

Clinical trial application process: Canada

Before starting a clinical trial in Canada, a clinical trial application (CTA) must be filed. Health Canada will review the application and will notify the sponsor within 30 days if it is found to be deficient. Applications must be submitted for clinical trials that are phase I, II or III. If a sponsor wishes to conduct a clinical trial for a new indication of a marketed drug, a CTA is also required. Phase IV trials do not require a CTA. A phase IV trial is one that involves a marketed drug that is being used within the parameters for which it has been approved (i.e., for the same indication, dosage regimen, target patient population, and route of administration).

Note: While this article provides an overview of the process of submitting a clinical trial application in Canada, complete details are provided in *Health Canada's Guidance for Clinical Trial Sponsors* (http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctdcta-ctddec-eng.pdf).

Pre-CTA consultation meeting

Sponsors are invited to meet with Health Canada to discuss a CTA, particularly for new active substances or applications that may be related to complex issues. This provides an opportunity for the sponsor to discuss its drug development plans and obtain guidance and feedback from Health Canada.

A request for a pre-CTA meeting should include a pre-CTA information package. The package is required to be submitted 30 days in advance of the meeting. It should include all of the following:

- a brief summary of all data including a tabular listing of all preclinical and clinical studies, an outline of observed toxicological manifestations and their potential impact on humans, an outline of observed adverse events and a discussion of potential safety problems
- a proposed global clinical plan for the current stage of development and the regulatory status in other countries
- details of the proposed clinical trials to be conducted in Canada, including statement of:
 - o trial design
 - o indications and clinical use
 - o patient population and routes of administration
 - o dosage form, regimen and formulation
 - o proposed procedures for patient monitoring
 - o efficacy and safety assessments
 - o alternative treatments
 - o premature patient discontinuation
 - o other considerations
- significant chemistry and manufacturing aspects of the drug

Exhibit 1: Summary of parts of a CTA

Part of submission		Contents
Module 1	Table of contents	
	Application information	Drug submission application form, information on prior related applications, investigator's brochure, protocol synopsis, study protocol, informed consent documents, clinical trial site information, Canadian REB* refusals, foreign refusals, letters of access for related drug master files if needed
Module 2	Common technical document summaries	Table of contents, quality overall summary
Module 3	Quality	Table of contents, body of data with additional supporting information beyond that in Module 2

*REB: research ethics board

Source: Health Canada, *Guidance for Clinical Trial Sponsors*,
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctdcta-ctddec-eng.pdf

CTA amendments

If a sponsor wishes to change a protocol or make changes to a manufacturing process, a CTA amendment must be submitted, and Health Canada must provide its approval prior to the implementation of these changes. Health Canada requires a thirty-day review period for this approval process starting from the date it receives the amendment application.

A subsequent or additional amendment cannot be submitted to a CTA if a review of a previous amendment is still underway at Health Canada (i.e., during the thirty-day review period). The subsequent amendment will not be accepted. The sponsor will then be required to withdraw the CTA, re-file with the updated, amended information, and be subject to a new thirty-day review period.

Expedited review

Comparative bioavailability trials and phase I trials in healthy adult volunteers are subject to an expedited review. For this, Health Canada targets a seven-day review period. The following products are excluded from expedited review: treatments for somatic cell therapies, xenografts, gene therapies, prophylactic vaccines, and reproductive or genetic technologies.

A sponsor can only proceed once it receives a *No Objection Letter* (NOL) during the thirty-day review period, or if they have received no notification by the time the thirty-day period has elapsed.

CTA review process

The first step of the CTA review is a screening process. The target period for the screening process is seven days. If any deficiencies are identified, Health Canada will issue either a request for clarification (called a *Clarifax*) identifying the issues, or a screening rejection letter if there are major concerns. In the case of a screening rejection letter, Health Canada will detail the deficiencies.

During the screening process, a sponsor must respond to a request for clarification within two calendar days otherwise a rejection letter will be issued.

During the review of the CTA, Health Canada can issue requests for clarification (Clarifax), or a *Not Satisfactory Notice* (NSN) if there are significant deficiencies or if the response to a Clarifax is not provided in a timely manner. Sponsors are once again given only two calendar days to respond to a Clarifax.

If no deficiencies are identified, a NOL will be issued within the review period.

Sponsors are subsequently required to submit a *Clinical Trial Site Information* form before they start or amend a trial. This form provides information on the approval of the study by various ethics committees and information on the participating investigators.

Notifications

Minor amendments to a protocol are not required to be reviewed in advance of implementation. They are required to be submitted as notifications to Health Canada within 15 days of the change. Examples of these include:

- protocol changes that do not affect safety
- information on site closure or completion of the trial
- discontinuation of the clinical trial for reasons unrelated to safety
- changes to chemistry and manufacturing that do not affect the quality or safety of the drug such as production scale-ups with no change to process, tightening of specifications, changes in testing labs, changes in packaging material, or extension of shelf life

Continuous assessment

The CTA is required to be regularly updated with information relating to certain aspects of a trial:

1. **Research ethics boards:** Information regarding refusals by other regulatory authorities or research ethics boards should be submitted as notifications.
2. **Premature discontinuation of a trial:** Health Canada must be notified within 15 calendar days of the premature discontinuation of a trial in its entirety or at a specific site. The regulatory agency should also be notified if there is premature discontinuation of a trial outside Canada for a drug for which trials are ongoing in Canada.
3. **Adverse drug reactions:** Only adverse drug reactions that are serious, unexpected and considered related to the study drug are required to be reported in an expedited manner. If an adverse event is serious but expected, it is not required to be reported expeditiously. The following parameters apply:
 - a. when neither fatal nor life-threatening, submit within 15 days
 - b. when fatal or life-threatening, submit immediately and within seven days
 - c. within eight days after having informed Health Canada, submit as complete a report as possible including an assessment of the importance and implication of any findings

Other situations may also require communication with Health Canada, such as expected serious adverse events occurring more frequently than expected, a significant hazard to the patient population (such as lack of efficacy when used to treat a life-threatening disease), or a major finding from a newly completed animal study.

4. **Updated investigator's brochure:** This is required to be submitted annually.

Research ethics board review

A study is not permitted to start until the research ethics board (REB) at a clinical site has approved the trial. In addition, the sponsor must have received a *No Objection Letter* from Health Canada, or the thirty-day review period must be complete. Sponsors must report all serious, unexpected, drug-related adverse events to the REB as soon as possible and annually update the REB on the progress of the study including all safety information.