

# Regulatory Essentials

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## Types of Clinical Trials and Clinical Trial Application (CTA)

The number of investigator driven studies in Canada and in BC is on a sharp rise. Investigators and their coordinators embarking on these valuable studies realize that they suddenly in the role of sponsor. A majority of questions from 'new sponsors' center around the clinical trial application (CTA) process. The CTA process in Canada is relatively streamlined and straightforward. This article provides an overview of the steps along with references to some helpful guidance documents.

## Brief Regulatory History and Definition of Clinical Trial in Canada

Health Canada is the regulatory body that governs the sale and importation of drugs in Canada. The Food and Drug Regulations were amended September 1, 2001 to include Division 5 on Clinical Trials. Instead of an Investigational New Drug submission (IND), sponsors have since been required to file a Clinical Trial Application (CTA),

A 'Clinical Trial' as interpreted in Section C.05.001 of the Canadian Food and Drug regulations means "an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical or pharmacological or pharmacodynamic affects of the drug, identify any adverse events in respect of the drug, study the absorption distribution, metabolism and excretion of the drug or ascertain the safety or efficacy of the drug."

It is in the amendment noted above that the ICH guidance document E6: Good Clinical Practice –Consolidated Guideline was incorporated into the food and drug regulations along with other general guidelines. Sponsors should consult this to ensure that their clinical trial is conducted in accordance with good clinical practice and that the regulatory documents are prepared appropriately for CTA submission from a content perspective.

## Types of Clinical Trials in Canada

Canada does not use the model of classification by type of study (human pharmacology, therapeutic exploratory, therapeutic confirmatory or therapeutic use) but rather by the more traditional categories of four phases (I, II, III and IV). In this model, each successive phase usually involves a larger number of subjects as the drug is tested to establish safety and efficacy. A variety of clinical designs can be used in the four phases the most common being: placebo, multicentre and double-blind.

**Phase 1:** This is the phase where the first administration of the drug in humans occurs. It follows the pre-clinical animal studies. The initial human dose is usually one fifth or one tenth of the maximum tolerated dose per body weight in the most sensitive animal species seen in previous non-clinical studies. Phase 1 studies are mainly for establishing the safety and pharmacokinetic properties of the drug. Very small numbers of subjects are used in this phase. Both placebo and double-blind designs are commonly used in phase 1.

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

**Phase III:** These trials are typically large scale studies that can involve thousands of patients. These studies use double-blind, randomized and controlled techniques to make the trials more significant. The data from these trials is central in the application for the investigational drug to be given a Notice of Compliance (NOC). An NOC indicates that a drug is allowed to be advertised and sold in Canada.

**Phase IV:** Clinical Trials in this phase are performed according to approved indications and conditions after the drug has received a Notice of Compliance (NOC). These studies look at how the drug is used as intended on the market. Long term side effects are sometimes detected.

## Applicability of a CTA

Sponsors are required to submit a CTA to Health Canada if they wish to conduct a Phase I, II or III drug development and comparative bioavailability trial or a Phase I, II or III clinical trial using marketed products where the proposed use is outside of the approved indications and conditions. Maintaining the target population(s), route(s) of administration, or dosage regimen(s), is considered to be within the approved conditions.

Sponsors that wish to conduct a clinical trial with products that received only a NOC with conditions or no NOC or Drug Identification Number (DIN), are also required to file a CTA.

Phase IV Clinical Trials in Canada are performed after the product has been approved and products in Phase IV studies are evaluated based on approved conditions for use. The sponsor is not required to file a CTA for a Phase IV study, but they must follow good clinical practice as outlined in Division 5.

## The CTA Process

### Pre-CTA Consultation Meeting (optional)

When a sponsor decides to submit a CTA for authorization or sell or import a drug for a clinical trial, the sponsor may request a pre-CTA consultation Meeting with Health Canada. A pre-CTA consultation meeting is an excellent opportunity for both parties to address any concerns. This interaction with the regulatory authority can optimize the review and approval process for any CTA submission. There is a guidance that outlines the process for a pre-CTA meeting. Guidance to Industry: Management of Drug Submissions Health Canada Policy; Appeals Procedures for Drug Submissions

A formal written request and a pre-CTA package are submitted to the Therapeutic Products Directorate (TPD) for clinical trials involved in pharmaceutical drugs. The sponsor must document the meeting (within 14 days). Health Canada will add the meeting record to the Health Canada Central Registry File for the drug.

## The CTA Process (continued)

### Preparation of a CTA

Regulation C.05.005 defines what is required in a CTA submission and C.05.008 (3) specifies what is required in a CTA amendment (CTA-A). CTA submissions should be prepared in the Common Technical Document (CTD) format. There is a guidance document *Guidance for Industry: Preparation of New Drug Submissions in the CTD format*, which is quite useful for detailed formatting information. Another useful document is *the ICH M4 Guidance: Organisation of the Common Technical Document*. The third and probably the most useful document is the one developed by Health Canada titled *Guidance for Clinical Trial Sponsors – Clinical Trial Applications*. The title says it all.

### Authorization

When submitting a CTA, sponsors are applying for authorization to sell or import a drug for the purposes of conducting a clinical trial as regulated under C.05 of the regulations. Health Canada reviews the application within 30 days and notifies the sponsor in writing whether the CTA is approved or rejected.

### Applicability

A sponsor cannot change any part of a CTA that is under review. If a change is necessary the sponsor should withdraw that CTA and submit a new application. Upon approval the sponsor may, 1) make changes to the chemistry and manufacturing information that does not affect the quality or safety of the drug or 2) make changes to the protocol that do not alter the risk to the health of the clinical trial subject provided these changes are other than a change for which an amendment is required.

### Review

An acknowledgement letter will be issued to notify the sponsor that the review clock for submission has indeed begun. All CTA and CTA-A submissions are screened for acceptability for review. If there are deficiencies in the application, the sponsor may receive a full rejection letter (major deficiencies) or a request for clarification (minor deficiencies). It is very important that the sponsor follow the correct format and include all information required. If a clarification is required during the review, the sponsor must submit a satisfactory response within 2 days or an NSN (non Satisfactory Notice) is issued. A sponsor can appeal a NSN.

Full review with approved leads to a NOL – No Objection Letter

Full review with rejection leads to a NSN.

## Post CTA Approval Comments

There are of course post-approval requirements for sponsors. There are follow-up notes in the Guidance for Clinical Trial Sponsor: Clinical Trial Applications. Of particular note are the very specific labelling requirements for a drug used in a clinical trial.

The sponsor has obligations under Good Clinical Practice and privacy law. These are covered in the HC Regulations Division 5 and in provincial or federal privacy legislation as applicable. Sponsors and their coordinators should familiarize themselves with this information.

## Applicable Regulations and Guides and Documents

Guidance for Clinical Trial Sponsors: Clinical Trial Applications

Guidance to Industry: Management of Drug Submissions Health Canada Policy: Appeals Procedures for Drug Submissions, 4 April 2003

Guidance for Industry: Preparation of New Drug Submission in the CTD format

Health Canada Food and Drug Regulations

Health Canada, Food and Drug Regulations Amendment (Schedule 1024) Clinical Trial Framework, June 20, 2001

Health Canada – Regulatory Impact Analysis Statement (to Schedule 1024)

ICH M4 Guidance: Organization of the Common Technical Document

ICH E8 General Considerations for Clinical Trials

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