days of making the change, Health Canada must be notified in writing within those 7 days. The notice must explain what change was made and why, including describing any risks to the health of participants or other persons.

The notice should also include confirmation from the sponsor that a CTA-A will be submitted within 30 days of implementing the change, as required by the regulations.

Note: Under subsection 24(1) of the regulations, sponsors cannot add a sub-study as part of an immediate change amendment. After implementing immediate changes to the trial protocol or informed consent form, if those documents have been amended, sponsors must also obtain approval from a Research Ethics Board (REB). The approval is required for each trial site, unless the revised protocol and/or informed consent form have been approved by a national REB.

5.1 Clinical trial application-amendment (CTA-A): Clinical

Sponsors are required to file CTA-As for changes to the protocol made after the approval of the original CTA that may have an impact on the safety of the participants or may affect the analysis and the interpretation of the safety and efficacy of each drug under investigation. More specifically, as per subsection 19(2) of the regulations, a CTA-A must be filed when the proposed amendment to the protocol:

- affects the selection, monitoring or dismissal of clinical trial participants (including the number of participants)
- affects the evaluation of the clinical efficacy of a drug used in the trial
- alters the risk to the health of a clinical trial participant or other persons
- affects the safety evaluation of a drug
- changes the duration of the clinical trial
- introduces a sub-study (as part of a master protocol trial) **or**
- adds or changes a selective approach to keeping records of adverse events in respect of a drug used in the clinical trial

Examples of protocol changes that require a CTA-A are provided in this section to aid in determining whether a CTA-A should be filed. These examples are not comprehensive. When in doubt of whether a CTA-A is required, sponsors should contact the corresponding directorate.

Clinical amendments

Examples include:

- a change to criteria, tests or procedures required to select or dismiss a clinical trial participant, such as any change to:
    - an eligibility (inclusion or exclusion) criterion
    - a test or procedures for selecting the study population
    - a test, procedure or criterion for the early discontinuation of clinical trial participants
- a change to criteria, tests or procedures required for the ongoing monitoring of clinical trial participants or to the assessment of safety, such as any change to:
    - participant safety, efficacy monitoring and assessment or safety oversight/pharmacovigilance
        - For example, a change to safety monitoring might be implemented after the occurrence of a suspected unexpected serious adverse reaction (SUSAR), such as more frequent or closer participant follow-up and/or new or expanded testing or procedures.
        - An example of a change to safety oversight could include a change in the frequency of safety data reviewed by a monitoring committee or the length of time that safety data is to be collected.
- a change to study design, study population, duration of use, objectives or hypotheses
    - Adding a study arm that was not included in the authorized trial would qualify as a design change requiring a CTA-amendment.
- a change to a master protocol trial to add a sub-study, either by adding a new sub-study or applying to Health Canada for the authorization to include the sub-study that had not been reviewed and authorized before
    - For example, if a sub-study was previously included in the master protocol, but the sponsor did not seek authorization for it as it was not intended to be conducted in Canada, and now the sponsor wishes to conduct that sub-study in Canada, a CTA-amendment is needed.
- a change to the primary or secondary efficacy or safety endpoints (for example, this would include a change to what qualifies as a dose limiting toxicity (DLT) in a dose escalation study or a change to a secondary efficacy endpoint that could be used in support of a marketing application), sample size estimation or the

addition, removal or change to interim analyses that could affect the analysis and interpretation of the study results

- changes to the dose level, dosage schedule, formulation, route of administration or number of dosing cycles
- changes to the post-treatment follow-up period that may affect the safety evaluation of the drug
- adding or removing a concomitant medication, which may impact the analysis of efficacy or increase the risk to clinical trial participants
- changes to the criteria for expedited reporting of serious, unexpected adverse drug reactions
- increases in blood draw volume, changes in procedures, enrolling additional participants in pharmacokinetic (PK) studies or confirmatory testing in PK studies that were not specified in the original CTA protocol and/or to other people
- changes to the conduct of the study that may increase the risk to the health of clinical trial participants or to other people

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

Refer to section 5.3 for more information on filing a clinical CTA-A.

Protocol changes that modify (in other words, extend or shorten) the duration of the clinical trial pertain to the screening, treatment and/or follow-up periods. 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 or rationale to support the extension in treatment duration.

5.2 Clinical trial application-amendments (CTA-A) and clinical trial application-notification (CTA-N): Quality (chemistry and manufacturing)

Sponsors must file a CTA-A to a previously authorized application when changes that may affect the quality or safety of the clinical trial drug supplies are proposed. Changes

that do not affect the quality or safety of the drug would require the filing of a CTA-N. Any relevant updates should be made to the quality summary subsections of Module 2 and Module 3 (if applicable), including those listed in Tables 2, 3, 4 and 5, within the filing of a CTA-A or a CTA-N.

For biologics and radiopharmaceuticals

A list of all proposed quality changes from the authorized application should be provided in the cover letter.

Note: 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 a change in the:

- source of drug substance (for example, from a fermentation process to transgenic milk)
- host cells used to express the same coding sequence
- strain of virus used in manufacturing a vaccine
- strain of oncolytic virus used in cancer treatment
- animal source of an immune globulin (for example, from rabbit to sheep)
- source of a radionuclide (for example, from nuclear reactor to cyclotron or linear accelerator) for labelling kits
- source of the parent radionuclide (for example, from nuclear reactor to cyclotron or linear accelerator) used in a generator
- design, structure and operation of a radionuclidic generator

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

For a product commercially available and used in clinical trials for which a quality change has been made according to the Post-NOC changes: Quality guidance, supporting data are not required in support of the same change affecting the clinical product. The change can be notified to the BRDD with cross-reference to the approved submission filed for the commercial product.

Where a change made to the commercial product has not yet been approved and is affecting the clinical material, a CTA-A or CTA-N must be submitted according to the

Tables 2 and 3 in this section. For Level 3 changes made to a biologic or radiopharmaceutical, a CTA-N is not required for the clinical product.

Table 2: Drug substance (biologics and radiopharmaceuticals)

Type of change		Submission type
1. Replacement or addition of a manufacturing site	a. production of the starting material, intermediate, or drug substance	Amendment
	b. testing (for example, release, stability)	Notification
2. Change in the manufacturing process for the drug substance intermediate	a. the fermentation process (for example, 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 (for example, addition, removal or 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

Type of change		Submission type
	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 or systems for the storage and shipment of the drug substance provided the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties and the change does not concern a sterile drug substance		Notification
5. Change in the shelf life for the drug substance	a. (i) extension if the approved shelf life is less than or equal to 18 months	Amendment
	a. (ii) extension if the approved shelf life is more than 18 months	Notification
	b. reduction (due to stability concerns)	Amendment
* For the manufacture of some radiopharmaceuticals, "critical components" (for example, F-18 radionuclide used to manufacture F-18-FDG and F-18-NaF) are considered analogous to drug substances (consult BRDD).		

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Table 3: Drug product (biologics and radiopharmaceuticals)

Placebos with a biological component should follow Table 3 for chemistry and Manufacturing changes, whereas placebos without a biologic component should follow Table 5 (pharmaceuticals).

Type of change		Submission type
1. Replacement or addition of a drug product manufacturing site	a. production of a drug product (including primary packaging)	Amendment
	b. secondary packaging	Notification
	c. testing (for example, release, stability)	Notification
2. Change in the drug product manufacturing process (for example, 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 or manufacturing site, primary or secondary packaging site or testing site		Notification
4. Change in the specifications for the drug product	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

Type of change		Submission type
5. Change in the shelf life for the drug product	a. (i) extension, if the approved shelf life is less than or equal to 18 months	Amendment
	a. (ii) extension, 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 final product dosage form (for example, liquid to lyophilized formulation)		Amendment
8. Changes in final product strength		Amendment
9. Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution by a diluent that is commercially available in Canada, is water for injection (WFI) or a salt solution, and after reconstitution, there is no change in the drug product specifications outside of the approved ranges		Notification
10. Change in radiolytic protective agent or antioxidant		Amendment

For pharmaceuticals

For a product commercially available and used in clinical trials for which a quality change has been made according to the Post-NOC changes: Quality guidance, supporting data are not required in support of the same change affecting the clinical product. The change can be notified to the PDD with cross-reference to the approved submission filed or the commercial product.

Where a change made to the commercial product has not yet been approved and is affecting the clinical material, a CTA-A or CTA-N must be submitted according to Tables 4 and 5.

Table 4: Drug substance (pharmaceuticals)

Type of change		Submission type
1. Replacement or addition of a manufacturing site	a. production of drug substance	Amendment
	b. testing (for example, release, stability)	Notification
2. Change in the manufacturing process for the drug substance intermediate or starting material (for example, reaction conditions, solvents, catalysts, synthetic routes, reagents, etcetera)		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	Notification

Type of change		Submission type
	tightening of an acceptance criterion	
5. Change in the re-test period (or shelf life) for the drug substance, involving:	a. extension	Notification
	b. reduction (due to stability concerns)	Amendment

Table 5: Drug product (pharmaceuticals)

Type of change		Submission type
1. Addition of a dosage form or strength		Amendment
2. Change in the composition of a dosage form		Amendment
3. Qualitative or quantitative addition, deletion or replacement of a colour or flavour with no negative impact on stability		Notification
4. Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution		Amendment
5. Replacement or addition of a drug product manufacturer or manufacturing site	a. production of an immediate release drug product (tablet, capsule, liquids, semi-solids) within the same manufacturer	Notification

Type of change		Submission type
	b. production of an immediate release drug product (tablet, capsule, liquids, semi-solids) to a new manufacturer	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 (for example, release, stability)	Notification
6. Change in the drug product manufacturing process		Amendment
7. Change in the specification for the drug product tests 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	Notification

Type of change		Submission type
	new impurity) or tightening of an acceptance criterion	
8. Change in the shelf life for the drug product	a. extension	Notification
	b. reduction (due to stability concerns)	Amendment
9. Change in the storage conditions for the drug product		Amendment

5.3 Clinical trial application-amendment (CTA-A) format

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

CTA-As should be submitted in eCTD or non-eCTD format.

CTA-As should include information on the sponsor and the drug required for a regular CTA pertaining to the applicable change that requires the CTA-amendment, including a completed 3011 Form.

Furthermore, CTA-As must also contain the following additional information:

- a statement that identifies the proposed changes
- updated documents (clean and annotated copies, as applicable)

Health Canada will base its decision on whether to authorize the amendment on the information provided by the sponsor and any other available information that is relevant.

For more information, consult the 3011 Form.

6. Clinical trial application (CTA) and clinical trial application-amendments (CTA-A) review and authorization process

Health Canada reviews the documents submitted in CTAs and CTA-As to assess the quality of the products and determine that the:

- conduct of the clinical trial, including the use of any drug for the purposes of the clinical trial, is not likely to result in unacceptable risks to the health of clinical trial participants or other persons
- clinical trial is not contrary to the best interests of its participants **and**
- objectives of the clinical trial are achievable

Also, the sponsor must demonstrate that the drug may result in a therapeutic benefit for a human if a drug proposed to be used in the clinical trial contains a:

- prohibited substance referred in in sections C.01.036, C.01.037, C.01.038 or C.01.040 of the FDR **or**
- a colouring agent other than one listed in subsections C.01.040.2(3) and (4) of the FDR

6.1 Screening process

All CTAs and CTA-As will be screened for administrative completeness in accordance with the requirements outlined in the regulations. If deficiencies (for example, missing documents or information, incomplete forms) are identified at screening, the sponsor will be notified and have an opportunity to address the deficiencies to complete their application.

Once Health Canada determines that the application is administratively complete (all elements of the submission are received), an acknowledgement letter will be sent. The letter will confirm that the target review timeline began on the date the complete submission was received.

For CTAs, the acknowledgement letter will be issued with a “contingent authorization” within 7 calendar days of receipt of a complete application.

Similarly, although not required for CTA-As, Health Canada will aim to issue an acknowledgement letter within 7 calendar days of receipt of a complete application. Since the authorization already exists, a contingent authorization is not needed in case of CTA-As.

This acknowledgement letter will also advise sponsors that if the CTA or CTA-A is authorized, Health Canada may publish or update, respectively, information about the clinical trial in Health Canada's publicly accessible clinical trials search portal. There are certain exceptions, such as bioavailability or bioequivalence trials.

Access the clinical trial search database.

6.1.1 Requests for clarification during screening

Requests for clarification that are issued during screening must be responded to within the time specified in the request letter. This will generally be in accordance with the administrative timeline target (2 business days). On a case-by-case basis, if more time is required for the sponsor, Health Canada may accommodate a reasonable adjustment to the response timeline.

6.1.2 Screening rejection letter

A screening rejection letter may be issued when any required information 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.

Consult:

- Guidance on the management of drug submissions and applications

6.2 Review process

Once the review process has begun, no new information will be accepted, unless requested by Health Canada or required by the regulations (such as foreign decisions or REB refusals). Refer to section 4.6.

During the review of an application for authorization, the sponsor is responsible for resolving issues identified by Health Canada. Health Canada may request that the sponsor submit any additional information or material, including samples, that is necessary for Health Canada to determine whether to issue or amend an authorization. Sponsors must provide the requested information within the time, form and manner specified by Health Canada. Sponsors can generally expect to have 2 business days to respond to a standard request of this nature.

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

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.

Consult:

- Guidance on the management of drug submissions and applications

An intent to issue a not satisfactory notice (NSN), followed by the NSN, may be issued if:

- significant deficiencies are identified during the review of the CTA or CTA-A **or**
- a response to information or material, including samples, requested has not been provided in the time, form and manner specified in the request

If an NSN is issued, the contingent authorization will not become a full authorization and the CTA will no longer be under review. The sponsor would need to resubmit the CTA addressing any concerns that were previously identified.

If Health Canada determines that there are no grounds to object to the trial or the proposed amendment, in accordance with subsection 15(2) or subsection 22(2) of the

regulations, as applicable, Health Canada will send the sponsor an NNO within the review period. On the day on which Health Canada sends the NNO:

- in case of CTAs, the contingent authorization becomes an authorization that authorizes the sponsor to conduct the clinical trial **or**
- in case of CTA-As, the authorization is amended accordingly

If the 30- or 60-day (if extended) period passes and Health Canada has still not issued an NSN or NNO, then the trial is amended accordingly. Or, the “contingent authorization” becomes an authorization, in accordance with sections 15 and 22 of the regulations. The sponsor may begin to conduct the clinical trial and import the drug(s) for the purposes of the clinical trial, as applicable.

7. Extended review timeline criteria

Typically, Health Canada will complete the review of CTAs and CTA-As within 30 days from the date of receipt of a complete submission. If a CTA meets certain criteria for extension, the review period may be extended up to 60 days in total. Note: There is no option to extend the review of CTA-As.

Sponsors will be notified if extra time is needed and will be issued a notice that reflects the new timeline of 60 days for review. As with the initial contingent authorization, this will become an authorization after 60 days from the date of receipt of the complete submission has passed.

For CTAs, as per subsections 16(1) and (2) of the regulations, Health Canada may extend the review time from 30 days to 60 days, if at least 1 of the following criteria is met. The examples provided do not represent the full range of scenarios. At the same time, even if a trial falls under 1 of the criteria, the extension may not be needed. Health Canada will consider whether the review timeline requires extension on a case-by-case basis once the CTA is submitted.

The criteria for extending a CTA review to 60 days are:

- The trial has a degree of complexity, such that there is a potential need to add terms and conditions to the authorization.
    - Refer to section 8 for details on terms and conditions.
- The trial design is complex (involve either a dynamic design or multiple related sub-studies, which could include certain types of master protocol trials, such as platform, basket or umbrella, or adaptive trial designs).
- The drug represents an emerging or innovative technological, scientific or medical development. Health Canada will assess innovative drugs on a case-by-case basis. A drug may be described as emerging or innovative if it incorporates recent technological or scientific advances for which there is limited existing knowledge (for example, novel delivery systems, emerging biotechnology or new mechanisms of action).

- The manufacturing or the quality control of the drug involves a process that is emerging or innovative. Complex or novel chemistry, manufacturing and controls (CMC) approaches may require additional review timelines to assess suitability, consistency, comparability and oversight mechanisms given lack of established precedence.
- Additional assessment is needed, on a case-by-case basis, to protect a particular vulnerability of the proposed participant population or sub-population. For example:
    - There is increased uncertainty of adverse outcomes or unpredictable responses to interventions where more information or a more detailed data analysis is required.
    - Enhanced measures may be required to mitigate risks associated with the trial design or potential unique drug-related risks.
- There is a need for tailored consent processes where additional risk has been identified with respect to the participant or another person due to the nature of the trial.

8. Terms and conditions

Health Canada can impose terms and conditions (T&Cs) on any authorization. This can be done on a case-by-case basis at any time from the decision to issue the authorization to the point of revocation under section 18 of the regulations. Health Canada may also amend the T&Cs at any time.

In all cases, the sponsor must still submit a complete application that meets all criteria established under the regulations. T&Cs cannot be used as a way to authorize significantly flawed trial designs or protocols, or to address risks that could otherwise be reasonably mitigated. For example, if a study lacks adequate safety monitoring, proposes to use inappropriate comparators or fails to justify key design elements, a T&C cannot be used to override these fundamental issues. In such cases, an authorization would not be issued until the protocol deficiencies are resolved either within the review timelines allotted by the regulations or in a subsequent filing of a CTA following an NSN or withdrawal by the sponsor.

For sponsors of clinical trials:

- There is no limit to how many T&Cs may be added to a clinical trial authorization or how often they may be amended.
- Health Canada takes a case-by-case approach, assessing each trial individually while consistently applying all regulatory requirements.
- T&Cs may need to be met before the conduct of the trial begins or may be required to stay in effect throughout the trial.
- Each T&C may have its own specific deadline.
- Sponsors will be given a fair and transparent process for reviewing, and responding to any T&Cs to be imposed.
- Health Canada aims to provide sponsors with an opportunity to be heard before finalizing the T&Cs.

Prior to imposing or modifying any T&Cs on a clinical trial, Health Canada assesses the situation based on the following criteria outlined in section 18 of the regulations:

- Regulatory sufficiency: whether existing requirements under the FDA, including the regulations, are sufficient for the following objectives to be met:
    - mitigate the risks associated with the conduct of the clinical trial, including those related to the drugs used
    - support the collection of information needed to understand and manage the uncertainties of those risks
- impact of the Proposed T&Cs: evaluate whether the proposed T&Cs will help achieve these objectives
- feasibility for sponsors: whether sponsors can realistically comply with the proposed T&Cs from a technical standpoint
- consideration of burden: whether there are less burdensome alternatives that could allow for the objectives to be met effectively

Examples of the potential requirements that could be imposed under T&Cs include**:**

- more frequent safety and/or efficacy reporting (for example, copies of development safety update report (DSUR), data safety monitoring board (DSMB) reports and/or safety review committee reports)
- adjusting inclusion and/or exclusion criteria for further recruitment to the trial to mitigate a risk or potential safety signal
- adapting the participant populations throughout the trial (for example, limiting the number of participants prior to expanding to additional participants)
- monitoring of specific populations because of potential increased risk **and**
- additional information to characterize and mitigate a newly identified risk or safety signal

These examples do not represent the full range of scenarios or capture additional circumstances for which T&Cs may be imposed.

Terms and conditions to address uncertainty or to mitigate a risk with respect to the conduct of the trial would be dependent on the circumstances and details of the trial, such as:

- the potential options for other therapies
- the seriousness of the indication
- the risks associated with the study interventions **and**
- whether and how various potential risks can be mitigated

8.1 Process for imposing and amending terms and conditions

The following sections outline the process for imposing and amending T&Cs.

T&Cs can be imposed on authorizations of CTAs or CTA-As:

- during the review period (for CTA-As)
- at the time of initial authorization (for CTAs or CTA-As)
- at any time post-authorization but prior to revocation of the authorization in whole

Prior to imposing or amending any T&Cs, the sponsor will generally be sent a written notification. The written notification to the sponsor would:

- specify the legal authority under which T&Cs are imposed
- explain the risks and/or uncertainties and/or information gaps that were identified
- identify the T&Cs to be fulfilled (new or amended) and when it comes into effect
- outline the time frame for fulfilling the T&Cs (if applicable)
- outline the requirements to fulfill the T&C, instructions on what to include in the response and how to submit the response
- provide the sponsor with the opportunity to be heard
- describe any potential consequences of not complying with a T&C

The sponsor should respond to the proposed T&Cs in writing. The sponsor should include the control number and details of a plan to fulfill the T&Cs or provide an alternative approach to address the deficiencies outlined in the T&Cs. Sponsors should submit the response via eCTD or non-eCTD format within 2 business days of notification of the intent to impose a T&Cs. In some cases, Health Canada may request a different timeline depending on the T&Cs or the particular circumstances and level of urgency of the risk to be addressed.

During the review, a clarification may be requested. Health Canada will review information the sponsor provides and refer to any other information that could inform the review. Submission of new information, unless requested by Health Canada, will not be accepted during the review and may result in rejection of the application.

Following the review, Health Canada will finalize the T&Cs and will notify the sponsor in writing.

8.2 Opportunity to be heard on proposed terms and conditions

Typically, sponsors will be given an opportunity to be heard prior to the imposition of a proposed T&Cs, whether new or amended. Sponsors have up to 2 business days to submit a written response to the proposed T&Cs.

Health Canada will inform the sponsor when the T&Cs must be fulfilled, as applicable. If the sponsor objects to the proposed T&Cs, they should ensure clear reasons are provided for their objections.

For example, sponsor's response may:

- suggest an alternative proposal with a supporting rationale and/or comment on the technical feasibility of the T&Cs
- propose less burdensome means of achieving the objectives of the T&Cs
- withdraw their submission and resubmit at a later date without prejudice to refiling

Note: In rare and urgent cases, Health Canada may apply T&Cs without giving the usual opportunity to be heard, if it is needed to protect the health of participants or other persons. If such T&Cs are imposed, sponsors will be notified accordingly.

8.3 Imposing final terms and conditions

Health Canada will inform sponsors of the final T&Cs in writing, including when the T&Cs comes into effect. The timeline for a response from Health Canada about the final T&Cs may vary.

8.4 Amending terms and conditions

Health Canada can initiate a change to T&Cs, including amending T&Cs currently in effect, or proposing additional T&Cs.

The sponsor may also propose a revision to an existing T&Cs. In the request, the sponsor must provide a:

- supporting rationale for the proposed revision to T&Cs
    - for example, the sponsor concludes that an activity imposed through a T&Cs cannot be completed for technical or scientific reasons
- detailed description of the proposed revision

Some T&Cs may require the sponsor to update the protocol post-authorization. If a protocol change is needed, the sponsor must either notify Health Canada or apply to amend the authorization depending on the nature and extent of the change.

8.5 Fulfilling terms and conditions

T&Cs may include 1 or many conditions, each with different timelines for completion. Where applicable, the sponsor must submit the information required to fulfill the T&Cs by the date indicated.

In some cases, for international clinical trials, similar conditions may have been imposed in another country and the foreign regulator later removed these conditions. Notwithstanding the status of the conditions imposed in another country, the sponsor must fulfill their obligations as specified in the T&Cs issued by Health Canada.

Once the sponsor submits the information to fulfill the T&Cs, Health Canada will review the submitted information in a timely manner, while considering the complexity and context of each submission. After reviewing, the sponsor will be informed of the outcome or next steps, if any. Health Canada will remove any T&Cs that have been fulfilled and inform the sponsor if remaining conditions need to be amended.

If further conditions are to be imposed, Health Canada will inform the sponsor in writing. Sponsors will be given 2 business days to respond, unless specified otherwise.

Once the sponsor provides satisfactory evidence that all of the requirements in the original (or amended) T&Cs have been met, they will be notified in writing to confirm that the T&Cs have been fulfilled and that the T&Cs are removed. Health Canada may also remove a T&C if new data or circumstances demonstrate that it is no longer necessary.

8.6 Failure to comply with terms and conditions

Compliance and enforcement actions may be taken if there are reasonable grounds to believe that a sponsor is not complying with a T&Cs imposed on their authorization.

Non-compliance with T&Cs may lead to:

- suspension, and potentially revocation, of an authorization, in whole or in part, in accordance with paragraph 26(1)(c) and section 30 of the regulations
- fines or even imprisonment

For more information on compliance and enforcement, consult:

- Compliance and enforcement policy for health products (POL-0001)
- Compliance and enforcement policy for clinical trials (POL-0030)

9. Notifications

Notifications must be provided for changes to CTAs that do not meet the criteria for CTA-As.

For details, refer to:

- Section 5.1 (CTA-A: Clinical)
- Section 5.2 (CTA-As and CTA-Ns: Quality)

The changes may be implemented immediately, but Health Canada must be informed in writing, within 15 days after the day of making the change or having become aware of the change (depending on the nature of the change). Information regarding the change should be submitted in the form of a cover letter accompanied by any supporting documentation (or an updated CTSI form) to the appropriate directorate (or ROEB). This information will be reviewed and added to the file. Notifications should be submitted in eCTD or non-eCTD format in accordance with current electronic specifications. (Refer to Appendix D).

Under the regulations, situations that would require a notification include the following:

- changes to the protocol that do not change the risk to the health of trial participants or other persons and would not be considered an amendment under section 19 of the regulations. For example:
    - minor changes to the inclusion and exclusion criteria, such as editorial changes to improve clarity
    - 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
    - updating the ICF with safety information that does not require a protocol amendment
    - annual updates to the investigator's brochure or equivalent document
        - Refer to section 11.6. and paragraph 49(1)(h) of the regulations

- changes to quality (chemistry and manufacturing) information that does not affect the quality or safety of the drug
    - Refer to paragraph 49(1)(i) of the regulations and section 5.2.
- notifications as described in section 55 of the regulations
    - Refer to section 11.1.
- information the sponsor becomes aware of:
    - decisions from a foreign regulatory authority or a foreign REB concerning the clinical trial as detailed in paragraph 50(1)(a) of the regulations
        - Refer to section 4.6, Table 1, Module 1, 1.2.7
    - name and contact information of any REB that refused to approve the protocol, its reasons for doing so and the date on which the refusal was given (CTA-N), as per paragraph 50(1)(a) of the regulations
    - name and contact information of the REB (except a national REB) that withdrew its approval, including its reasons for doing so and the date on which the withdrawal of approval occurred (CTA-N), as per paragraph 50(1)(b) of the regulations
- changes to administrative information, such as new contact names and contact information of individuals, organizations or other entities involved in the conduct of the trial, including any change to the:
    - name or contact information of an investigator, including whether another person has become the investigator at the clinical trial site (update to CTSI form), as per paragraphs 49(1)(d) and 49(2)(c) of the regulations respectively
    - address of the clinical trial site's main location where the physical location of the site has not changed (for example, street name change), if different from the investigator's address (update to CTSI form), as per paragraph 49(1)(e) of the regulations
        - If the address of the site's main location changes due to a change in physical location, this would be considered a new site and would require a REB approval and the submission of a new CTSI form.
    - name and contact information of the REB (except a national REB) that approved the protocol and the ICF at a clinical trial site (update to CTSI form), as per paragraph 49(1)(g) of the regulations
    - name or contact information of the sponsor, as per paragraph 49(1)(a) of the regulations, except in cases of transfer of authorization
        - Refer to section 25 of the regulations and section 9.1.

- name or contact information of the sponsor's representative in Canada (in case of a foreign sponsor) or sponsor's representative who is responsible for importation or sale of the drug, or if another person becomes such a representative, as per paragraphs 49(1)(b), 49(1)(c), 49(2)(a) and 49(2)(b) of the regulations, respectively
    - Refer to section 10.5.

If information about a service provider was not known at the time of filing the application, the sponsor is required to submit the name and contact information of the service provider to Health Canada within 15 days after the day the service provider begins to provide a service to or on behalf of the sponsor. This is set out in section 51 of the regulations. This requirement applies whether:

- this is the start of a new trial
- the sponsor has decided to change the service provider that has already started to provide a service **or**
- the information previously provided in respect of a service provider has changed, as per paragraph 49(1)(f) of the regulations

A notification is not suitable for substantive changes that could potentially affect the conduct of the trial (for example, changes to aspects of the drug that affect its quality or safety, or the introduction of a new drug in the trial).

Refer to the tables in section 5.2 for more information on the circumstances under which a notification is permissible instead of an amendment. Sponsors can also contact the Regulatory Affairs Section of the appropriate Directorate at Health Canada, if there is any uncertainty about how to file a notification.

9.1 Transfer of authorization

On occasion, a sponsor may wish to transfer their clinical trial authorization to another person or legal entity as the result of an agreement between the 2 parties and submitted to Health Canada as a CTA-N. In these circumstances, and according to section 25 of the regulations, the following conditions must be met and documentation included in the CTA-N filing:

- The current sponsor must provide a written statement indicating their intent to transfer the authorization. The control number of the initial clinical trial application, the clinical trial protocol number and the name of the drug product under investigation should be referenced.
- The new sponsor must also provide a written statement indicating that they will assume sponsorship of the corresponding trial once the authorization is transferred.
- A complete drug submission application 3011 Form reflecting the new sponsor information must be provided.
    - Refer to Table 1, Module 1, section 1.2.1 for more information.
- The new sponsor must complete and sign Appendix 3 (of the form) confirming:
    - they will take full responsibility for overseeing the conduct of the clinical trial
    - the trial will be carried out in compliance with GCP and the regulations

Note: The clinical trial authorization is generally transferred on the day on which the notification requirements are fulfilled. However, the notifying parties may propose a later effective date on which the parties wish the transfer to take place by including an explanation as part of the notification. Health Canada may take into account the date in determining the effective date of transfer.

10. Additional requirements prior to commencing a clinical trial

Prior to initiating conduct of a clinical trial at a clinical trial site, the sponsor must ensure:

- the research ethics board (REB) attestation has been completed and kept on file by the sponsor **and**
- the clinical trial site information (CTSI) form has been filed with Health Canada

For all biologics, the BRDD requires that the lot release information be provided by the CTA sponsor/manufacturer before its use in the trial.

Refer to section 10.4.

10.1 Research ethics board review

Prior to initiating a clinical trial or implementing an amendment to a clinical trial at a clinical trial site, the proposed trial protocol and informed consent form (ICF) must be reviewed and approved by:

- an REB for each site **or**
- a national REB set out in the List of National Research Ethics Boards for the trial as a whole

The sponsor must:

- submit the name and contact information of the REB that approved the trial prior to the commencement of the trial at that site (CTSI form)
- retain as records an 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.
        - Additional information follows.

An REB may use its own letter of attestation in lieu of the form provided by Health Canada. If an REB uses its own letter, it should explain how the REB complies with the membership requirements for REBs defined in the regulations and must attest to the following 2 points:

1. The REB carries out its functions in a manner consistent with GCPs.
2. The REB has reviewed and approved the clinical trial protocol and ICF for the trial, which is to be conducted by the 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 Parts 1, 2 and 3 of the REB attestation form.

If the REB or a national REB is approving the clinical trial for multiple sites, the sites may be identified by duplicating Part 3 of the REB attestation form as many times as necessary to capture all site addresses approved by the same REB. Only the final page of the REB attestation form 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 (for example, 1 of 5, 2 of 5).

The REB attestation form should not be submitted unless requested by Health Canada but must be available for each clinical trial site as per the regulations.

10.2 Investigators

There must be no more than one (1) investigator at each clinical trial site, who is responsible to the sponsor for the conduct of the clinical trial and who is the responsible leader of the team at that site. If there is a change in the investigator at a site, a revised Clinical Trial Site Information Form must be submitted to Health Canada.

10.3 Filing of trial commencement information

Prior to commencement of the clinical trial that involves the initiation of a new site, sponsors are required to complete and submit a clinical trial site information (CTSI) form for each clinical trial site.

A single clinical trial site may sometimes consist of multiple locations. The main location is considered the coordinating centre of the trial conducted at a particular site. It is typically linked to the investigator's institutional address (or the sponsor's facility, if the sponsor is also the investigator). As required by the regulations, an investigator must be a person who is entitled to provide health care under the laws of the province or territory in which the main location of a clinical trial site is situated. Only 1 investigator may be appointed as the lead researcher accountable for trial conduct at a clinical trial site.

Remote locations that are part of a clinical trial site can be where participants are recruited, treated and monitored by members of the investigator's team. Trial coordination and monitoring activities at these locations can be facilitated with telecommunications, video or other technologies. It can also be a physical location such as a lab or community clinic to recruit, treat and monitor participants. The investigator oversees the staff, who must have the appropriate training and qualifications to conduct their respective activities at each trial location of the clinical trial site.

Other remote locations (for example, where ancillary medical procedures such as X-rays, magnetic resonance images (MRIs) or blood collections are conducted) are not generally considered to be part of a clinical trial site.

When the 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 (for example, 1 of 5, 2 of 5).

Health Canada recognizes that all information requested in the CTSI form may not be available at the time of submission. Even if this information is not available when filing the CTA, it is required prior to commencement of the trial at a clinical trial site. The forms should be submitted to the appropriate review directorate. If any changes are made to the CTSI form, a revised form should be submitted.

10.4 Lot release information (for biologics)

Biologic drug product lots to be used in an authorized clinical trial may be subject to the lot release requirements. The evaluation group is called Group 1A: Clinical trial materials.

For details on these requirements, consult:

- Guidance for sponsors: Lot release program for Schedule D (biologic) drugs

10.5 Sale and importation of clinical trial drugs

For trials that require a submission of a CTA, drugs intended for use in a clinical trial may only be sold or imported if a sponsor holds a valid authorization from Health Canada that allows them to conduct their clinical trial.

If Health Canada revokes or suspends an authorization or has issued a direction to cease conduct for exempt trials, the sponsor must inform the seller or importer of the drug without delay. Upon being notified, the seller or importer must immediately cease providing the drug for the clinical trial in question. However, if the revocation or suspension only affects part of the trial, the sale and/or importation of the drug may continue for the portion of the clinical trial that is not affected.

For sponsors who wish to import a drug into Canada for the purpose of a clinical trial, a proof of authorization from Health Canada should be provided at the time of importation to facilitate shipment and to demonstrate compliance with the Regulations. Contingent authorization may not be used for the purposes of importation. Only a contingent authorization that has become an authorization may permit sale and importation as per the regulations.

Refer to section 8 of the regulations and section 6.

Any delegation of importation duties to third parties should be clearly articulated through a written agreement. Systems must be in place for the monitoring, storage conditions, transportation and disposition of the drug to be imported. The sponsor is ultimately responsible for the correct handling and storage of the product used in the clinical trial. If the sponsor is not located in Canada, they must have a representative in Canada who is responsible for the importation and sale of the drug. The representative for both the sale and importation of the drug can be the same person.

If a clinical trial drug is to be imported, importers should be approved by the sponsor to import the drug. This information should be included in Appendix 1 of the 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. A copy of Appendix 1 should be included with the shipment along with the proof of authorization.

10.5.1 Importation of drugs

If drugs (for example, comparator, concomitant and rescue medications) are being imported for the purpose of the clinical trial, a list of these drugs should be provided in section 1.2.3 of the CTA. Use the Summary of Additional Drugs Form (SOAD) found in Appendix F.

The SOAD may be replicated to capture all additional drugs to be imported. This is to facilitate processing at the port of entry.

If this information is not known at the time of application or changes after the CTA is authorized, sponsors may submit a SOAD to the appropriate review directorate as a CTA-notification.

The SOAD will be signed by a Health Canada official and returned to the sponsor. Both a copy of the signed form as well as the letter of authorization (and Appendix 1 of the 3011 Form, if applicable) should be included with the shipment to facilitate processing at the port of entry.

For drugs listed on the SOAD, note the following:

- **Pharmaceuticals:** Should have an authorized Canadian equivalent and be sourced from an acceptable foreign jurisdiction (for example, ICH member countries). These drugs and how they will be used in the trial should also be specified in the protocol, along with details of the drug's formulation and dose strength.
- **Biologics and radiopharmaceuticals:** For comparators or concomitant drugs authorized in Canada but sourced from an acceptable foreign jurisdiction (for example, ICH member countries), a rationale should be provided demonstrating the equivalence with the authorized product in Canada. These drugs and how they will be used in the trial should also be specified in the protocol, along with details of the drug's formulation and dose strength.

Drugs that are not authorized for marketing in Canada (for example, new drugs) or products intended to be used outside of the equivalent Canadian label would not qualify

for inclusion on the SOAD. They should, however, be included on the 3011 Form at the time of filing.

Refer to section 4.5 for filing requirements.

10.5.2 Clinical trials involving controlled substances

Investigators of clinical trials (Phase I to IV) involving a controlled substance as defined in the Controlled Drugs and Substances Act (CDSA) must apply to Health Canada for an exemption. Exemptions can be requested for any controlled substance listed in Schedules I to V of the CDSA. Exemptions may be protocol, investigator, site and substance specific.

In addition to the investigator, the exemption may extend to all colleagues, assistants and technicians conducting the trial to possess and use the controlled substance, as long as these individuals are under the direction and control of the investigator. The investigator is responsible for any portion of controlled substance used by any of these individuals. Sufficient information must be supplied to Health Canada to support the use of a controlled substance in the trial or protocol and to provide confirmation that the controlled substance will be stored in a secure manner.

Exemptions may be valid for 2 years from the issuance date. The investigator may apply for an extension if required. In general, for controlled substances that are restricted drugs as defined in Part J of the FDR, an authorization under Part J may be required to conduct a clinical trial rather than a CDSA exemption.

Note: Requesting an exemption or an authorization to allow for the use of controlled substances in a clinical trial is a separate process from a CTA (in other words, submitting a CTA for a clinical trial involving a controlled substance will not automatically trigger a request for an exemption or an authorization from the CDSA). CTAs must be submitted to the relevant bureau, while exemption and authorization requests to the CDSA must be submitted to the Office of Controlled Substances at exemption@hc-sc.gc.ca.

Sponsors are ultimately responsible for ensuring that they comply with all relevant provisions of the FDA. Investigators are ultimately responsible for ensuring that they comply with all relevant provisions of the CDSA.

Find more information on the use of controlled substances for scientific purposes, including the application form.

11. Post-authorization requirements

Clinical trials may be subject to changes after they have been authorized. Those changes may relate to the:

- design, methodology, any drug involved in the trial as described in the protocol
- changes to the manufacturing information for any drug being used for the needs of the trial (including any drug being tested, comparator products or others)
- the addition of a sub-study under a master protocol trial
- changes to the regulatory status of the same trial in other jurisdictions
- changes to the contact information of the sponsor, an investigator or a service provider involved

The sponsor who is the holder of an authorization is required to inform Health Canada of certain changes to the information previously provided to Health Canada. The sponsor submits a notification or an application to amend the sponsor's authorization, depending on the nature of the change.

Although changes that require the submission of a notification may be implemented immediately, they will still be reviewed by Health Canada and the dossier on the clinical trial will be updated accordingly. Where applicable, Health Canada's Clinical Trials Database will also be updated to reflect the change.

If a safety concern arises during the review of a notification, Health Canada will rely on its post-authorization authorities, as appropriate, to address the concern. Authorities include requesting information or samples, imposing terms and conditions on the authorization or suspending the authorization.

11.1 Discontinuation of a trial

11.1.1 Sponsor's responsibilities

In the event of the discontinuation of a trial prior to its completion in whole or in part (a part of the protocol, such as an arm or a sub-study), the sponsor must, without delay, send a written notice to:

- all investigators who conduct the trial and
- the national REB, if applicable, that approved the trial protocol, including the following:
    - the trial is being discontinued and the reasons for the discontinuation, and
    - any potential risks to the health of participants or other persons

At each affected trial site where the trial is discontinued, the sponsor must immediately stop the sale and, if applicable, the importation of the drugs, as of the date of discontinuation. The sponsor must also take all reasonable steps to recover any unused quantities of the drugs, except for authorized drugs used in accordance with the purpose and conditions of use, that have already been distributed.

Furthermore, as soon as possible, but no later than 15 days after the date of discontinuation, the sponsor must notify the responsible directorate in writing and include the following information:

- the trial is being discontinued and the reasons for the discontinuation
- any impacts that the discontinuation may have on any other trial for which the sponsor holds an authorization that involves the drugs
- any potential risks to the health of participants or other persons
- confirmation that all 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 participants or other persons
- confirmation that the sale or importation of the drug to the discontinued sites has been stopped **and**
- confirmation that reasonable measures to ensure the return of all unused quantities of the drugs, except for authorized drugs used in accordance with the conditions of use, 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 if such discontinuation was carried out for safety reasons.

11.1.2 Investigator's responsibilities

When an investigator is notified by the sponsor that a clinical trial is being discontinued, in whole or in respect of a part that includes the investigator's clinical trial site, the investigator must, without delay, send a written notice to:

- the clinical trial participants at their site and
- the REB, except a national REB, that approved the protocol for their site, including the following:
    - the trial is being discontinued and the reasons for the discontinuation, and
    - any potential risks to the health of participants or other persons that the investigator was informed of by the sponsor

11.2 Resumption of a trial after discontinuation in part

To restart a trial that has been discontinued in part, the sponsor may submit a CTA-A to amend the protocol to reintroduce the part that was discontinued. This is subject to Health Canada authorizing the amendment.

If the sponsor wishes to restart a clinical trial that had been discontinued in whole, a new application for authorization would need to be submitted.

11.3 Closure and recommencement of a clinical trial site

The sponsor is required to notify the relevant directorate (via CTA-notification) when a clinical trial site is closed within 15 days after that day. Note that other sites may still be open in clinical trials involving multiple sites until the trial is completed or discontinued.

Under the regulations, the sponsor may resume the trial at a clinical trial site by filing a CTA-notification using a CTSI form with the following information:

- any change in the name and contact information of the investigator for each site and of the REB that approved the recommencement of the trial at each site

- the proposed date of recommencement of the clinical trial at each clinical trial site

11.4 Clinical trial completion

The sponsor is required to notify the relevant directorate (via CTA-notification) when a clinical trial, or a sub-study, is completed within 15 days after that day. The authorization will be deemed revoked in part following the completion of a sub-study or in whole following completion of the clinical trial.

Notwithstanding a suspension, revocation in part or arm or sub-study completion (or discontinuation), in its entirety in Canada, a study is considered to be completed after the last participant in Canada completes the "end of study" visit as defined in the protocol. This is the final visit for study-related tests and procedures, including the capture of any final potential study-related adverse events. This visit usually occurs some time after the participant has completed or discontinued study drug administration. This visit is normally in person, but for some studies it can also be carried out over the telephone.

Some trials, such as oncology trials, involve long-term follow-up for outcomes (for example, survival) where the participant or the participant's family will be contacted to determine the outcome in question. However, the trial would not be considered to still be ongoing if all participants enrolled in Canada have ceased study-related therapies, tests and procedures, and have completed the "end of study" visit. This includes any follow-up for safety.

There may be certain scenarios (for example, gene therapies, drugs with very long half-lives (several months)) where a study may be considered to be ongoing well beyond the period of study treatment. This is when long-term safety monitoring and reporting would be required in accordance with the regulations. The reporting requirements with regards to such long-term follow-up of safety are normally specified in the study protocol and agreed to between the sponsor and Health Canada prior to the authorization of the clinical trial in Canada.

11.5 Safety reporting post-authorization

11.5.1 Adverse drug reactions (ADRs)

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

- where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information
- 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.

If an authorized drug being used in accordance with the authorized (as per NOC or DIN) purpose and conditions of use, sponsors are exempt from this requirement with respect to that drug. Sponsors are still subject to reporting requirements as per the drug's market authorization.

11.5.2 Post-trial reporting

Following revocation of the authorization in whole, sponsors may be required to report to Health Canada any serious unexpected adverse reactions and/or serious adverse reactions that they become aware of in respect of a drug for up to 15 years. This obligation would only apply if Health Canada has reasonable grounds to believe the reaction originated from the use of the drug in the trial inside or outside of Canada.

Specifically, sponsors could be required to:

- report the reaction to Health Canada within 15 days after becoming aware of the information if it is neither fatal or life threatening, or within 7 days after becoming aware of the information if it is fatal or life threatening

- submit a complete report to Health Canada in respect of a fatal or life-threatening reaction within 8 days after originally reporting it to Health Canada, which must include an assessment of the importance and implication of any findings made

Health Canada would only rely on this post-trial reporting requirement:

- when warranted **and**
- where there could be a risk of health consequences associated with the use of the drug in the trial that could arise over the long term

This post-trial reporting requirement could only be imposed for drugs that do not currently have a market authorization for any purpose. It would cease to have an effect if the drug receives a market authorization at any point.

11.5.3 Adverse drug reactions (ADRs) reporting criteria

Each ADR that is subject to expedited reporting to Health Canada should be reported individually in accordance with the data elements specified in the ICH guidance document E2A: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*. Expedited reports are required for events that meet all these 3 criteria: serious, unexpected and a suspected causal relationship.

- **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 or incapacity
  - is a congenital malformation or birth defect, **or**
  - requires medical intervention to prevent any of those outcomes
- **Expectedness:** An "unexpected" adverse reaction is when the nature or severity is not consistent with information in the relevant source documents, such as the IB or PM. Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.
  - Reports that add significant information on specificity or severity of known, already documented serious ADRs 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 (such as hepatitis with a first report of fulminant hepatitis).

- **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.
  - Serious unexpected adverse reactions that are considered to be unrelated to the study drug by both the investigator and the sponsor should not be reported.

For clarification on ADR reporting requirements, consult:

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

11.5.4 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 can be e-mailed or faxed.

Biologic and Radiopharmaceutical Drugs Directorate

Reports for all serious and unexpected ADRs for biologics and radiopharmaceuticals should be:

- faxed to 613-957-0364 **or**
- submitted electronically via the E2B Electronic Gateway
  - recommended if your company or institution has electronic gateway capability
  - contact the Trading Partner Management Office (TPMO) by email at tpmo-bgpc@hc-sc.gc.ca for more information

Pharmaceutical Drugs Directorate

Reports for all serious and unexpected ADRs for therapeutics only should be:

- faxed to 613-941-2121 **or**
- submitted electronically via the E2B Electronic Gateway
    - recommended if your company or institution has electronic gateway capability
    - contact the Trading Partner Management Office (TPMO) by email at tpmo-bgpc@hc-sc.gc.ca for more information

11.5.5 Submission of case and summary reports

For the purpose of assessing the safety of a drug involved in a clinical trial, Health Canada may request in writing that a sponsor who holds an authorization submit any of the following:

- case reports relating to the ADRs and serious ADRs to the drug that are known to the sponsor **or**
- issue-related summary report that must contain a concise, critical analysis of the ADRs, as well as case reports of all or specified ADRs and serious ADRs that are known to the sponsor in respect of the issue that Health Canada directs the sponsor to analyze in the report

Health Canada's request will identify the time, form and manner that are reasonable in the circumstances for the submission of case reports and/or an issue-related summary report. Sponsors can generally expect to have 2 business days to respond to a standard request of this nature from Health Canada. Some triggers that could elicit a request for these reports could include safety signals from foreign jurisdictions, published reports or scientific articles and the receipt of 1 or multiple related serious unexpected adverse reactions.

11.5.6 Study endpoints

When a fatal or other serious outcome is the primary efficacy endpoint in a clinical trial, the protocol should clearly indicate the serious events that will be treated as disease-related and not subject to expedited reporting.

11.5.7 Additional information

There are other situations that may necessitate rapid communication to Health Canada. Appropriate scientific and medical judgment should be applied to each situation. For example, information that:

- might influence the risk-benefit assessment of a drug
- would be sufficient to consider changes in drug administration or in the overall conduct of a clinical trial, including:
    - for an "expected" serious ADR, an increase in the rate of occurrence that is judged clinically important
    - a significant hazard to the patient population, such as lack of efficacy with a drug used in treating a life-threatening disease
    - a major safety finding from a newly completed animal study

This information should be submitted where applicable to either of the following directorates:

Biologic and Radiopharmaceutical Drugs Directorate: Biologics and radiopharmaceuticals

- faxed to 613-957-0364 (for biologics and radiopharmaceuticals only) **or**
- submitted electronically via the E2B Electronic Gateway
    - recommended if your company or institution has electronic gateway capability
    - contact the Trading Partner Management Office (TPMO) by email at tpmo-bgpc@hc-sc.gc.ca for more information

Office of Clinical Trials, Pharmaceutical Drugs Directorate: Pharmaceuticals

- faxed to 613-941-2121 (for therapeutics only) **or**
- submitted electronically via the E2B Electronic Gateway
    - recommended if your company or institution has electronic gateway capability
    - contact the Trading Partner Management Office (TPMO) by email at tpmo-bgpc@hc-sc.gc.ca for more information

Sponsors should refer to ICH guidance documents E6: Guideline for Good Clinical Practice and E2A: Clinical Safety Data Management for safety reporting requirements for investigators and research ethics boards.

11.6 Updated investigator's brochure or equivalent document

In accordance with ICH GCP, the IB or equivalent document, 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 is 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 (ideally in tracked changes), including a rationale for each change.

11.7 Records related to clinical trial applications (CTAs) and clinical trial application-amendments (CTA-As)

As required in the regulations, sponsors and service providers conducting clinical trial-related activities are required to, as applicable to the activities they are conducting, record, handle and store all clinical trial information. This must be done in a manner that allows for the complete and accurate reporting as well as the interpretation and verification of the information. All clinical trial sponsors need to ensure that the record-keeping requirements are met where other parties (for example, investigators, service providers) carry out these activities on their behalf.

Sponsors are required to ensure that records are retained for 15 years. The retention period begins on the date that the clinical trial is:

- for authorized trials, on the day the authorization is revoked in whole

- for trials not requiring Health Canada's authorization, on the day on which the trial is:
    - completed in whole
    - discontinued in whole by the sponsor **or**
    - under a direction to cease conduct that has become permanent

The types of documents that must be retained include:

(a) a copy of all versions of the document containing the following information:
    - the physical, chemical, and pharmaceutical properties of the drug
    - any non-clinical and clinical information, and any additional information that might be required, to support the use of the drug in the clinical trial, and
    - if the drug is a radiopharmaceutical as defined in section C.03.201 of the FDR, information regarding directions for preparing the radiopharmaceutical, the radiation dosimetry in respect of the prepared radiopharmaceutical and a statement of the storage requirements for the prepared radiopharmaceutical

(b) records respecting each change made to the document or information referred in paragraph (a) above, including the rationale for each change and documentation that supports each change

(c) 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; however, modified requirements exist for trials for which the sponsor is exempt from section 3.1 of the FDA or that have a selective approach to collecting information on adverse events (see section 11.5 of this guidance document on Safety Reporting Post Authorization for further details)

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

(e) records respecting the shipment, receipt, disposition, return and destruction of the drug

(f) the lot number of the drug used in the clinical trial

(g) for each clinical trial site, a copy of the protocol, informed consent form (if applicable) and any amendment to the protocol or informed consent form that have been approved by the research ethics board for that site; and

(h) for each clinical trial site, an attestation, signed and dated by a research ethics board, 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.

11.7.1 Exceptions to the record keeping requirements

The requirement for record keeping regarding changes to the Investigator's Brochure (or equivalent document) for the trial (requirement 'a' and 'b' in section 11.7 of this guidance document) does not apply for drugs used in a clinical trial that have already been assigned an NOC or DIN and that are used in the trial in accordance with the authorized purpose and conditions of use. Any changes to the master document for these drugs are to be addressed under the market authorization process.

The requirement for record keeping regarding adverse events (requirement 'c' in section 11.7 of this guidance document) does not apply in respect of a clinical trial for which the clinical trial has been authorized with a protocol that outlines a selective approach to the collection of adverse events. However, at a minimum, sponsors (and service providers, as applicable) of these trials must maintain:

- records respecting all serious unexpected adverse reactions 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 reaction, and
- records respecting any other adverse events in the approach outlined in the protocol, 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

The requirement for record keeping regarding adverse events (requirement 'c' in section 11.5 of this guidance document) does not apply in respect of a clinical trial for which the sponsor is exempt from section 3.1 of the FDA. However, sponsors are required to

maintain records respecting all serious adverse reactions and serious unexpected adverse reactions 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 reaction. This is a minimum requirement that aligns with international guidelines (in other words, ICH E19); sponsors may choose to adhere to more fulsome data collection methods/requirements where appropriate.

The requirement for record keeping regarding records respecting the shipment, receipt, disposition, return and destruction of the drug (requirement 'e' in section 11.7 of this guidance document) does not apply in respect of a drug used in a clinical trial if that drug has already been assigned an NOC (and the NOC has not been suspended) or DIN (and the DIN has not been cancelled). This exception applies whether or not the drug is being used within the parameters of the market authorization (in other words, whether or not it is being used in accordance with the authorized purpose and conditions of use).

Health Canada has the authority to require sponsors to submit records at any time. Sponsors can generally expect to have 2 business days to respond to a standard request of this nature from Health Canada.

11.7.2 Selective approach to collection of adverse events

Sponsors may propose a selective approach to collection of adverse events in respect of a drug in their clinical trial if the safety profile of the drug has been sufficiently characterized (well-understood and documented), in accordance with the ICH E19 Guidance that has been adopted by Health Canada. At a minimum, all serious unexpected adverse reactions must be collected.

Trials to be considered for selective safety data collection should meet all of the following criteria:

- Phase IV trial or late-stage trial involving a drug used outside the conditions of use for which the drug has received market authorization or, in rare cases, a phase III trial of a drug that has not yet received market authorization.

- Examples of appropriate use of ICH E19 include:
    - Clinical trials to support a new indication of an authorized drug where the two populations are similar (for example, with respect to demographic characteristics, comorbidities, concomitant therapies), or when the patient population in the new indication was well represented in the trials that supported the approved indication.
    - Clinical trials intended to expand the label information of an authorized drug with additional endpoints in the same patient population.
    - Safety trials designed to further investigate potential safety concerns focussing on specific parameters.
    - Clinical trials designed to provide additional evidence of efficacy.
- The trial does not involve a gene therapy or a rare disease.
- The safety profile of the drug is well-understood and documented.

Sponsors requesting selective approach should provide the following information in their CTA or CTA-A:

- The application should contain sufficient evidence to support the conclusion that the safety profile of the drug has been sufficiently characterized to justify selective adverse event collection, and
- The protocol should sufficiently outline:
    - which adverse events will not be collected, or be collected at a reduced frequency, and
    - how the selective adverse event collection will be implemented (for example, for all participants, for a subset of participants, after an initial period of the trial, etcetera)

The sponsor will be required to demonstrate, at the time of application, that they are eligible for selective approach to adverse event collection. As part of the assessment of the sponsor's application, Health Canada will assess whether the above requirements are met, and if necessary, may request additional information from the sponsor.

The selective adverse event collection approach outlined in the protocol must not compromise the ability to meet the study objectives or have the potential to create unacceptable risk to the safety of clinical trial participants. Requirements regarding records retention are only applicable to adverse events that are collected (i.e., under the selective collection of adverse events). Note that records of serious unexpected adverse drug reactions must be collected and retained.

While the trial is under way, changes to the protocol to increase the collection of adverse events would require the filing of a notification whereas a change to decrease adverse event collection would require the filing of an amendment application because such a change would affect the risk to participants.

If the selective approach to adverse event collection in respect of a clinical trial is no longer appropriate, depending on the situation, Health Canada could take action up to and including the imposition of a T&C on the authorization or suspension of the authorization.

12. Suspension and revocation of an authorization to conduct a clinical trial

Health Canada may suspend an entire trial or part of a trial, such as at a trial site, an individual arm within a trial, a sub-study under a master protocol trial, an activity (for example, recruitment) or the use of a particular drug in a trial. Except in circumstances where immediate suspension is necessary, Health Canada will provide the sponsor with an opportunity to be heard before proceeding with a suspension. Health Canada will reinstate a suspended authorization if the sponsor provides information demonstrating that the situation giving rise to the suspension did not exist or has been corrected; otherwise, the suspended authorization will be revoked.

12.1 Post-authorization requests for information and samples

Health Canada has the authority to request a sponsor (whether or not they are an authorization holder) to submit information, records and/or samples of the drugs at any time during the trial. This authority applies in respect of any drug(s) involved in the clinical trial (in other words, drug(s) being tested and, if applicable, comparator product(s) or other drug(s) used for the needs of the trial).

Health Canada may use this authority to help determine whether to suspend or revoke the authorization.

It is at Health Canada's discretion to decide the time, form and manner that are reasonable in the circumstances for the submission of this information, records and/ or samples; sponsors can generally expect to have two business days to respond to a standard request of this nature from Health Canada.

12.2 Suspension with prior opportunity to be heard

Health Canada may suspend, in whole or in part, an authorization to conduct a clinical trial if there are reasonable grounds to believe any of the following:

- Any provisions of the Regulations or of the FDA have been contravened.
- There has been a failure to comply with a terms and conditions imposed on the authorization.
- Any information submitted in respect of a drug or clinical trial is false or misleading.
- There has been a failure to comply with good clinical practices.
- The authorization holder has failed to provide information or material (including samples) requested by Health Canada.
- The conditions of the threshold for authorization are no longer met (refer to section 6 in this guidance document).

Under such circumstances, Health Canada will, prior to suspending an authorization:

- send the authorization holder a written notice that indicates whether the authorization is intended to be suspended in whole or in part and the reason for the intended suspension, and
- give the authorization holder an opportunity to be heard in writing concerning the intended suspension

Health Canada will not suspend the authorization if the authorization holder provides, within 30 days after the day on which the sponsor receives the notice of suspension, information or material (including samples) that demonstrates that the situation giving rise to the intended suspension did not exist or has been corrected.

Upon suspension of the trial, Health Canada will send the authorization holder a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in whole or in part and the reason for the suspension. The authorization holder must then notify investigators, and any service providers involved in the conduct of the clinical trial, and those who import or sell a drug for use in the clinical trial, of the suspension without delay and ensure that those who conduct the trial under the oversight of investigator(s) or service provider(s) are notified of the suspension as soon as possible.

12.3 Suspension without prior opportunity to be heard

Health Canada may suspend the authorization to conduct a clinical trial, in whole or in part, before giving the authorization holder an opportunity to be heard if there are

reasonable grounds to believe that it is necessary to do so to prevent injury to the health of a clinical trial participant or other person.

In these circumstances, Health Canada will send the authorization holder a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in whole or in part and the reason for the suspension. The authorization holder must then notify investigators, and any service providers involved in the conduct of the clinical trial, and those who import or sell a drug for use in the clinical trial, of the suspension of the authorization without delay and ensure that those who conduct the trial under the oversight of investigator(s) or service provider(s) are notified of the suspension as soon as possible.

12.4 Suspension of multiple clinical trial authorizations

Health Canada may suspend multiple clinical trial authorizations involving a single or multiple authorization holders to address systemic non-compliance issues. Health Canada may suspend multiple clinical trial authorizations without providing the authorization holder(s) with an opportunity to be heard if there are reasonable grounds to believe that a suspension is necessary to prevent injury to the health of a clinical trial participant or other person, and the circumstance giving rise to the suspension is present across multiple clinical trials involving the same person (for example, the same authorization holder, service provider or investigator).

Examples of when this authority could be used include:

- When a service provider (for example, contract research organization (CRO)) is conducting activities in relation to multiple clinical trials at their location for different authorization holder and, during inspection, it is determined that activities are not conducted in accordance with GCP. This may impact all trials that the CRO is conducting at that location, it could impact trials at other locations, with different sponsors, or it may only impact one trial. This would be determined by the inspector based on the evidence available at the time of the inspection. The inspector may need to collect additional information to determine the extent of the non-compliance.
- If Health Canada has reasonable grounds to believe that non-compliant or potentially dangerous pharmacy practices and/or drug administration procedures

by the service provider are common in other clinical trials authorized under the same or different sponsor that have not been inspected.

- When the non-compliance rating relates to serious non-compliance related to activities under the responsibility of the investigator and the study team that are also in charge of other clinical trials.
- When unsanitary conditions of premises or equipment is used for several clinical trials that potentially could put the health of the clinical trial participants in danger.
- When data management or pharmacovigilance systems are not valid and present serious data integrity issues that make the clinical data unreliable and unsafe. Clinical trials using the same data management system but that have not been inspected could also be considered for suspension.
- When persons (for example, investigators, sub-investigators) conducting clinical trial activities are unlicensed and unqualified and these persons are conducting activities at multiple trials.

12.5 Reinstatement and revocation of a suspended authorization

Health Canada will reinstate, in whole or in part, a suspended authorization if the sponsor submits, within the time specified in paragraphs (a) and (b) below, information or material (including samples) that demonstrates that the situation giving rise to the suspension did not exist or has been corrected.

(a) For a suspension with prior opportunity to be heard, within 30 days after the effective date of the suspension.
(b) For an immediate suspension without prior opportunity to be heard, within 60 days after the effective date of the suspension.

If the sponsor does not meet the above timelines, Health Canada may nonetheless reinstate, in whole or in part, a suspended authorization if the situation giving rise to the suspension did not exist or has been corrected. Health Canada may also impose terms and conditions on the reinstated authorization to address the situation giving rise to the suspension.

Alternatively, if the sponsor does not meet the above timelines or if Health Canada is not satisfied that the information submitted by the sponsor is sufficient to demonstrate that the situation giving rise to the suspension did not exist or has been corrected,

Health Canada may revoke, in whole or in part, a suspended authorization. Health Canada may also request additional information from the sponsor to further assess the situation.

In the event of a revocation, Health Canada will send the sponsor a notice that sets out the reason for the revocation, the day on which the revocation is effective and indicating whether the authorization is revoked in whole or in part. The sponsor must then notify investigators and any service providers involved in the conduct of the clinical trial, and those who import or sell a drug for use in the clinical trial, of the revocation of the authorization.

13. Authorities for a clinical trial for which the sponsor is exempt from section 3.1 of the FDA

As mentioned in section 2 of this guidance document, sponsors are not required to file a CTA for clinical trials only involving authorized drugs where the use of the drug(s) in the investigation falls within the parameters of the approved conditions for use. These trials are referred to as Phase IV clinical trials and are exempt from section 3.1 of the of the FDA. However, Health Canada nonetheless has certain authorities with respect to these types of trials, as detailed below.

Health Canada may request a sponsor of a Phase IV trial to submit information concerning the clinical trial or the drug(s) involved in the clinical trial, or samples of the drug(s), to help determine whether to direct the sponsor the cease the conduct of the clinical trial.

It is at Health Canada's discretion to determine, on a case-by-case basis, the time, form, and manner that are reasonable in the circumstances for the submission of this information or samples.

13.1 Order to cease conduct with prior opportunity to be heard

Health Canada may order a sponsor exempt from section 3.1 of the FDA to cease the conduct of a clinical trial, in whole or in part, if there are reasonable grounds to believe that:

- any of the following applies:
  - the conduct of the clinical trial, including the use of any drug in it, is likely to result in unacceptable risks to the health of its participants or other persons
  - the clinical trial is contrary to the best interests of its participants
  - the objectives of the clinical trial are not achievable
- the applicable provisions of the regulations or the FDA relating to the clinical trial have been contravened

- any information submitted in respect of a drug or the clinical trial is false or misleading
- there has been a failure to comply with good clinical practices, or
- the sponsor has failed to provide the information or samples requested by Health Canada

Prior to ordering the cease conduct, Health Canada will:

- send the sponsor a written notice of the intent to order a cease conduct, and
- give the sponsor an opportunity to be heard in writing concerning the intended order

Health Canada will not order a cease conduct if the sponsor has provided, within 30 days after the day on which the sponsor receives the notice referred to above, information or material (including samples) that demonstrates that the situation giving rise to the intended order did not exist or has been corrected.

If Health Canada orders the sponsor to cease conduct, Health Canada will send the sponsor a written notice of the order to cease conduct that indicates the effective date of the order, whether the conduct must cease in whole or in part and the reason for the order. The sponsor must then notify investigators, and any service providers involved in the conduct of the clinical trial, and those who import or sell a drug for use in the clinical trial, of the cease conduct order without delay, and ensure that those who conduct the trial under the oversight of investigator(s) or service provider(s) are notified of the cease conduct order as soon as possible.

13.2 Order to cease conduct without prior opportunity to be heard

Health Canada may order a sponsor exempt from section 3.1 of the FDA to cease the conduct a clinical trial, in whole or in part, before giving the sponsor an opportunity to be heard if there are reasonable grounds to believe that it is necessary to do so to prevent injury to the health of a clinical trial participant or other person.

If Health Canada orders a cease conduct, Health Canada will send the sponsor a written notice of the order to cease conduct that indicates the effective date of the order, whether the conduct must cease in whole or in part and the reason for the order. The

sponsor must then notify investigators, and any service providers involved in the conduct of the clinical trial, and those who import or sell a drug for use in the clinical trial, of the cease conduct order without delay, and ensure that those who conduct the trial under the oversight of investigator(s) or service provider(s) are notified of the cease conduct order as soon as possible.

13.3 Ability to lift a cease conduct order

Health Canada will lift a cease conduct order, in whole or in part, if the sponsor submits, within the time specified in paragraphs (a) and (b) below, information or material (including samples) that demonstrates that the situation giving rise to the order did not exist or has been corrected.

(a) For a cease conduct order with prior opportunity to be heard, within 30 days after the effective date of the order.
(b) For a cease conduct order without prior opportunity to be heard, within 60 days after the effective date of the order.

If these timelines are not met by the sponsor, Health Canada may nonetheless lift a cease conduct order, in whole or in part, if the situation giving rise to the order did not exist or has been corrected, but only within 15 days following the applicable period in (a) or (b), after which the direction to cease conduct becomes permanent.

Appendices

Appendix A: Abbreviations

AR	Adverse reaction
BRDD	Biologic and Radiopharmaceutical Drugs Directorate
CIOMS	Council for International Organizations of Medical Sciences
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
DCT	Decentralized clinical trial
DIN	Drug identification number
FDA	Food and Drugs Act
GCP	Good clinical practice
ROEB	Regulatory Operations and Enforcement Branch
ICF	Informed consent forms
ICH	International Council for Harmonisation
ITA	Investigational testing application
MF	Master file
MDD	Medical Devices Directorate
NOC	Notice of compliance

2034	**NNO**	Notice of no objection
2035	**NSN**	Not satisfactory notice
2036	**QIS**	Quality information summary
2037	**QIS-PER**	Quality information summary - positron-emitting radiopharmaceuticals
2038	**QIS-R**	Quality information summary - radiopharmaceuticals
2039	**QOS**	Quality overall summary
2040	**QOS-CE**	Quality overall summary - chemical entities (clinical trial applications)
2041	**REB**	Research ethics board
2042	**SUSAR**	Suspected unexpected serious adverse reaction
2043	**T&C**	Terms and conditions
2044	**PDD**	Pharmaceutical Drugs Directorate

Appendix B: Definitions

Most of the definitions listed below were taken from the Regulations, the Food and Drugs Act, and Health Canada / ICH guidance documents E6: Guideline for Good Clinical Practice: Harmonized Guideline (ICH E6) and E8: General Considerations for Clinical Trials.

Adverse drug reaction

Any adverse and unintended occurrence in the health of a participant who is administered a drug in a clinical trial, for which there are reasonable grounds to believe that the occurrence could be a noxious response to any dose of the drug.

Adverse event

Any adverse occurrence in relation to the health of a participant who is administered a drug in a clinical trial that may or may not be caused by the administration of the drug. It includes an adverse drug reaction.

Authorization

An authorization from the Minister for a sponsor to conduct a clinical trial, as well as to import and sell clinical trial drugs for the purposes of the trial.

Business day

Is a day other than a Saturday, Sunday or other holiday.

Case report

A detailed record of all relevant data associated with the use of a drug in a clinical trial participant.

Clinical trial

A study, involving human participant(s), for the purpose of discovering or verifying the effects of a drug, a device or a food for a special dietary purpose.

Clinical trial site(s)

A clinical trial site includes a main location, at which the clinical trial is conducted under the oversight of the investigator, and can include one or more locations that are remote from the main location.

Contingent authorization

A notice issued by Health Canada confirming that the clinical trial application is complete, which indicates the day on which the application was submitted and is sent to the sponsor within seven days after the day on which the application is submitted. The contingent authorization relates only to the completion of the application and does not constitute a decision on whether the trial should be authorized. Unless Health Canada objects, the contingent authorization becomes an authorization that authorizes the sponsor to conduct the clinical trial as per section 15 of the Regulations.

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 enroll patients in the clinical trial.

Drug

A drug for human use that is to be tested in a clinical trial. Note: for the purposes of this guidance document, ‘drug’ does not include natural health products within the meaning of the *Natural Health Products Regulations*.

Good clinical practices

Generally accepted good clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial participants and other persons, and the reliability of results, including good clinical practices outlined in the Regulations, and further detailed in the ICH E6 Guideline.

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 importation 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 form

A document that describes: 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.

Investigator

A 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 or territory in which the main location of the clinical trial site that is under their purview is situated, who has the relevant clinical expertise, within their regulated scope-of-practice, to exercise their profession in the course of the clinical trial given its objectives; and in the case of a clinical trial conducted by a team, the responsible leader of that team.

List of National Research Ethics Boards

The List of National Research Ethics Boards, that is published by the Government of Canada on its website, as amended from time to time.

Master protocol trial

Is a clinical trial that meets all of the following criteria:

- it includes one or more sub-studies
- the research questions of the sub-studies fall within the scope of those of the clinical trial, and
- a framework exists to support a common organizational approach for the sub-studies and the other parts of the clinical trial, as well as the sharing of research infrastructure, which may include clinical trial sites, resources and personnel

The protocol in a master protocol trial may describe several objectives and involve coordinated efforts to evaluate one or more products in one or more indications within

the overall trial structure. Types of master protocol trials include basket trials, umbrella trials, and platform trials. See Appendix E of this guidance document for further information.

National research ethics board is a research ethics board that is set out in the List of National Research Ethics Boards.

Participant

A human subject who participates in a clinical trial.

Phase I

Clinical trials are typically designed to assess the pharmacokinetics/pharmacological actions of the drug, and to identify an initial safe and tolerable dose level and the initial potential risks associated with increasing doses. Drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development. Depending on the drug type and proposed indication, Phase I trials may be conducted in either healthy volunteers or in patients.

Phase II

Clinical trials are typically designed to evaluate the early efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented, and to better characterize the potential risks associated with the drug.

Phase III

Clinical trials that are conducted after preliminary evidence suggesting efficacy of the drug have been demonstrated. Sometimes referred to as “Pivotal trials,” these are intended to gather additional information regarding the clinical efficacy and safety under the proposed conditions of use for the purposes of a drug approval application.

Phase IV

All studies performed within the approved conditions for use after the drug has been approved by the regulator for the market. These studies are often important for optimizing the use of the drug. They include many different study designs but must have valid scientific objectives. Commonly conducted studies include long-term safety studies

and studies designed to support use under the approved indication (for example, mortality and morbidity studies, or epidemiological studies).

Protocol

A document that describes the objectives, design, methodology, study population, statistical considerations, and organization of a clinical trial. It includes a master protocol for a master protocol trial, which is defined above.

Research ethics board

A body, the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human participants in order to ensure the protection of their rights, safety, and well-being. The board must have at least five members, a majority of whom are Canadian citizens or permanent residents under the *Immigration and Refugee Protection Act*, or persons registered as Indians under the *Indian Act*. It must include at least:

- one man and one woman,
- 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.
- one member knowledgeable in ethics,
- one member knowledgeable in Canadian laws relevant to the research to be approved,
- one member whose primary experience and expertise are in a non-scientific discipline, and
- 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.

Other than the member from the community or a representative of an organization (who cannot have any affiliation with the sponsor), members of the board must have no affiliation with the sponsor that could compromise the member’s ability to fulfill the board’s principal mandate, or that could be perceived to do so.

Senior Executive Officer

The Senior Executive Officer (SEO) is the most senior person with policy and operational decision-making authority within the sponsor or is an official who has this delegated authority in respect of the clinical trial. The SEO 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 3011 Form.

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 3011 Form.

Sell

Includes offer for sale, expose for sale, have in possession for sale—or distribute to one or more persons, whether or not the distribution is made for consideration, and also includes lease, offer for lease, expose for lease or have in possession for lease.

Serious adverse drug reaction

An adverse drug reaction, that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening, results in death, or requires medical intervention to prevent any of those outcomes.

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 equivalent document or on the label of the drug.

Service provider

A person (which would also include an organization) who conducts a clinical trial by providing a service to or on behalf of the sponsor or an investigator. This does not include an investigator or members of the team under the oversight of the investigator.

Sponsor

A person (which would also include an organization) who a) conducts a clinical trial solely or in combination with other persons; and b) takes responsibility for the overall conduct of a clinical trial. Unless exempt from section 3.1 of the FDA by the Regulations, the sponsor would also be required to hold an authorization that authorizes the conduct of a clinical trial.

Study (clinical trial) completion

A clinical trial is considered completed after the last participant at all sites in Canada completes the "end of study" visit as defined in the protocol. The "end of study visit" is the final visit for study-related tests and procedures, including the capture of any final potential study-related adverse events.

Sub-study

A study that meets both of the following criteria: a) the study is or is proposed to be part of a master protocol clinical trial; and b) the study is aimed at discovering or verifying the effects of one or more of the drugs used - or proposed in the study to be used - in the clinical trial.

Appendix C: Relevant addresses

Pharmaceutical Drugs Directorate (PDD)

PDD regulates human prescription pharmaceutical (for example, chemically synthesized) products.

The Office of Clinical Trials (OCT) manages and evaluates information related to clinical trial applications for drug products used in phase 1, 2 or 3 clinical trials. Among its responsibilities, OCT receives and reviews clinical trial applications, including serious unexpected adverse drug reactions related to clinical trials. It also provides guidance to stakeholders.

Office of Clinical Trials
Pharmaceutical Drugs Directorate
5th Floor, Holland Cross, Tower B
Address Locator: 3105A
1600 Scott Street
Ottawa, Ontario
Canada
K1A 0K9

Fax: 613-946-7996

General enquiries email: OCT_BEC_Enquiries@hc-sc.gc.ca

Clinical trial notifications email: OCT_BEC_CTA-N-DEC@hc-sc.gc.ca

Clinical trial site information forms email: clinical.trials.site@hc-sc.gc.ca

Biologic and Radiopharmaceutical Drugs Directorate (BRDD)

BRDD is the Canadian regulatory authority that regulates within the scope of this guidance document:

- clinical trials of biologics and radiopharmaceuticals
- biologic drugs for human use
- radiopharmaceutical drugs for human use

The Office of Regulatory Affairs within BRDD manages submissions and applications associated with the products that the directorate regulates. It:

- screens and validates submissions and applications
- coordinates and facilitates meetings with sponsors
- provides regulatory and policy guidance to sponsors
- receives and issues all regulatory correspondence for BRDD

Office of Regulatory Affairs
Biologic and Radiopharmaceutical Drugs Directorate
100 Eglantine Driveway,
Address Locator: 0601C
Ottawa, Ontario
Canada
K1A 0K9

Fax: 613-946-9520

General enquiries email: BRDD.ORA@hc-sc.gc.ca

Clinical trial notifications email: brdd.ctan-ndec.dmbr@hc-sc.gc.ca

Clinical trial site information forms email: : brdd.ctsi-filec.dmbr@hc-sc.gc.ca

Regulatory Operations and Enforcement

Clinical Trial Compliance Program
Email: GCP_BPC@hc-sc.gc.ca

Business Facilitation and Modernization Directorate (BFMD)

Sponsors expressing interest in the eCTD format for their clinical trial regulatory activities, or eCTD modules and or file structures should send an email to the Health Canada e Review group for further guidance and to request a dossier ID in advance of filing as needed.

Email: ereview@hc-sc.gc.ca

Appendix D: Useful websites

- Bioavailability and Bioequivalence
- Biologics, radiopharmaceuticals and genetic therapies
- Clinical Trials for Natural Health Products
- Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework
- Good Clinical Practices
- Health Canada
- Health Products and Food Branch
- International Conference on Harmonisation
- Medical Devices Guidance Documents
- Drug Products
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2nd edition)

Application preparation

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

- ADR Expedited Reporting Summary for ADRs Occurring During Clinical Trials
- Application Form For An Exemption To Use A Controlled Substance For Scientific Purposes
- CIOMS Form I
- Clinical Trial Site Information Form
- Draft Guidance Document: Applications for Medical Device Investigational Testing Authorizations [2017-10-06]
- E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting - Reminder for Sponsors
- Guidance Document: Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format
- Guidance Document - Development Safety Update Report (DSUR) - International Conference on Harmonisation (ICH) Topic E2F
- Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals

- Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice
- Guidance for Industry: Management of Drug Submissions
- Guidance for Records Related to Clinical Trials (GUIDE-0068)
- Guidance on Combination Products
- Importing and exporting health products for commercial use (GUI-0117)
- Health Canada 3011 Form: Drug Submission Application Form for Human, Veterinary, Disinfectant Drugs and Clinical Trial Application/Attestation
- Notice: Preparation of Clinical Trial Regulatory Activities in the "Non-eCTD Electronic-Only"
- Post-Notice of Compliance (NOC) Changes: Framework Document
- Post-Notice of Compliance (NOC) Changes: Quality Document
- Preparation of an Application for Investigational Testing - In Vitro Diagnostic Devices (IVDD) V.3 [1999-02-22]
- Protocol Safety and Efficacy Assessment Template - Clinical Trial Application
- Quality Overall Summary - Chemical Entities (Clinical Trial Applications Phase I) (QOS-CE (CTA - Phase I)) [2008-11-12]
- Quality Overall Summary - Chemical Entities (Clinical Trial Applications - Phase II) (QOS-CE (CTA - Phase II)) [2008-11-12]
- Quality Overall Summary - Chemical Entities (Clinical Trial Applications - Phase III) (QOS-CE (CTA - Phase III)) [2008-11-12]
- Research Ethics Board Attestation
- Draft Guidance Document SGBA Plus Demographics Action Plan [pivotal Phase III trials]

For Biologics

Guidance Documents:

- Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotherapeutic and Blood Products, Date: 2024-04-29
- Guidance Document Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application, Date: 2016-06-16

- Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs, Date: 2005-06-01

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

For Radiopharmaceuticals

Templates:

- Blank QIS-R template
    - Email: BRDD.ORA@hc-sc.gc.ca
- Blank QIS-PER template
    - Email: BRDD.ORA@hc-sc.gc.ca

Appendix E: Clinical trial applications and amendments involving master protocols trials

Background

Master protocol trials are designed with multiple sub-studies and involve coordinated efforts to evaluate one or more products being tested in one or more indications within the overall trial structure. Types of master protocol trials include:

- **Basket trials**, which are designed to investigate the safety/efficacy/effect of a product across a variety of indications;
- **Umbrella trials**, which are designed to investigate the safety/efficacy/effects of several products in a single indication;
- **Platform trials**, which are designed to investigate several products in one or multiple indications in a highly dynamic design.

In general, the overall design and framework of these studies is described in a master protocol document. During the trial's lifecycle, sponsors may introduce sub-study protocol(s) as appendices to be read in conjunction with the master protocol and conducted under the established study framework.

Considerations prior to master protocol trial submission

Developing the protocol

When developing the protocol for a master protocol trial, with the exception of basket trials which involve the use of a single product, sponsors should consider preparing a master protocol document that does not include the use of any specific drugs to be investigated. Working off this established framework, sponsors may consider developing and introducing sub-study documents specific to a cohort or intervention during the lifecycle of the trial.

For the filing strategy, the sponsor should submit the master protocol and first sub-study together, and each additional arm, cohort or intervention should be submitted as a separate sub-study, in the form of a CTA-Amendment.

Pre-CTA Meetings

Due to the innovative trial designs and complexity of master protocols, Health Canada encourages sponsors to request a pre-CTA consultation meeting. The pre-CTA consultation meeting provides an opportunity for the sponsor to receive advice and considerations from Health Canada on the design and conduct of the trial, while also allowing for discussion on the filing process and submission contents to ensure well-prepared submissions and an efficient review process.

The cover letter for all meeting requests should clearly state that the meeting request is in relation to a master protocol. For example: “REQUEST FOR PRE-CTA MEETING – MASTER PROTOCOL.”

Submitting regulatory activities to Health Canada

To facilitate the review of clinical trials involving master protocols, the cover letter for each regulatory submission (CTA, CTA-A and CTA-N) should clearly identify the submission to be a master protocol (for example, a Basket, Umbrella or Platform Trial).

Health Canada encourages the sponsor to contact the relevant directorate in advance of filing their CTA or CTA-A if there are specific questions regarding the required information for filing.

Clinical trial applications (CTAs)

To ensure compliance with the regulations, sponsors must submit each master protocol as a new CTA to Health Canada. To facilitate the processing and review of the submission, sponsors should provide the following within their submission:

- A cover letter that is clearly marked as “CTA-MASTER PROTOCOL;”
- A protocol lifecycle table (see Table 1, below)
- Tabular listing of all sub-studies associated with the master protocol (see Table 2, below)

Due to the complexity of master protocols, Health Canada requests that the initial CTA submission consist of:

1. the master protocol, and
2. no more than one sub-study (if applicable; refer to the Developing the protocol section of this Appendix)

Completion of the 3011 Form

Sponsors are requested to provide only one 3011 Form within a CTA package. For the initial CTA package, in the Part 2 - Drug product formulation information section of the form, sponsors should list the product(s) that are intended for use in the included initial sub-study. Section # 82 of the form (“Clinical Trial Protocol Number”) should identify the overarching protocol number that was assigned to the master protocol, as well as the sub-study identifier (if applicable).

Clinical trial application-amendments (CTA-As)

For CTA-As, the cover letter should clearly identify the type of amendment, for example:

- amendments that modify the master protocol
- amendments that introduce a sub-study
- amendments that modify a sub-study
- amendments to the chemistry, manufacturing, and controls (CMC) information

Amendments that modify the master protocol

The cover letter should clearly identify how the amendment is modifying the master protocol.

With the exception of safety amendments, sponsors should not submit nor include additional amendments to introduce or amend sub-studies while the master protocol amendment is still in review.

When completing the 3011 Form, sponsors should list all drugs that have been authorized thus far within the context of the trial in the part 2 - Drug product formulation information section (in other words, all drugs intended for use in the authorized sub-studies). Section # 82 of the form (“Clinical Trial Protocol Number”) should identify the overarching protocol number that was assigned to the master protocol.

In addition to the documents required for a CTA-A under Division 5 of the Food and Drug Regulations or the Clinical trials for medical devices and drugs relating to COVID-19 regulations, the following should be provided:

- a cover letter that is clearly marked as “CTA-A – Modification(s) to the master protocol”
- an updated protocol lifecycle table (see Table 1, below, for an example)
- an updated tabular listing of all clinical studies and sub-studies (see Table 2, below, for an example)

Amendments that introduce a sub-study

Sponsors are advised to only introduce one sub-study per CTA-Amendment submission. For these types of amendments, Health Canada is willing to accept multiple unique clinical amendments (CTA-As) for the same dossier at the same time, provided the master protocol itself remains unchanged.

When completing the 3011 Form for each sub-study, sponsors should list only the drug(s) that is/are being employed in the sub-study in the part 2 – Drug product formulation information section. Section # 82 of the form (“Clinical Trial Protocol Number”) should identify the overarching protocol number that was assigned to the master protocol, as well as the sub-study identifier (if applicable).

For amendments that introduce a new sub-study, in addition to the documents required for a CTA-A under Division 5 of the Food and Drug Regulations or the Clinical trials for medical devices and drugs relating to COVID-19 regulations, the following should be provided:

- a cover letter that is clearly marked as “CTA-A – Addition of sub-study X”
- an updated protocol lifecycle table (see Table 1, below, for an example)
- an updated tabular listing of all clinical studies and sub-studies (see Table 2, below, for an example)
    - 1.a.i.1. A copy of the new sub-study protocol document;
    - 1.a.i.2. A current Investigator’s Brochure or Canadian Product Monograph for each product that needs authorization;
    - 1.a.i.3. An ICF document for the sub-study;
    - 1.a.i.4. Chemistry, Manufacturing, and Controls (CMC) information for the product(s) that needs authorization.

Amendments that modify a sub-study

Where changes are specific to only one sub-study, the sponsor is advised to file the changes within a separate CTA-A.

When completing the 3011 Form for the amendment, sponsors should list only the drug(s) that is/are being employed in the sub-study in the part 2 – Drug product formulation information section. Section # 82 of the form ("Clinical Trial Protocol Number") should identify the overarching protocol number that was assigned to the master protocol, as well as the sub-study identifier (if applicable).

For amendments that modify a sub-study, in addition to the documents required for a CTA-A under the Regulations, the following should be provided:

- a cover letter that is clearly marked as "CTA-A – Modification(s) to Sub-study X"
- an updated protocol lifecycle table (see Table 1 for an example)
- an updated tabular listing of all clinical studies and sub-studies (see Table 2 for an example)

For changes that impact multiple sub-studies, the sponsor should consider whether the changes are interrelated in determining an appropriate filing strategy. If the changes are similar (example: safety update for same drug used across multiple sub-studies, changes to inclusion criteria across sub-studies etcetera), the sponsor may file the changes to multiple sub-studies together in a single CTA-A. Changes to the sub-stud(ies) may warrant related updates to the master protocol. In those cases, the related master protocol changes should be filed together within the same CTA-A as the related sub-stud(ies). Sponsors should not submit nor include additional amendments to introduce or amend sub-studies while a CTA-A including the master protocol is still in review or while another CTA-A impacting the same sub-study is currently under review.

Amendments to the chemistry, manufacturing, and controls (CMC) information

The requirements for amendments to the chemistry, manufacturing, and controls (CMC) information remain unchanged.

The cover letter should clearly indicate which sub-studies are impacted by the CMC updates (that is, which sub-studies are employing the implicated product being tested).

When completing the 3011 Form, sponsors should list only the implicated drug(s) that is/are the subject of the CMC amendment in part 2 – Drug product formulation information section. Section # 82 of the form ("Clinical Trial Protocol Number") should identify the overarching protocol number that was assigned to the master protocol.

To facilitate the submission process, sponsors should provide the following:

- a cover letter that is clearly marked as "CTA-A – CMC updates for Drug X"
- an updated protocol lifecycle table (see Table 1, below, for an example)
- an updated tabular listing of all clinical studies and sub-studies (see Table 2, below, for an example)

Tracking of regulatory activities

While it is acknowledged that sponsors may use separate protocol numbering or sub-study identifiers for sub-studies, there is no change to Health Canada's direction regarding the protocol numbering. As such, the current processes for the submission of clinical trial site information (CTSI) forms, research ethics board attestation form, and QIU form are not impacted, and the protocol number to be tracked on these documents would be the overarching protocol number. The submission of separate documents per sub-study or inclusion of sub-study protocol numbers on these documents is not required. Furthermore, it is not considered mandatory to include sub-study protocol numbers on clinical trial labels.

To facilitate screening and review activities, sponsors should provide a protocol lifecycle table within each regulatory activity made for the protocol (for example, CTA, CTA-A, CTA-N, responses etcetera). Sponsors should include the table in Module 1.2.9 of each submission. See Table 1 below for an example:

Table 1. Example of a protocol life cycle table for a master protocol.

Sequence Number (eCTD only) *	Date Submitted	Control Number	Regulatory Activity Type	Sequence Description
*For eCTD dossiers, sponsors should identify the sequence number of the regulatory activity. For non-eCTD submissions, sponsors should omit this column.				

In addition, sponsors are advised to also keep a list of all sub-studies and include it in Module 1.7.4 of each CTA(-A). Table 2 below gives an example of how a sponsor can compile a list of all the sub-studies.

Table 2. Example of a tabular listing of all sub-studies.

Study Identifier	Associated Control Numbers (CTA[-A])	Products that need authorization	Sub-study status	Conducted in Canada (Y/N)
Master [protocol#]				
[sub-study 1 name]				
[sub-study 2 name]				
[sub-study 3 name]				

Joint review/establishing the lead directorate

There is no change to Health Canada's process of joint review for clinical trials involving multiple product lines or combination products. The initial CTA with the master protocol and one sub-study will establish the lead Health Products and Food Branch Directorate for the master protocol. The lead directorate will remain consistent throughout the lifecycle of the trial. All subsequent regulatory activities should be submitted to the lead directorate. The lead directorate will be responsible for communicating regulatory decisions to the sponsor.

Appendix F: Summary of additional drugs to be imported for a clinical trial

Summary of additional drugs to be imported for a clinical trial

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

Name of the drug product as stated on the marketed label:
Name of the country where the product is sourced:
Name of the company as stated on the marketed label:
Common name of the active ingredient:
Dosage form:
Strength:

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 (YYYY/MM/DD):
Name of Signing Official:
Title:
DSTS Control Number:
Telephone:
Fax:
Signature:
Date Sent (YYYY/MM/DD):