CLINICAL TRIAL APPLICATIONS IN CANADA

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ABSTRACT

Clinical trials in Canada in Phases I to III or for a new indication in Phase IV are required to conform to specific regulations that are monitored by Health Canada. These regulations apply to manufacturers and independent researchers. The process involves a Clinical Trials application, required practices that are performed during and after the clinical trial and inspection activities.

Key Words: *Regulations, clinical trials, Health Canada*

Clinical trials in Canada are subject to the Clinical Trial Regulations defined in Division 5 of the Food and Drug Regulations. The regulations are consistent with Good Clinical Practice as defined by the International Conference on Harmonization (ICH). Although Clinical Trial Regulations apply to all phases of clinical trials, Phase IV trials are exempt from filing clinical trial applications (but not from Good Clinical Practices (GCP) Guidelines). Phase IV trials are those that are conducted within the parameters of the Product Monograph.

The provisions of these regulations apply to all sponsors conducting a clinical trial in Canada, including researchers who initiate a clinical trial. The treatment of an individual patient with a drug in an off-label manner is not defined as a clinical trial. It is the responsibility of Health Canada to review and authorize the sale of an experimental drug for purposes of conducting a clinical trial and such authorization will be granted only if the design of the trial is scientifically valid, it meets regulatory requirements, and it does not pose an unacceptable risk to the patient and his/her health.

Clinical Trials: Regulations and Process

Before a clinical trial can be approved it is necessary to submit a Clinical Trial Application (CTA) to Health Canada. Unlike Investigational New Drug Applications (INDs) in the United States, CTAs in Canada include only summary information; except for CTAs involving biologics, where complete chemistry and manufacturing data are required. For bioequivalence/Phase I studies carried out in normal volunteers Health Canada has an administrative target review time of seven days from receipt of the CTA (with some exceptions). By regulation, clinical trials can start after 30 days unless the applicant has received a Not Satisfactory Letter. However, for all trials subject to the Clinical Trial Regulations Health Canada issues either a Letter of No Objection or a Not Satisfactory Letter, leaving no doubt as to whether a trial may start or not. Although, by regulation, clinical trials can start after 30 days unless the applicant has received a Not Satisfactory Letter, it is recommended that a Sponsor not start until the Letter of No Objection is received.

A pre-CTA meeting is encouraged and can be requested in writing at any time with Health Canada. It is especially recommended if the trial is for a New Chemical Entity or if the company/researcher has not filed a CTA before. Usually four dates are provided, with the earliest being 30 days in the future, although there is sufficient flexibility to allow for date adjustments. A pre-meeting package from the Sponsor is

expected at least 2 weeks before the meeting date. All information on the drug should be summarized and the areas in which the company/researcher would like guidance should be highlighted. The company/researcher is responsible for developing the minutes of the meeting and providing them to Health Canada for agreement within 10 days (15 days for Biologics) of the meeting. Once the minutes are finalized they are to be included in the CTA when it is filed. Good clinical practices are defined in the Canadian regulations as well as by ICH in the Good Clinical Practice Consolidated Guideline E6 and, for adverse event reporting in greater detail, ICH E2A, Clinical Safety Data Management Definitions and Standards for Expedited Reporting. Canadian regulations also require that clinical trial records be kept for a 25-year period (the equivalent of one generation).

Filing of Clinical Trial Applications

Prior to September 2001, when the Clinical Trial Regulations came into effect, about 800 INDs were filed in Canada each year, approximately 75% for drugs and 25% for biologics. Since then, clinical trials applications have had to be submitted for bioequivalence studies and for studies initiated and conducted by researchers. In 2004, approximately 2000 CTAs were filed annually, with about 900 additional bioequivalence applications and 300 other clinical trial applications.

Excluding the bioequivalence studies, 17% of studies were Phase I, 31% were Phase II and 43% were Phase III based on the 2004 Performance Reports for the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate (Table 1). The remainder was either unclassified or combined phase studies.

TABLE 1 CTAs Received by TPD/BGTD in 2004

Phase	**Phase Type**	**TPD No. of CTAs (%)**	**BGTD No. of CTAs (%)**	**Total No. of CTAs (%)**
I	Bioequivalence	937 (54%)	0 (0%)	937 (45%)
	Healthy Human – 7	82 (5%)	0 (0%)	82 (4%)
	Healthy Human – 30	4 (<1%)	2 (1%)	6 (<1%)
	Other	60 (4%)	31 (11%)	91 (5%)
I/II		11 (1%)	5 (2%)	16 (1%)
II		257 (15%)	70 (24%)	327 (16%)
II/III		9 (1%)	1 (<1%)	10 (1%)
III		315 (18%)	139 (48%)	454 (23%)
Unassigned		34 (2%)	42 (14%)	76 (4%)
Total		1709 (100%)	290 (100%)	1999 (100%)

Format and Content of a Clinical Trial Application

A CTA should be organized according to the Common Technical Document format with the categories of information listed in Table 2. Items with an asterisk are required to be submitted on paper and on CDR-ROM in either Word or Word Perfect format. Once the clinical trial application has been authorized, it is necessary to file information on the Clinical Trial Site for each site before the drug is shipped. A properly constituted research ethics board (REB) must grant approval of the research and subject informed consent document before the research can commence.

TABLE 2 Common Technical Document Categories

Module 1	
1.1	Table of Contents
1.2	Application Information
1.2.1	Application Form and Appendices
1.2.2	Information on Prior Related Submissions
1.2.3	Investigational Brochure*****
1.2.4	For drugs, a Preclinical and Clinical Evaluation Review Template***** (PCERT) and for biologics a Submission Rationale*****
1.2.5	Protocol*****
1.2.6	Informed Consent
1.2.7	Clinical Trial Site Information
1.2.8	Research Ethics Board Refusals
1.2.9	Foreign Refusals
1.2.10	Letters of Access
1.2.11	Other, e.g., minutes of Pre-CTA meeting
Module 2	
2.1	Table of Contents
2.2	Not applicable
2.3	Quality Overall Summary
Module 3	
3.1	Table of Contents
3.2	Any required data

For CTAs submitted by researchers (external to the pharmaceutical manufacturer) a variety of special options exist. The researcher can sign as the Chief Medical Officer and for the institution's Department Head to serve as the Chief Executive Officer of a company/sponsor. If the drug is marketed and the clinical trial is to study a use outside of the approved indications, it is sufficient to use a copy of the Product Monograph as the Investigator's Brochure. A copy of the label of the drug can serve as the Chemistry and Manufacturing information required.

Changes to Clinical Trials

After the CTA has been authorized, significant changes to either the protocol or the clinical trial supplies require prior authorization by Health Canada. Small changes can be made immediately with notification to Health Canada in 15 days. If it is necessary to change the protocol for patient safety then the change should be made and Health Canada can be informed within 15 days or as soon as possible. Aside from this very urgent situation, significant clinical changes (which are considered as amendments) are described in Table 3. Significant Chemistry and Manufacturing changes are also considered amendments (Table 4). Other changes are defined as minor changes and may be made immediately, with a notification to Health Canada within 15 days. Label requirements for clinical trial supplies are listed in Table 5. The labels must be bilingual regardless of where the trial is being conducted in Canada.

TABLE 3 Significant Clinical Changes

- The changes affect the selection, monitoring or dismissal of subjects in
- The changes affect the evaluation of the clinical efficacy
- The changes alter the risk to the health of the subject
- The changes affect the safety evaluation of the drug
- The changes extend the duration of the clinical trial

TABLE 4 Significant Chemistry or Manufacturing Changes

- Using a new ingredient to synthesize the drug substance.
- Identification of a new impurity.
- Removing or relaxing a test in the specifications.
- Adding a new ingredient to the drug product.
- Changing the method of sterilization.
- Removing or relaxing the drug product specification.

TABLE 5 Clinical Trial Supply Labels

- "Investigational Drug. To be used by Qualified Investigator only."
- Name, Number or identifying mark of the drug.
- Expiry date
- Storage conditions
- Lot No.
- Name and address of sponsor
- Protocol No.

Adverse drug reactions are defined as reactions that are both noxious and unintended. If an adverse drug experience may be related to the drug or is serious and unexpected, then an expedited report must be submitted within 15 days. If the adverse event is fatal or life-threatening it must be reported within 7 days of the adverse event coming to the attention of the sponsor, with additional follow-up within another 8 days in order to complete the case analysis. Safety considerations are linked to adverse reactions, but also include other issues relating to standards for general good clinical practice. Since the intent of the regulations is to place the safety of the subject of the clinical trial as paramount, if Health Canada considers that the safety or security of subjects in a trial are being compromised, the trial may be suspended or cancelled. In either case there is a period during which the decision may be reconsidered if adequate information is provided to Health Canada demonstrating that the safety and well-being of the subjects of research are not being compromised.

Investigational Brochures are required to be updated once a year and submitted to Health Canada, as an update to the CTA. Records must be kept for 25 years (Table 6), which is regarded as one generation. During that 25-year period, if there is a safety issue, these records must be made available to Health Canada within a 2-day timeframe. If there are other questions, the records must be made available within 7 days. All records should be kept in accordance with good clinical practices.

TABLE 6 Records to be kept for 25 years

- Enrollment records and dropouts
- Documentation on shipping, receipt, distribution, return and destruction of the drug.
- Qualified Investigator's Undertaking
- Copies of protocol, Informed Consent and amendments
- Research Ethics Board Attestation
- Records of self-audits.

Good Clinical Practices

The protocol and informed consent must be reviewed and approved by a Research Ethics Board (REB) before the enrollment can start. REBs are required to certify that they operate under Good Clinical Practice provisions. Canadian Clinical Trial regulations also specify the required membership of a REB. Sponsors of clinical trials are required to inform Health Canada of the REB they are using and provide contact information. Sponsors are also required to inform Health Canada of any refusals of the study by other REBs. Amendments to protocols must be approved by the REBs.

A Qualified Investigator must be a physician or a dentist licensed in the jurisdiction where the research is to take place. There can only be one qualified investigator per site and they are responsible for the medical decisions, regarding the patients as well as their safety and welfare. Companies must submit the name and contact information for the Qualified Investigator. The Qualified Investigator must complete the Qualified Investigator Undertaking. The Inspectorate has the authority, under Section 23 of the Food and Drugs Act, to inspect Sponsors (including clinical sites), Clinical Research Organizations, Site Management Organizations and Research Ethics Boards, which are involved in the approval of protocols of clinical trials, as well as any other third parties to whom tasks have been delegated. The average time for an inspection is about a week. The Inspectorate inspects up to 2% of clinical trial sites in Canada on a yearly basis, which represents up to 80 inspections per year. Annually the Inspectorate issues a summary report of the findings of inspections of clinical trials. The first and second reports are posted on the Inspectorate website (under Drugs and Good Clinical Practices headings).

The reports indicate that the records created in the conduct of clinical trials are the most common area of deficiency, followed by insufficient quality systems and procedures for the proper conduct of clinical trials. The process for obtaining informed consent from subjects and deviations from the approved protocol are also areas needing improvement. These reports include examples of deviations noted by Inspectors and are meant to communicate expectations for the proper conduct of clinical trials in Canada.

In conclusion, Canada's regulatory system for authorizing clinical trials is well defined and relatively straightforward. Reducing the approval time to 30 days has made Canada competitive with the US. Although in the US it is only necessary to wait 30 days for the first protocol, most companies wait 30 days for all protocols to determine if there is any immediate concern from the FDA. Since May 2004 all European member states are required to adapt or develop regulations for the approval of clinical trials, although there is some confusion as to how this will be implemented in individual countries. However, Canada has remained competitive with these countries.