Health Canada Santé Canada

Our Mandate:
To manage and deliver a national compliance and enforcement program for blood and donor semen; cells, tissues and organs; drugs (human and veterinary); medical devices and natural health products, collaborating with and across, all regions.

Health Products and Food Branch Inspectorate

Summary Report of Inspections of Clinical Trials Conducted from April 2004 to March 2011

Date issued:
March 28, 2012

Disclaimer:
This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

Canada

Table of Contents

Executive Summary

This document provides the results of clinical trial inspections conducted by Health Canada's Inspectorate Program (Inspectorate) between April 1, 2004 and March 31, 2011. This is the third summary report of inspections of clinical trials issued since the inspection program was launched in 2002.

Inspections of clinical trials are conducted to strengthen the protection of the rights and safety of clinical trial participants and validate the integrity of the data generated through the conduct of clinical trials. This is done by assessing that the generally accepted principles of Good Clinical Practices are met, and by verifying compliance with Division 5 of Part C of the *Food and Drug Regulations*. The objective of sharing inspection results, including observations noted during inspections, in an anonymous manner in this report is to increase awareness of Canadian regulatory requirements within the clinical research community, while maintaining the confidentiality and privacy of those involved in the inspections.

During the seven year period covered in this report, a total of 329 inspections were conducted by the Inspectorate, of which 14 were at the sites of contract research organizations (CROs), 27 were at the sites of sponsors, including qualified investigator-sponsored study sites, and 288 at the sites of qualified investigators (QIs) conducting clinical trials under either commercial or non-commercial sponsorship. In focusing on the premises of QIs, the Inspectorate aims to assess sites where clinical trials are conducted. During the inspection of a clinical trial site, other facilities performing trial-related activities, such as the sponsor's facilities and testing laboratories, may also be inspected. In addition, 31 research ethics boards (REBs) were assessed from 2004 to 2008.

Of these inspections, 92% were assigned an overall compliant ("C") rating while the remaining 8% were assigned a non-compliant ("NC") rating. REB assessments were not issued a compliance rating. Overall, the inspectors made 3148 observations, including findings at REBs, each of these representing a non-compliance with Division 5 of the *Food and Drug Regulations*. Of these observations, 54% were considered minor, 39% major and 1% were considered critical. The remaining 6% were findings noted during REB assessments. The number and type of observations noted are taken into account when assigning the inspection a compliant ("C") or a non-compliant ("NC") rating. Corrective actions are required for each observation whether the overall inspection rating is "C" or "NC." In cases where an "NC" rating was assigned, the Inspectorate took the appropriate enforcement actions.

In general, there is a trend in the types of observations noted during the inspections. The main types of observations noted were related to:

- quality systems and procedures,
- records,
- deviations from clinical trial protocols,
- qualifications, education and training of personnel,
- process for informing and obtaining informed consent from subjects.

This third summary report on inspection findings endeavours to inform stakeholders and the public about clinical trial inspections in Canada as Health Canada continuously aims to promote greater regulatory compliance, improve transparency, and provide a better understanding of regulatory oversight of Canadian clinical trials.

1.0 Background

The Inspectorate Program 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*, which integrate good clinical practices (GCP) as described by the International Conference on Harmonization, Guidance document E6 (Tripartite Agreement)[1], adopted by Health Canada. The Compliance and Enforcement Policy (POL-0001)[2] provides the guiding principles for the fair, consistent and uniform application and enforcement of the *Act* and *Regulations*.

Division 5 of the *Regulations* "Drugs for clinical trials involving human subjects"[3] was promulgated pursuant to Section 30 of the *Food and Drugs Act*. These *Regulations* provide the Minister with the authority to regulate 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. Division 5 of the *Regulations* came into force on September 1st, 2001.

An inspection strategy for clinical trials[4] was published and adopted in January 2002. The primary focus of the strategy is the protection of human subjects enrolled in clinical trials. A secondary objective is the verification of the integrity of the data generated through the conduct of clinical trials and subsequently submitted for evaluation for the next step in the drug's development and eventually for marketing approval. The Inspectorate is responsible for the selection of clinical trial sites for inspection in collaboration with the Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD). As outlined in the *Inspection Strategy*, selection is guided by risk-based criteria and applies to all on-going or closed clinical trials in Canada including those belonging to Phases I, II, III and IV.

In addition to conducting clinical trial inspections, the Inspectorate also conducts compliance verifications (CVs) and investigations on an as-needed basis. These are conducted in response to complaints received from various sources such as sponsors, QIs, study participants, research ethics boards (REBs), foreign regulatory authorities and internal sources at Health Canada. Given that CVs and investigations fall outside the scope of this document, the results from these activities are not included in this report.

In accordance with the guidance document entitled *Classification of Observations Made in the Conduct of Inspections of Clinical Trials* (GUI-0043)[5], observations cited during inspections are classified as critical (Risk 1), major (Risk 2) and minor (Risk 3) observations based on the severity of the deviation from the *Regulations*. The number and type of observations noted are taken into account when assigning the inspection a compliant ("C") or a non-compliant ("NC") rating. In cases where an "NC" rating was assigned, the Inspectorate took actions including requiring the immediate implementation of corrective actions from the regulated party or recommending to the Health Canada Directorate which issued the authorization, TPD or BGTD, the suspension or cancellation of the authorization to conduct the inspected clinical trial.

2.0 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: Division 5 of the *Food and Drug Regulations* 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 organizations' (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority". See ICH-E6 Good Clinical Practices (1.29).

Inspector: A person designated under section 22 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.

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-Good Clinical Practices E6, (1.52).

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

3.0 Inspections

The main objectives of a clinical trial inspection are as follows:

- to minimize the risks associated with the use of a drug used in a clinical trial,
- to verify compliance to Division 5 of the *Food and Drug Regulations*, including good clinical practices,
- to validate the integrity of the data generated,
- to request corrective actions from the inspected party whenever observations are made, and,
- to take compliance and enforcement actions when deemed necessary.

Inspections are usually conducted over five days, at the premises of the regulated parties. Inspections can be announced or unannounced and can involve open or closed clinical trials. A pre-inspection package is provided to inspected parties to assist in their preparation for an inspection by the Inspectorate. The selection of clinical trial sites for inspection is based on a variety of criteria, but ultimately, the Inspectorate takes risk factors into consideration when selecting a site for inspection. The status of a study (open or closed to enrolment), the number of subjects enrolled, the therapeutic area and study population, the level of clinical trial activity at a centre, and the compliance and inspection history of a site are some of the factors which may be taken into account.

From April 2004 to March 2011, a total of 329 inspections were conducted by the Inspectorate, of which 14 were at the sites of CROs, 27 at the sites of sponsors, including qualified investigator-sponsored study sites, and 288 at the sites of QIs conducting clinical trials under either commercial or non-commercial sponsorship. Inspectors across Canada are located in regional offices in Halifax, NS, Longueuil, QC, Toronto, ON, Winnipeg, MB, Edmonton, AB and Burnaby, BC[1]. Resources are allocated regionally in accordance with indicators of clinical trial activity (namely the population distribution), and the numbers of inspections conducted in each region are reflective of this. Please refer to Table 1 for a regional distribution of inspections across Canada and to Figure 1 for the total of inspections conducted yearly. Inspections include trials involving pharmaceutical drugs, biological drugs, radiopharmaceuticals, as well as narcotics and controlled substances.

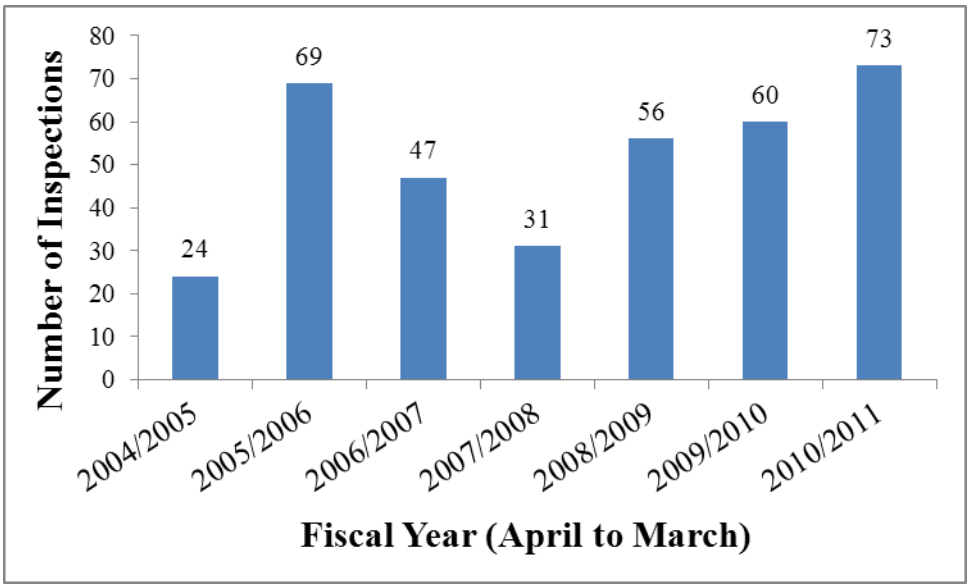
In addition to the aforementioned inspections, 31 REBs were assessed by the Inspectorate from 2004 to 2008, with no compliance ratings issued. While REBs are not currently in Health Canada's clinical trial inspection focus, they are indirectly assessed through inspections of other regulated parties.

Table 1 Distribution of good clinical practices (GCP) inspections and research ethics board (REB) assessments in Canada (April 2004 to March 2011)

Operational Centres	Number of Inspections	Percentage of Inspection Total
Atlantic (Nova Scotia, New Brunswick, Newfoundland/Labrador and Prince Edward Island)	21	**6%**
Quebec	81	**23%**
Ontario and Nunavut	127	**35%**
Manitoba and Saskatchewan	33	**9%**
Western (British Columbia, Alberta, Northwest Territories, Yukon)	98	**27%**
Total	**360**	**100%**

[1] A sixth centre was created in April 2011 when the Western Operational Centre was separated into two centres; Alberta and British Columbia. Operational Centres have since then been referred to as "Regions".

Figure 1 Number of GCP inspections conducted annually from fiscal year 2004/2005 to 2010/2011



The annual number of inspections conducted is based on the resources available to the program, in accordance with the organization's priorities for that year. It is also determined by other factors (for example, complexity of the sites and/or trials inspected), and could potentially be impacted by other activities, such as compliance verifications, in a given year.

Of the 329 inspections, 303 (92%) were assigned a compliant ("C") rating while 26 (8%) inspections at 11 sites were assigned a non-compliant ("NC") rating. In some cases, sites were inspected with respect to more than one protocol; hence an "NC" rating was issued for each study. Some establishments also received a subsequent "NC" rating during an inspection conducted in follow up to a previously issued "NC" rating. In each of these cases, the Inspectorate issued an Exit Notice with an accompanying notice of intent to suspend the study's authorization, thereby requiring the sites to implement timely corrective actions to achieve compliance with the *Regulations*, protect the rights and safety of the trial subjects, and to maintain the validity of the clinical trial data. Corrective actions are required for each observation whether the overall inspection rating is "C" or "NC." No ratings were issued in regards to REB assessments.

4.0 Analysis of Observations

During the 329 inspections and 31 REB assessments, 3148 observations were noted. Of these, 82% of the observations were noted at QI sites, 7% at sponsor sites, 6% during REB assessments, and the remaining 5% of observations were noted at CRO sites. The percentages are proportional to the number of inspections or assessments conducted at each type of organization. The highest total number of observations for a particular inspection was 29, and the lowest was 1, with an average of 9 observations per inspection.

Observations made at the sites of sponsors, QIs and CROs and during REBs assessments were compiled and classified in Table 2 according to the section of the *Regulations* to which they corresponded.

Table 2 Distribution, by Division 5 section, of the observations cited (April 1, 2004 to March 31, 2011) for all regulated parties, including during REB assessments

Section of the *Regulations*	Description	Percentage of Observations
C.05.010	Good Clinical Practices	64.5%
C.05.012	Records	25.4%
C.05.001	Interpretation	6.3%
C.05.011	Labelling	2.0%
C.05.008	Amendment	0.5%
C.05.014	Serious Unexpected Adverse Drug Reaction Reporting	0.4%
C.05.006	Authorization	0.4%
C.05.007	Notification	0.3%
C.05.005	Application for Authorization	0.1%
C.05.003	Prohibition	0.1%

Table 2 illustrates that the majority of observations were cited against sections C.05.010 (Good Clinical Practices) and C.05.012 (Records). Almost all (97%) of the REB findings were cited against C.05.001 (Interpretation).

Table 3 Distribution, by sub-section of C.05.010, of the observations cited (April 1, 2004 to March 31, 2011) for all regulated parties, including during REB assessments

Sub-section of C.05.010	Description	Percentage of Observations
C.05.010*(c)*	Systems & Procedures	26.7%
C.05.010*(b)*	Protocol Deviations	9.7%
C.05.010*(g)*	Qualification	8.9%
C.05.010*(h)*	Informed Consent	6.0%
C.05.010*(j)*	GMP	5.4%
C.05.010*(f)*	Medical Decision	4.2%
C.05.010*(d)*	REB Approval	0.9%
C.05.010*(a)*	Protocol	0.3%
C.05.010*(e)*	Number of QIs per clinical trial site	0.2%
C.05.010*(i)*	Records	0.2%

* 2% of observations were not cited against a specific sub-section of C.05.010.

Table 3 illustrates that observations cited against a sub-section of C.05.010 for regulated parties pertained most frequently to deficiencies related to quality systems and procedures used in the conduct of clinical trials.

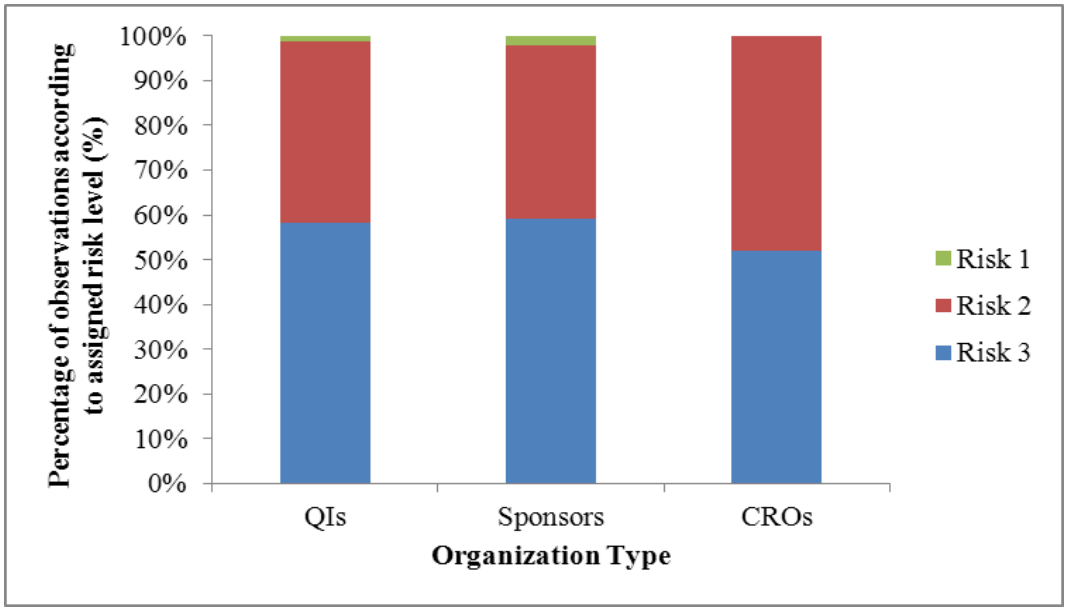
Observations relating to the conduct of the clinical trial in accordance with the study protocol (C.05.010*(b)*) were common at the sites of sponsors and QIs while observations regarding medical care and decisions made under the supervision of a QI (C.05.010*(f)*) were more common at CROs.

Other types of observations frequently noted for sponsors, QIs, and CROs related to the informed consent being obtained in accordance with applicable laws, and to personnel qualifications, education and training.

Observations were rated according to the assessed level of risk. Of the 3148 observations, 54% were considered minor, 39% major and 1% were considered critical. The remaining 6% were findings noted during REB assessments.

The percentages of observations assigned each level of risk at the sites of sponsors, QIs and CROs can be found in Figure 2.

Figure 2 Classification of observations based on their assigned level of risk*



*REB findings are not included in Figure 2.

Thirty-five of the observations noted with respect to the 329 inspections were classified as Risk 1 (critical) observations, five of which were made at the sites of sponsors and thirty at the sites of QIs. All the inspections for which critical observations were recorded were assigned an "NC" rating. In addition, certain inspections where a significant number of major observations were noted also were assigned an "NC" rating.

Examples and explanations of the five most frequently cited Division 5 sections in observations during inspections at the sites of sponsors, QIs and CROs and during REB assessments are provided in Section 5 of this report.

5.0 Examples of Observations

This section provides examples of the observations made by Health Canada's inspectors at the sites of sponsors, QIs, CROs and REBs. As mentioned above, corrective actions are required for each observation whether the overall inspection rating is "C" or "NC."

5.1 Protocol – C.05.010(b)

Section C.05.010*(b)* of *the Regulations* states that a clinical trial must be conducted in accordance with the protocol and the *Regulations*. Of the overall observations, 9.7% pertained to protocol deviations.

Examples of deficiencies cited against this sub-section include:

Example 1 – The sponsor notified the QI on (date) that additional tests not included in the current version of the protocol were required to ensure the subjects' safety and that implementation was to be immediate. This included informing enrolled subjects, obtaining their verbal consent, registering that information in the source file and informing the REB. All the steps were completed but with an unexplainable delay. The first monitoring visit took place three months after sending the notification letter and there was no sufficient follow-up to ensure that the changes were put in place.

Example 2 – In the case of Subject XX, the blood pressure was measured 3 times on each arm as required per the protocol. However, the third reading on the right arm was taken 15 minutes after the second reading, which is a deviation from the clinical trial protocol that specifies a 5 minute interval between measurements.

Example 3 – Between (date) and (date), Subject XX had 14 instances of drug overdoses recorded in the subject's electronic diary that were not all reported by the site within 30 days, as required by the protocol.

5.2 Systems and Procedures – C.05.010(c)

According to subsection C.05.010*(c)*, systems and procedures that ensure the quality of every aspect of the clinical trial should be implemented for every clinical trial. These should also be reviewed and approved by qualified study personnel.

A lack of procedures and/or implementation of existing procedures represented 26.7% of all observations cited.

Examples of deficiencies cited against this sub-section include:

Example 1 – There was no procedure for on-site monitoring of the study by the sponsor, and no monitoring plan for the study to describe the extent and nature of monitoring to be conducted, based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. As a result, there was no review of the accuracy and completeness of the case report form (CRF) entries, source documents and other trial-related records against each other. Also, there was no documented evidence that the review and follow-up for issues identified during monitoring visits were adequately addressed by the site.

Example 2 – The randomization procedures were not outlined in any of the study documents, namely, the study protocol and/or the study manual. Furthermore, the sponsor had not provided sites with a process for the unblinding of subjects in the event of an after-hours emergency. At site XX, blinding information is maintained by the pharmacy, which operates during weekday business hours. There is no provision for breaking the blind outside of normal pharmacy operating hours.

Example 3 – There were no standardized procedures in place for obtaining informed consent, for handling biological samples, for receiving and accounting for investigational products, for recording temperature, for handling emergencies and for archiving research files.

Example 4 – Systems and procedures were lacking for scheduling all staff involved in the conduct of the clinical trial and for training key personnel on the study specific protocol.

Example 5 – As a result of overlooking the positive test results on (date) and (date) for Subject XX, an investigation report was initiated on (date). Five preventative actions were recommended with completion dates as late as (date). As there was no system in place to ensure that Corrective and Preventative Actions (CAPAs) were implemented by their assigned due date; three of the five identified CAPAs had not been completed.

5.3 Qualifications, Education and Training of Personnel – C.05.010(g)

According to subsection C.05.010*(g),* each individual involved in the conduct of the clinical trial must be qualified by education, training and experience to perform his/her respective tasks. Deficiencies relating to inadequate qualifications, education and training of personnel accounted for 8.9% of the all observations cited.

Examples of deficiencies cited against this sub-section include:

Example 1 – There was no documented evidence that the personnel, including study coordinators, at all sites involved in the conduct of the study were trained on the protocol, good clinical practices and regulatory requirements.

Example 2 – There was no explicit documentation to indicate that all sub-investigators and nurses to whom significant trial-related duties have been delegated had been informed of all protocol-specific requirements.

Example 3 – No curriculum vitae were available for three co-investigators.

Example 4 – There was no documented evidence that the office administrator to the qualified investigator was trained in any aspects of the study. However, the office administrator's name appeared on the delegation log indicating that he/she was assigned the task of randomized medication assignment. His/her signature appeared on the relevant worksheet, which was co-signed by the qualified investigator. The office administrator also indicated that he/she assisted in performing ECG procedures on study subjects.

5.4 Informed Consent – C.05.010(h)

Section C.05.010*(h)* requires that written informed consent must be obtained from every person that participates in a clinical trial but only after the person has been informed of all aspects of the clinical trial that are necessary for that person to make a decision to participate in the trial including the risks and anticipated benefits from participation in the clinical trial. Deficiencies related to the informed consent process represented 6.0% of all observations.

Examples of deficiencies cited against this sub-section include:

Example 1 – The informed consent form (ICF) did not include the following key elements:

- guardian's responsibilities for the duration of the clinical trial
- anticipated circumstances under which a subject's participation may be terminated, such as failure to keep to scheduled visits
- the size of the trial

- statement that the guardian had read and understood pages 1 to 3 of the informed consent form.

Example 2 – The ICF version XX did not state that three of the drugs used in the clinical trial would not be provided to the subject at no cost.

Example 3 – The amended ICF version 2 was signed by Subject XX on (date); however, the subject had been available to sign at an earlier visit when the revised ICF had already been approved and implemented.

Example 4 – A francophone participant, Subject XX, signed the French version of the ICF which had not yet been approved by the REB (English version had been approved).

Example 5 – The clinical trial screening procedures that include taking subjects' height and weight for the purposes of entering into the study was performed prior to written consent being given by subjects.

5.5 Records – C.05.012

According to section C.05.012, sponsors shall record, handle, maintain and store all information that pertains to their activities in a way that allows complete and accurate retrieval of records, reporting, interpretation and verification, and to establish that the clinical trial is conducted in accordance with GCP and the *Regulations*. The records referred to in section C.05.012 (3) must be kept for 25 years. Observations relating to the accuracy and adequate maintenance of records constituted 25.4% of all observations.

Examples of deficiencies cited against this section include:

Example 1 – A qualified investigator undertaking form for each clinical trial site, signed and dated by each qualified investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, was not on file with the sponsor at the time of the inspection.

Example 2 – Computer validation was not achieved for the Interactive Voice Response System (IVRS) and for several electronic forms developed by the study personnel. When data is captured using electronic tools, necessary controls and validation steps to prevent errors are required.

Example 3 – There was no assurance that electronic records would be maintained for the required period of 25 years. Although a procedure on record retention was in place, electronic records were not addressed. Further hospital charts/records considered to be source documents were not addressed for archiving purposes of 25 years.

Example 4 – Research subject files were incomplete. Documentation of such information as the date of initial subject contact, instructions regarding dosing, confirmation of inclusion/exclusion criteria and/or enrolment, and progress reports after each visit or phone call was not consistently reported in writing in the subject files.

Example 5 – Records respecting the shipment, receipt, disposition, return and destruction of the drug were not adequately completed. In one instance, two boxes were acknowledged while they were actually missing in a shipment from the distributor. In another situation, a bottle was returned to the sponsor but the kit number did not appear on the shipping log.

Example 6 – Records could be changed in the subject screening log used to document entries made by recruiters for the study specific telephone screening questionnaire. There was no audit trail available for changes made to the information entered. In addition, the electronic copy of these records is the only one retained by the site.

5.6 Other Observations

Amendment – C.05.008

Section C.05.008 states the conditions under which a sponsor may sell or import a drug for the purposes of the clinical trial in accordance with an amended authorization.

Example 1 – Authorization of an amendment was not obtained prior to importation and sale of study drug. Specifically, Amendment X was approved by REB on (date) and implemented, while Health Canada's No Objection Letter (NOL) was issued at a later date.

Example 2 – Protocol version X dated (date) was submitted to Health Canada for approval four months later. There was no documented rationale to explain this lag in submission time.

Medical Care and Decisions – C.05.010*(f)*

Section C.05.010*(f)* requires that at each clinical trial site, medical care and medical decisions, in respect of the clinical trial, are under the supervision of the qualified investigator.

Example 1 – For Subject XX, there was no evidence on file to prove that the QI has reviewed and signed off on the results of the urine pregnancy test. Similarly, there was no evidence on file to prove that the QI has reviewed and signed off on the vital signs during two of the patient visits.

Example 2 – Adverse events are recorded on a paper CRF completed by a study coordinator, including an assessment of the causality of the events. There was no documentation to demonstrate that the assessment of causality was performed by the QI or sub-investigator.

Example 3 – Some screening labs and electrocardiograms were signed and dated by the QI subsequent to the enrolment of some of the subjects.

Labeling – C.05.011

Section C.05.011 states the information that is required to be included on the label of a drug used in a clinical trial.

Example 1 – Drug products were dispensed to subjects past the labeled expiry date. Subjects were verbally assured that the expiry date was extended. The drug product and placebo should have been re-labeled with the extended expiry date.

Example 2 – The labels on certain vials were not in both official languages.

5.7 Research Ethics Board (REB) Assessments

REB assessments were not issued an overall rating of either compliant or non-compliant.

The following list provides examples of the findings identified during the assessment of REBs:

- Voting members of the REB were not independent of the QI and/or sponsor of the clinical trial.
- Clinical trials were approved without a quorum of members with the required representation.
- Amendments to previously approved protocols that possibly increased health risks to subjects were documented as needing expedited review only.
- REB membership did not include all the representative expertise set out in the *Regulations.*
- REB did not have written procedures in accordance with ICH E6: GCP.
- REB did not maintain adequate written minutes of meetings.
- REB did not have evidence that it considered the qualifications of QIs before approving trials.
- REB did not have written procedures for the conduct of periodic reviews of continuing clinical trials.
- REB procedures did not require that records be retained for the requisite 3 year period, as per section 3.4 of ICH E6: GCP, and/or the sponsors did not ensure that records were retained for 25 years as stated in C.05.012(4), in regards to those records outlined in C.05.012(3)*(h)*.

6.0 Conclusion

Overall, of the 329 inspections conducted by the Inspectorate, 92% were assigned a compliant rating while a non-compliant rating was assigned to the remaining 8%. Health Canada issued Exit Notices with an accompanying notice of intent to suspend the authorization for the clinical trial to the non-compliant parties thereby requiring corrective actions to be implemented immediately.

The two most common deficiencies noted during inspections of clinical trials since 2004 were regarding the inadequate documentation or implementation of systems and procedures that ensure the quality of every aspect of the clinical trial, and the lack of appropriate record retention. These deficiencies represented respectively 26.7% and 25.4% of all observations cited. Other significant deviations related to informed consent not being obtained in accordance with regulatory requirements, and to inadequate, or inadequately documented, personnel qualifications, education and/or training.

This third summary report on inspection findings endeavours to inform stakeholders and the public about clinical trial inspections in Canada. By providing examples of common deficiencies cited during inspections, Health Canada aims to promote greater regulatory compliance, improve transparency, and provide a better understanding of regulatory oversight of Canadian clinical trials.

Since the safe conduct of clinical trials is a shared responsibility among sponsors (commercial or non-commercial), qualified investigators, REBs, research institutions, human research subjects and Health Canada, the understanding, by all involved, of their respective roles and responsibilities is essential to ensure that the best outcomes are achieved. The Inspectorate Program continues to develop and implement compliance promotion initiatives to gather stakeholders' feedback which is subsequently used to shape future guidance and policies. A generic e-mail account is available for stakeholders' enquiries at gcp_bpc@hc-sc.gc.ca.

7.0 References

1. Good Clinical Practice: Consolidated Guideline, International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use - Topic E6 (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php)

2. Compliance and Enforcement Policy (POL-0001), Health Products and Food Branch Inspectorate. (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php)

3. Division 5 of Part C of the *Food and Drug Regulations* "Drugs for clinical trials involving human subjects" (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/reg/1024_tc-tm-eng.php)

4. Inspection Strategy for Clinical Trials (POL-0030), Health Products and Food Branch Inspectorate. (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/insp_strat_tc-tm-eng.php)

5. Classification of observations made in the conduct of inspections of clinical trials (GUI-0043), Health Products and Food Branch Inspectorate. (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_0043_tc-tm-eng.php)