



**Health Canada**  
**Health Products and Food Branch**

**OUR MANDATE:**

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

## **Health Products and Food Branch Inspectorate**

### **SUMMARY REPORT OF THE INSPECTIONS OF CLINICAL TRIALS CONDUCTED UNDER VOLUNTARY PHASE**

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## EXECUTIVE SUMMARY

This document provides the results and analysis of the findings of inspections conducted on clinical trials by the Health Products and Food Branch Inspectorate (Inspectorate) during the voluntary and confidence building phase. The objectives of conducting inspections of clinical trials, as announced by the Minister of Health in January 2000, are to increase the protection of subjects enrolled in clinical trials and to validate the data collected in the conduct of clinical trials.

Overall, 18 inspections were conducted, including 6 at Sponsor's sites and 12 at Qualified Investigator's sites. All inspections were initiated and completed within a 6 month time frame, starting in May 2002. A total of 108 observations were made during these inspections. These observations were classified according to the relevant sections of Division 5 of the *Food and Drug Regulations*, "*Drugs for clinical trials involving Human Subjects*" (Clinical trial Regulations).

The most prevalent deficiencies observed were related to records, with respect to accuracy, completeness and maintenance of source data, insufficient systems and procedures for processes, and informed consent forms for subjects enrolled in clinical trials.

Inspected Sponsors and Qualified Investigators were generally satisfied with the voluntary and phased-in approach used for implementation of the inspection program. The inspected stakeholders acquired a better understanding of the inspection process while Inspectors gained experience in the use of the new procedures and guidance documents developed to accomplish their inspections.

### 1. BACKGROUND

The Health Products and Food Branch Inspectorate (HPFBI) has the role of delivering a national compliance and enforcement program for regulated products under its mandate. The authority to deliver this compliance and enforcement program for these products is derived from the *Food and Drugs Act and its Regulations*. The Compliance and Enforcement Policy<sup>(1)</sup> provides the guiding principles for the fair, consistent and uniform application and enforcement of the Act and Regulations.

The new Division 5 of the *Food and Drug Regulations* "*Drugs for clinical trials involving human subjects*"<sup>(2)</sup> was promulgated pursuant to Section 30 of the *Food and Drugs Act*. The Act and this Division provides the Minister with the responsibility to apply the Regulations for the sale and importation of drugs used in clinical trials. It is within this context that clinical trials, and more specifically the drugs used in clinical trials, are regulated.

The Clinical Trial Regulations came into force on September 1<sup>st</sup>, 2001. A draft inspection strategy for clinical trials was published in August 2001. Comments were solicited from stakeholders and the final version of the strategy "*Inspection strategy for clinical trials*"<sup>(3)</sup> was published in January 2002.

The implementation of the inspection strategy for clinical trials consists of two phases. First, a one year confidence building and voluntary phase was initiated on January 1<sup>st</sup>, 2002. During this phase, inspections were performed upon request at sites of Sponsors and Qualified Investigators. The number of these inspections was limited and no formal ratings were issued to the sites inspected.

Inspections at sites were initiated in May 2002 and completed in November of the same year. A total of 18 inspections were performed, including 6 at Sponsors's sites, and 12 at Qualified Investigator's sites. The geographic distribution of inspected sites, as shown below, represented a fair distribution of clinical trials being conducted in Canada.

<b>Operational Centre</b>	<b>Number of sites inspected</b>
Atlantic	1
Quebec	4
Ontario	8
Manitoba and Saskatchewan	2
Western	3
Total:	18

Table 1: Geographic distribution of sites inspected

Qualified and trained Inspectors from every Operational Centre of the Inspectorate conducted these inspections using procedures and guidance documents developed for these inspections, including an inspection reporting system adapted to accomplish this new function. An analysis of the observations collected during this first phase is the objective of this report.

The final phase of implementation of the inspection strategy was implemented in January 2003. In this final phase, selection of sites for inspection is made by the Inspectorate, in consultation with Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD). The outcome of inspections will include a rating, expressing the level of compliance based on the observations made during the inspection. In cases of significant non-compliance, a suspension or a cancellation of an authorization could be considered by the TPD or the BGTD.

Investigations which are triggered whenever a complaint or a concern is received were initiated as of September 2001. Complaints were received from external stakeholders including Sponsors, Qualified Investigators, Subjects / Patients, Research Ethics Boards, Foreign Regulatory Agencies, or from internal sources within Health Canada.

## 2. DEFINITIONS

**Compliance:** The state of conformity of a regulated party or a product with a legislative or regulatory requirement or a recognized standard.

**Clinical trial:** Division 5 of the *Food and Drug Regulations* defines a Clinical Trial as, “an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.”

**Enforcement:** The range of actions that may be taken to induce, encourage, or compel observance of a legislative requirement.

**Food and Drugs Act:** A federal statute regulating the health and safety of food, drugs, cosmetics, and medical devices. The Minister of Health is responsible for the administration of the Act.

**Good clinical practices (GCP):** Division 5 defines Good Clinical Practices as, “generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons, and the good clinical practices referred to in section C.05.010.”

**Inspection:** “The act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority”. See ICH-E6 GCP (1.29)

**Inspector:** A person designated under section 22(1) of the Food and Drugs Act.

**Investigation:** Specific response to known or suspected non-compliance. Investigations typically are undertaken when there are reasonable grounds to suspect that non-compliance has occurred and that enforcement measures may be necessary (e.g. product quality complaints, reports from other regulatory authorities, reports of adverse reactions).

**Observation:** A deviation or deficiency noted by an Inspector during an inspection.

For additional definitions, please consult the *Food and Drugs Act* and Division 5 of the *Food and Drug Regulations*.

## 3. INSPECTION

Inspections were conducted in accordance to the Inspectorate’s Compliance and Enforcement Policy, which provides the Inspectorate with guiding principles for the fair, consistent, and

uniform application and enforcement of the *Food and Drugs Act* and its Regulations under the mandate of the Inspectorate. Inspections were conducted in accordance with the Inspection Strategy for Clinical Trials, which provides further guidance for the effective and uniform conduct of these inspections. Finally, the guidance document “Good Clinical Practice”<sup>(4)</sup> developed by the International Conference on Harmonization and adopted by Health Canada in 1997 was used for interpretation of the requirements of the Good Clinical Practices referred to in the Clinical Trial Regulations.

### **3.1 Objectives of an inspection**

The main objectives of a clinical trial inspection are:

1. To minimize the health hazard associated with the use of a drug used in a clinical trial,
2. To assess the level of compliance of a Sponsor or a Qualified Investigator with the Clinical Trial Regulations,
3. To request corrective actions from a Sponsor or Qualified Investigator whenever observations are made, and,
4. To take compliance and enforcement actions when deemed necessary.

### **3.2 Stages of an inspection**

Inspection of a Sponsor or Qualified Investigator involves six stages:

1. The preparation of the inspection: It is the initial stage in which Inspectors review all of the relevant files, protocols, investigator’s brochure, amendments, correspondence, from Health Canada files, as well as schedule the inspection and prepare an inspection plan that outlines the objectives, the areas to be inspected, and the duration of the inspection.
2. The conduct of the opening meeting: This meeting takes place on site and on the first day of the inspection. Its objective is to facilitate the process for the inspection and includes relaying the scope and focus of the inspection, the documents to be inspected, the staff to be interviewed, the facilities and equipment to be inspected and any other relevant activities.
3. The conduct of the inspection: This is the actual time for review of source documents, records, equipment and facilities. If deficiencies are observed and confirmed, this is brought to the attention of the responsible person at the site, with a request for a corrective action.
4. The writing of the report by the Inspector: Although notes are recorded throughout the inspection, a preset and standardized report format is used.

5. The conduct of the exit interview: At this stage, all observations made during the inspection are presented to the inspected stakeholder. Although these observations are discussed as the inspection proceeds, clarifications or corrections can be made at this last stage.

6. The issuance of the exit notice: This notice lists all observations noted with references to the relevant section / sub-section of the Regulations. Corrective actions to rectify deficiencies are expected from the inspected stakeholder, within a specific time frame. Should the inspected stakeholder object to observations listed, an appeal process can be initiated. This information is relayed as the exit notice is issued.

In cases when the inspection is conducted at a Qualified Investigator site, the Qualified Investigator receives a copy of the exit notice as well as the Sponsor of the clinical trial. As it is the Sponsor who requests and receives an authorization to conduct a clinical trial, the exit notice is always issued to the Sponsor of the clinical trial.

The Sponsor, and in the case of an inspection at a Qualified Investigator site, the Sponsor in collaboration with the Qualified Investigator, is requested to respond to all observations made in the exit notice with corrective actions for every observation. Within the requested time frame, the Inspector should receive responses from the Sponsor and assess the corrective actions. Should corrective actions be assessed as not satisfactory, additional actions are requested from the Sponsor, until they are assessed as satisfactory. Follow-up inspections on-site may be conducted if deemed necessary.

If a Sponsor does not respond to the exit notice with corrective actions by the stated deadline, the Inspector contacts the Sponsor to attempt to resolve the issue. If the Sponsor does not intend to respond, or there are no resolutions to the deficiencies reported in the exit notice, the file is reviewed internally and further action is considered.

### **3.3 Inspection frequency**

During the voluntary and confidence building phase, an arbitrary number of inspections were scheduled. A total of 18 inspections were conducted, out of 20 originally planned, which was considered to be sufficient to achieve the stated objective.

In the second and final phase, it is anticipated that up to 2% of all clinical trial sites will be scheduled for inspection on an annual basis. The total number of inspections will be adjusted by other operational requirements, namely the number of investigations required.

## **4. REGULATIONS**

All observations made during the voluntary inspection phase were referenced to sections / sub-sections of C.05.010 to C.05.012 of the Regulations (attached as Annex A). The Good Clinical

Practice Guideline, as developed by ICH was used for interpretation of C.05.010. Only observations referenced in the Regulations were reported.

## 5. ANALYSIS OF OBSERVATIONS

Following is a table of the sections and sub-sections of the Regulations listing the number of observations made against each of these sections / sub-sections. Observations made at both Sponsors and at Qualified Investigators sites are tabulated. Only sections or sub-sections linked to observations made during the inspections are listed.

Regulations Section / sub-section	Number of observations			Brief description of the section / sub-section
	Total	Sponsor sites	Qualified Investigator sites	
<b>C.05.010</b>	1	0	1	Clinical trial conducted according to Good Clinical Practice
<b>C.05.010(a)</b>	1	1	0	Protocol clearly described
<b>C.05.010(b)</b>	9	1	8	Clinical trial conducted in accordance with protocol and Regulations
<b>C.05.010(c)</b>	21	8	13	Quality systems and procedures in place for all aspects of the trial
<b>C.05.010(e)</b>	1	0	1	One Qualified Investigator per site
<b>C.05.010(g)</b>	9	3	6	Qualification, education and training of staff
<b>C.05.010(h)</b>	12	1	11	Informed consent obtained in accordance with applicable laws - subject fully informed
<b>C.05.010(j)</b>	9	5	4	Drug to be manufactured according to applicable Good Manufacturing Practices
<b>C.05.011</b>	1	0	1	Labelling requirements
<b>C.05.011(c)</b>	3	2	1	Labelling requirements - Expiration date
<b>C.05.012(1)</b>	23	2	21	Record, handle, and storage of all information
<b>C.05.012(2)</b>	11	1	10	Maintain complete and accurate records to establish that trial conducted in accordance with GCP
<b>C.05.012(4)</b>	7	6	1	Records to be maintained for 25 years
<b>Total</b>	108	30	78	

Table 2. Classification and distribution of observations made during voluntary inspection phase.



## **5.1 Inspections at Sponsor's sites**

### **5.1.1 Records - C.05.012(1), C.05.012(2) and C.05.012(4)**

The highest number of observations made at the 6 Sponsors inspected pertains to deficiencies with respect to records. Under these three subsections of the Regulations, all records must be complete, accurate and maintained for a period of 25 years. Access to source documents<sup>(5)</sup> is required for inspections. A total of 9 observations were reported under these subsections. An example of a deviation from C.05.012(2) is:

Example #1: *“There was no written assurance from (ABC Packaging) that drugs had been disposed of, in response to a written request from (Sponsor XYZ)”*

Although most Sponsors already had provisions to maintain records for the customary 15 years period, records must now be kept for 25 years to meet the regulatory requirement<sup>(6)</sup>.

### **5.1.2 Systems and procedures - C.05.010(c)**

The second highest number of observations relates to the use of standard operating procedures for all processes for the conduct of clinical trials. Subsection C.05.010(c) states that systems and procedures that assure the quality of every aspect of clinical trials are to be implemented. For example:

Example #2: *The Canadian local SOP No. (... ) “Reporting adverse events from Clinical Trials” version 1, effective date September 1997, was not updated according to actual procedures used. ...”*

Overall 8 observations were made under this sub-section. All important processes should be supported by detailed and approved standard operating procedures. Appropriate training for all staff involved should be an integral element to satisfy this requirement.

### **5.1.3 Quality of the drug - C.05.010(j) and C.05.011(c)**

Seven observations made at Sponsor's sites include insufficient evidence to confirm that the clinical trial drug was manufactured in accordance with the regulatory requirement of the applicable sections of Division 2 (Good Manufacturing Practices with some exceptions as specified in subsection C.05.010(j)) or the labelling did not meet the requirement of section C.05.011. In four cases, the expiration date was not indicated on labels.

### **5.1.4 Other observations**

Other less frequent observations made include delegation of tasks or responsibilities to staff without sufficient qualifications or training. Subsection C.05.010(g) specifies that

each individual involved in the conduct of a clinical trial is to be qualified by education, training and experience to perform their respective tasks. Supporting evidence should be on file to support meeting this requirement.

One observation pertained to deficiencies with respect to informed consent forms, namely with regards to the consistency of the format for the dating of forms. The sequence of the components of the date (day / month / year) was not prompted on the form, and created inconsistencies when subjects dated these forms.

## **5.2 Inspections at Qualified Investigator's sites**

### **5.2.1 Records - C.05.012(1), C.05.012(2) and C.05.012(4)**

The most prevalent deficiency among the 78 observations made during inspections at sites of Qualified Investigators were related to records, both with respect to records created in the conduct of clinical trials, and with respect to the maintenance of complete and accurate records. A total of 32 observations were made against subsections C.05.012(1), C.05.012(2) and C.05.012(4). This represents 41% of all observations made at Qualified Investigator sites. Examples of observations are:

Example #3, related to C.05.012(1): *“The adverse event reporting for subject 1201 at visit 4 was not consistent in that the Case Report Form (CRF) differed from the source document. On the CRF, the event was listed as a moderate headache but in the actual source document, the Qualified Investigator listed this event as a severe headache.”*

Example #4, related to C.05.012(1): *“The Study admission criteria form was not always being filled out completely and in accordance with the written procedure to ensure all critical information was recorded. (ie. inclusion / exclusion criteria and other yes / no questions)”*.

Example #5, related to C.05.012(2): *“The subject screening log for patient identified as (...) showed that the subject was consented on Mar, 4 2002, however source documents for this subject could not be located.”*

Example #6, related to C.05.012(2): *“Records pertaining to subject #0502, “...pattern diary” were missing for the period of September 17 to October 31, 2001.*

### **5.2.2 Systems and Procedures - C.05.010(c)**

The second most common deficiency observed at inspections conducted at Qualified Investigator sites were related to quality assurance, including insufficient systems and procedures to assure the quality of every aspect of the clinical trial. A total of 13 observations, representing 17% of all observations, pertained to this subsection. Two examples of this type of deficiency include:

Example #7: *“There was no written procedure available that outlined how informed consent was to be obtained from subjects considered for enrollment in clinical trials at the site.”*

Example #8: *“there was no system in place to ensure that the laboratory equipment and refrigerators, for blood samples, would be subject to routine maintenance calibration.”*

In practice, this regulatory requirement translates into implementing a sufficient number of standard operating procedures to ensure the consistent conduct of all aspects of a clinical trial. As relayed earlier, all processes for the conduct of a clinical trial should be supported by detailed and approved standard operating procedures. Evidence of satisfactory training of all staff involved is an integral element to meet this requirement.

### **5.2.3 Informed consent - C.05.010(h)**

Deficiencies related to informed consent forms were observed 11 times, representing 14% of all observations made at sites of Qualified Investigators. The Regulations state that written informed consent must be obtained before a person participates in a clinical trial and only after being informed of the risks and anticipated benefits to their health arising from participation in a trial, including all other aspects of the trial necessary for the person to make their decision. An example of such a deficiency observed is:

Example #9: *“The following concerns were noted with respect to the information sheet and informed consent form (version 1.2 - Jan. 19, 2001) that was signed by subjects and their legally acceptable representatives: - Information on the risks does not include mild fever and does not indicate the possibility of severe allergic reaction as indicated in section 10.2.2 of the protocol.”*

### **5.2.4 Protocol deviation - C.05.010(b)**

Protocol deviations accounted for 8 observations, representing 10% of all observations made at sites of Qualified Investigators. Once a protocol is authorized, any deviations can be initiated only to mitigate unanticipated health risks. Every deviation should be fully documented. An example of a deviation observed is:

Example #10: *“Subject 0724 was enrolled (visit #1) on August 17, 2001, without having completed all of the screening examinations specified by the protocol. The subject’s (.....) check was not performed on October 22, 2001 whereas per the protocol, this check should have been performed prior to subjects’ enrollment.”*

### **5.2.5 Qualifications and experience of staff - C.05.010(g)**

Staff responsible for the conduct of clinical trials are required to be qualified by education, training and experience. In 6 instances, deficiencies were noted in this regard and included inappropriate delegation of responsibilities, such as:

Example #11: *“There was no documented evidence that the Office Administrator to the Qualified Investigator was trained in any aspects of the study. However her name appeared on the Site Staff Signature Sheet with a Key Delegated Study Task: ...She also indicated that she assisted in performing ECG procedures on study subjects”.*

### **5.2.6 Quality of the drug - C.05.010(j)**

Overall, 4 observations were made against this subsection of the Regulations at sites of Qualified Investigators. These deficiencies were related to the lack of environmental control for the drug used in the clinical trial, and prior to distribution to subjects. An example is:

Example #12: *“The precautions that needed to be maintained during shipment of the drugs... to the qualified investigator site ... do not appear on the shipment documents... The label states that the products must be kept between 15 and 30 degrees C. and protected from humidity. The shipping of these drugs occurred during the months of November and February, ... when tablets and capsules must be protected from cold temperatures and humidity.”*

## **6. OTHER PERTINENT INFORMATION**

### **6.1 Time required for the conduct of inspections**

On average, a total of 66 hours (approximately 9 days) were required by each Inspector per inspection. This total time includes preparation, travel time, on-site inspection, report writing and follow-up. Actual time on site for any inspection never exceeded 5 days. Of the 18 inspections conducted, 8 inspections were conducted by an Inspector alone, 8 inspections were conducted with a team of two Inspectors, and 2 were conducted with a team of three Inspectors. Overall, 11 Inspectors were involved in these inspections.

### **6.2 Applicable Regulations**

Division 5 of the *Food and Drug Regulations* came into force on September 1<sup>st</sup>, 2001. Clinical trials authorized prior to September 1<sup>st</sup>, 2001 were subjected to Division 8 of the same Regulations. These trials were therefore not subjected to Division 5 as they were authorized prior to the coming into force of Division 5.

As many clinical trials extend over many years, it was expected that a significant proportion of clinical trials inspected under this voluntary phase were not subjected to the new and more explicit requirements of Division 5. Nevertheless, even though the present regulatory requirements cannot be enforced retroactively, all Sponsors and Qualified Investigators agreed to be inspected in accordance with the requirements of the new Division 5.

Of the 18 inspections conducted, 10 inspections were of clinical trials authorized under the former Division 8, and 8 inspections were authorized under Division 5.

### **6.3 Type of drugs used in clinical trial**

Of the 18 inspections conducted, 5 were with biological drugs and the remaining 13 were with pharmaceutical drugs. This represents a higher proportion of biological versus pharmaceutical clinical trial authorizations issued by the respective Directorate.

### **6.4 The stage of clinical trial during inspection**

Clinical trials inspected were either on-going, when subjects were currently enrolled in a trial, or completed. Overall, 10 out of the 18 inspections were on-going.

The high proportion of inspections of clinical trials which were on-going versus completed reflects the important focus of the inspection strategy, whereby the Inspectorate is planning to inspect clinical trials when subjects are enrolled. This strategy should allow a faster response time when health related concerns are observed during inspections.

### **6.5 The phase of the clinical trial**

All 18 inspections were conducted on clinical trials which were either Phase I (2 trials), II (6 trials) or III (10 trials), as identified by the respective Sponsors. Although Phase IV clinical trials can be subjected to inspection, none were inspected during this voluntary phase.

## **7. CONCLUSIONS**

1. The highest number of observations pertains to deficient records, with respect to the accuracy of records created in the conduct of clinical trials, the maintenance of complete records to establish that clinical trials are conducted according to the Regulations and the Good Clinical Practices. Overall, 38% of all observations made at both Sponsors and Qualified Investigators sites were related to this requirement.
2. The second highest number of observations pertain to deficiencies with respect to having and using adequate systems and procedures to assure that the quality of every aspect of the conduct of clinical trials are implemented. Standard operating procedures must be developed and implemented for all processes required for the conduct of clinical trials. Appropriate development and approval of procedures and training of staff on these procedures are integral elements to meet this requirement.
3. The third highest number of observations pertains to deficiencies related to informed consent. The informed consent forms should include every component listed in section 4.8 of the

Guideline on Good Clinical Practice. A total of 12 observations were made related to this requirement.

## 8. REFERENCES

1. Compliance and Enforcement Policy. No. POL-0001, Health Products and Food Branch Inspectorate.  
[http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/compliance\\_enf\\_policy\\_e.pdf](http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/compliance_enf_policy_e.pdf)
2. *Food and Drugs Act and Regulations*. Clinical trial Regulations.  
[http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/food\\_drug\\_reg\\_amend\\_1024\\_gcp\\_e.pdf](http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/food_drug_reg_amend_1024_gcp_e.pdf)
3. Health Products and Food Branch Inspectorate. Policy. POL-0030 “Inspection Strategy for Clinical Trials, January 15, 2002.  
[http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/insp\\_strat\\_clin\\_tria\\_e.pdf](http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/insp_strat_clin_tria_e.pdf)
4. Good Clinical Practice: Consolidated Guideline, International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use - Topic E6, commonly referred to as ICH-GCP E6.  
[http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/goodclin\\_e.pdf](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/goodclin_e.pdf)
5. Source documents: “Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)”. See ICH-GCP E6, 1.52 Source documents.
6. A Guidance document will be issued to clarify the requirements for compliance with the section on Records of the Regulations.

## Annex A

### Sponsor's Obligations

#### Good Clinical Practices

**C.05.010.** Every sponsor shall ensure that a clinical trial is conducted in accordance with good clinical practices and, without limiting the generality of the foregoing, shall ensure that

- (a) the clinical trial is scientifically sound and clearly described in a protocol;
- (b) the clinical trial is conducted, and the drug is used, in accordance with the protocol and this Division;
- (c) systems and procedures that assure the quality of every aspect of the clinical trial are implemented;
- (d) for each clinical trial site, the approval of a research ethics board is obtained before the clinical trial begins at the site;
- (e) at each clinical trial site, there is no more than one qualified investigator;
- (f) at each clinical trial site, medical care and medical decisions, in respect of the clinical trial, are under the supervision of the qualified investigator;
- (g) each individual involved in the conduct of the clinical trial is qualified by education, training and experience to perform his or her respective tasks;
- (h) written informed consent, given in accordance with the applicable laws governing consent, is obtained from every person before that person participates in the clinical trial but only after that person has been informed of
  - (i) the risks and anticipated benefits to his or her health arising from participation in the clinical trial, and
  - (ii) all other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial;
- (i) the requirements respecting information and records set out in section C.05.012 are met; and
- (j) the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 except sections C.02.019, C.02.025 and C.02.026.

#### Labelling

**C.05.011.** Despite any other provision of these Regulations respecting labelling, the sponsor shall ensure that the drug bears a label that sets out the following information in both official languages:

- (a) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator;
- (b) the name, number or identifying mark of the drug;

- (c) the expiration date of the drug;
- (d) the recommended storage conditions for the drug;
- (e) the lot number of the drug;
- (f) the name and address of the sponsor;
- (g) the protocol code or identification; and
- (h) if the drug is a radio pharmaceutical as defined in section C.03.201, the information required by subparagraph C.03.202(1)(b)(vi).

## **Records**

**C.05.012.** (1) The sponsor shall record, handle and store all information in respect of a clinical trial in a way that allows its complete and accurate reporting as well as its interpretation and verification.

(2) The sponsor shall maintain complete and accurate records to establish that the clinical trial is conducted in accordance with good clinical practices and these Regulations.

(3) The sponsor shall maintain complete and accurate records in respect of the use of a drug in a clinical trial, including

- (a) a copy of all versions of the investigator's brochure for the drug;
- (b) records respecting each change made to the investigator's brochure, 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;
- (d) records respecting the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the sale of the drug may endanger the health of the clinical trial subjects or other persons;
- (e) records respecting the shipment, receipt, disposition, return and destruction of the drug;
- (f) for each clinical trial site, an undertaking from the qualified investigator that is signed and dated by the qualified investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that

- (i) the qualified investigator will conduct the clinical trial in accordance with good clinical practices, and

- (ii) the qualified investigator will immediately, on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial subjects or other persons;



- (g) for each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the research ethics board for that clinical trial site; and
- (h) for each clinical trial site, an attestation, signed and dated by the research ethics board for that clinical trial site, stating that it has reviewed and approved the protocol and informed consent form and that the board carries out its functions in a manner consistent with good clinical practices.
- (4) The sponsor shall maintain all records referred to in this Division for a period of 25 years.

Source: *Food and Drug Regulations*, Division 5, “Drugs for clinical trials involving Human Subjects” (Clinical trial Regulations).

[http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/food\\_drug\\_reg\\_amend\\_1024\\_gcp\\_e.pdf](http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/food_drug_reg_amend_1024_gcp_e.pdf)