Health Canada
Health Products and Food Branch Inspectorate

OUR MANDATE:

Health Canada's mission is to help the people of Canada maintain and improve their health. With that mission in mind, the Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by minimizing health risk factors for Canadians while maximizing safety provided by the regulatory system for health products and food and promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch Inspectorate

SUMMARY REPORT OF THE INSPECTIONS OF CLINICAL TRIALS CONDUCTED IN 2003 / 2004

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EXECUTIVE SUMMARY

This document provides the results and analysis of the findings of inspections of clinical trials conducted by the Health Products and Food Branch Inspectorate (Inspectorate) in 2003 / 2004. This is the second annual report of inspections of clinical trials, and is intended to assess compliance of the conduct of clinical trials under the purview of Division 5 of the *Food and Drug Regulations* "Drugs for clinical trials involving human subjects".

The approach selected for inspections of clinical trials consisted of inspecting a number of clinical trials at 5 leading pediatric research institutions in Canada. This approach was qualified as "horizontal" inspections whereby common quality systems and procedures used for the conduct of all clinical trials at these institutions were assessed, in addition to the selected clinical trials. Assessing the level of compliance to the regulatory requirements in this manner was expected to achieve the greatest impact within this clinical research community.

A total of 45 clinical trials were selected for inspection, of which 23 were sponsored by commercial sponsors and 22 by non-commercial sponsors. These trials were conducted by 39 Qualified Investigators, some conducting simultaneously more than one clinical trial. The Inspectorate also inspected the 5 respective Research Ethics Boards that approved the inspected clinical trials.

Inspectors made a total of 292 observations, every observation representing a deviation from a regulatory requirement. The Inspectorate required every observation included in individual reports to sponsors and Qualified Investigators to be addressed through corrective actions, within a set time frame, in order to ensure that all observations noted during inspections were rectified. Although almost all observations made were considered non-critical, Inspectors deemed several observations to be sufficiently significant to warrant immediate corrective action. None of the significant deviations triggered a suspension or cancellation of an authorization to conduct a clinical trial.

The general types of deviations noted during inspections appear to be similar to those reported by regulatory authorities in other jurisdictions. The four main types of deficiencies that were noted, in decreasing frequency, were deficiencies related to:

- inadequate records,
- insufficient quality systems,
- inadequate process for informing and obtaining the informed consents from subjects, and,
- deviations from research protocols.

Overall, the second year of inspection of clinical trials was successful and provided an opportunity to assess regulatory compliance of Qualified Investigators and Research Ethics Boards involved in the approval of clinical trials. In sharing excerpts of observations made during these inspections in a manner that respect the confidentiality and privacy of those involved, Health Canada seeks to raise the awareness within the research community of the requirements for regulatory compliance, with a view to ensuring greater compliance.

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[(1)] provides the guiding principles for the fair, consistent and uniform application and enforcement of the Act and Regulations.

Division 5 of the *Food and Drug Regulations,* "*Drugs for clinical trials involving human subjects*"[(2)], also known as the clinical trial regulations, were promulgated pursuant to Section 30 of the *Food and Drugs Act*. The *Act* provides 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. The clinical trial regulations came into force on September 1st, 2001. Prior to that date, Division 8 of the same regulations were in effect. Clinical trials submitted to Health Canada prior to September 1st 2001 remain subject to Division 8.

An inspection strategy for clinical trials was published and adopted in January 2002[(3)]. The primary focus of the strategy is the protection of human subjects enrolled in clinical trials. The secondary objective is the verification of the data generated through the conduct of clinical trials and subsequently submitted for evaluation for the next step in the drug development and eventually for marketing approval.

Under the first phase of the inspection strategy in 2002, clinical trial sites were inspected on a voluntary basis, reflecting an initial confidence-building focus. A summary report of these inspections, highlighting common deficiencies using examples made anonymous, was later publicly released. A similar approach is used for this year's report.

Under the second and ongoing final phase of the strategy, which commenced in April 2003, selection of sites for inspections was made by the Inspectorate, in collaboration with the Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD). Inspections were conducted on on-going clinical trials in which subjects were enrolled, so that in the event that deviations from the regulations were noted, corrective actions could be implemented in a timely manner.

In accordance with the Inspection Strategy, a number of risk-based criteria were used to select the sites to be inspected. The criteria included the number of subjects enrolled at a trial site and the number of clinical trials conducted at a specific location. Other criteria used included the selection of an approximately equal number of clinical trials that were supported by commercial and non-commercial sponsors. Non-commercial sponsors consisted of clinical trials that were either initiated by a Qualified Investigator, or supported by a non-commercial sponsor. Finally, only clinical trials which were under the purview of Division 5 of the Regulations were to be selected.

The selection of trial sites inspected is important as the number of routine inspections that can be performed per year is limited. According to our inspection strategy, up to 2% of all clinical trial sites in Canada, including sites of Phase I, II and III and approved on a yearly basis, are selected for routine inspection. In addition, Phase IV clinical trials can also be inspected as needed.

Compliance inspections and investigations are conducted by the Inspectorate in response to complaints received concerning the conduct of a clinical trial subjected to the regulations. Since September 2001, the Inspectorate has been informed of specific concerns from sponsors, Qualified Investigators, subjects / patients / participants , Research Ethics Boards, foreign regulatory agencies, and from internal sources within Health Canada. On an annual basis, 15 to 20 compliance inspections are initiated and processed as a priority. The outcome of these activities are not included in this report.

The pediatric institutions selected were requested to submit a complete list of all on-going clinical trials. From that list, a selection of specific clinical trials was made, which included trials that were sponsored by both commercial and non-commercial sponsors. Research Ethics Boards were included as they are required to review and approve protocols and informed consent forms, in addition to ensuring compliance to good clinical practices, is a requirement under the regulations. The results of the selection of clinical trials inspected is shown on Table 1.

Table 1: Number of Qualified Investigators, Sponsors and Research Ethics Boards inspected.

		Number of clinical trials	Number of different Qualified Investigators	Number of Research Ethics Boards
Qualified Investigators	Commercial Sponsors	23	22 (2)	- - - -
	Non-Commercial Sponsors (1)	22	18 (3)	- - - -
Research Ethics Boards		- - - -	- - - -	5
Total :		45	39 (4)	5

Notes:

1. Includes clinical trials initiated by Qualified Investigator and other non-commercial sponsors.
2. One Qualified Investigator was involved in two different commercially sponsored trials.
3. Three Qualified Investigators were involved in the conduct of more than one non-commercial clinical trial.
4. One Qualified Investigator conducted one commercial and one non-commercial clinical trial.

Of the 45 clinical trials inspected, 31 involved pharmaceutical drugs and the remaining 14 related to biological drugs. This report outlines the findings of inspections at Qualified Investigator sites. The findings of the inspections are divided into three distinct subsections. The first section outlines observations made at sites of Qualified Investigators who conducted clinical trials under the sponsorship of a commercial sponsor. The second section presents observations made at sites of Qualified Investigators who were supported by non-commercial sponsors. This category includes Qualified Investigators who conducted clinical trials under their own sponsorship, often referred to a Qualified Investigator initiated clinical trials. The last section presents findings of the inspections at Research Ethics Boards which reviewed and approved clinical trials inspected within these research institutions.

For each clinical trial inspections, an overall rating is assigned. This rating represents an overall assessment of the level of compliance. The two ratings assigned are either "C" or "NC". The meaning of these ratings is as follows:

"C" means no objectionable conditions or practices were observed during the inspection

"NC" means that objectionable conditions or practices were observed, actions will be recommended

In cases of significant non-compliance, a "NC" rating is assigned, in which case the Inspectorate can require immediate corrective action or, if necessary, recommend a suspension or a cancellation of the authorization to conduct a clinical trial. The Health Canada Directorate which issued the authorization is responsible for suspending or cancelling an authorization. Other actions could also be considered, in accordance with the *Food and Drugs Act* and the Compliance and Enforcement Policy[1].

With the exception of one Inspectorate Operational Centre, all Centres were involved in these inspections. A total of 8 Inspectors conducted these inspections during the fiscal year of 2003 / 2004, starting on April 1st. Other Inspectors were involved in related compliance inspections and all were involved in other activities related to compliance and enforcement of the *Food and Drug Regulations*. The inspections were conducted using procedures and guidance documents developed for inspections of clinical trials.

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: 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 Good Clinical Practices (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.

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. INSPECTION

Inspections were conducted in accordance with the Inspectorate's Compliance and Enforcement Policy, which sets out guiding principles for the fair, consistent, and uniform application and enforcement of the *Food and Drugs Act* and corresponding Regulations. 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"[4] developed by the International Conference on Harmonization (ICH) and adopted by Health Canada in 1997, was used for interpretation of the requirements for good clinical practices.

3.1 OBJECTIVES OF AN INSPECTION

The main objectives of a clinical trial inspection are:

1. To minimize the health hazards 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 action regarding compliance and enforcement when deemed necessary.

3.2 STAGES OF AN INSPECTION

Inspection of a Sponsor or Qualified Investigator involves six stages:

1. Preparation of the inspection: This is the initial stage in which Inspectors review all of the relevant records, protocols, investigator's brochures, amendments and 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. Opening meeting: This meeting takes place during 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. 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. Drafting of report by the Inspector: Although notes are recorded throughout the inspection, a preset and standardized report format is used.

5. Exit interview: All observations made during the inspection are presented to the responsible party. Although these observations are discussed as the inspection proceeds, clarifications or corrections can be made at this last stage.

6. 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 responsible party, within a specific time frame. Should the inspected responsible party 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, must respond to every observation made in the exit notice with appropriate corrective actions. Within the requested time frame, the Inspectorate reviews responses from the Sponsor to assess the adequacy of 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 within the time frame provided, 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 actions are initiated.

4. REGULATIONS

All observations made during the inspections relate to specific requirements under the Regulations (Annex A - sections C.05.010, C.05.011 and C.05.012). The Good Clinical Practice Guideline, as developed by International Conference on Harmonization was used for interpretation of section C.05.010. Only observations referenced in the Regulations were reported.

5. ANALYSIS OF OBSERVATIONS

The following table (table 2) lists the number of observations against each of these sections / sub-sections of the Regulations. Observations made at sites of Qualified Investigators supported by commercial sponsors, by non-commercial sponsors and Research Ethics Boards are tabulated. Only sections or sub-sections linked to observations made during the inspections are listed.

Table 2. Number and types of observations made during inspections of clinical trials at sites of Qualified Investigators and Research Ethics Boards in 2003/2004.

Regulations	Number of observations								Brief description of the section / sub-section of the Regulations, Division 5 - Food and Drug Regulations "Drugs for clinical trials involving human subjects"	General classifi-cation of deficiency	Frequency %
	Total number of observations		Qualified Investigators				Research Ethics Board (REB)				
			Commercial Sponsor		Non Commercial Sponsor						
		%		%		%		%			
C.05.001	3		0		0		3	11%	Membership of Research Ethics Board		
C.05.003	3		0		3		0		General prohibition		
C.05.008(1)	8	3%	2		4		2		Amendments approved by Research Ethics Board (REB) and Health Canada		
C.05.010(a)	5		2		3		0		Protocol clearly described	Protocol	10%
C.05.010(b)	23	8%	11	10%	12	8%	0		Clinical trial conducted in accordance with protocol and Regulations		
C.05.010(c)	68	23%	23	20%	34	22%	11	40%	Quality systems and procedures in place for all aspects of the trial	Quality Systems	23%
C.05.010(d)	3		1		1		1		Approval by REB before initiation of trial		
C.05.010(e)	4		1		3		0		No more than one Qualified Investigator per site		

Regulations	Number of observations								Brief description of the section / sub-section of the Regulations, Division 5 - Food and Drug Regulations "Drugs for clinical trials involving human subjects"	General classifi-cation of deficiency	Frequency %
	Total number of observations		Qualified Investigators				Research Ethics Board (REB)				
			Commercial Sponsor		Non Commercial Sponsor						
		%		%		%		%			
C.05.010(f)	7	2%	1		4		2		Medical care under supervision of Qualified Investigator		
C.05.010(g)	9	3%	3	3%	6	4%	0		Qualifications education and training		
C.05.010(h)	59	20%	25	22%	32	21%	2		Informed consent obtained in accordance with applicable laws	Informed Consent Process	20%
C.05.010(j)	18	6%	6		12	8%	0		Drug manufactured, handled, stored in accordance with applicable Good Manufacturing Practices. Includes Labelling C.05.011		
C.05.012(1)	44	15%	25	22%	19	13%	0		Record, handle, and storage of all information	Records	28%
C.05.012(2)	12	4%	6		2		4	15%	Maintain complete and accurate records to establish that trial conducted in accordance with Good Clinical Practices		
C.05.012(3)(c)	5		1		3		1		Adverse events reporting. Includes C.05.014 (Serious and unexpected)		
C.05.012(3)(e)	4		2		2		0		Drug accountability		
C.05.012(3)(f)	7		1		6		0		Undertaking by the Qualified Investigator. Includes C.05.005(c)(ix) Name of Qualified Investigator at every site.		
C.05.012(4)	10	3%	3		6		1		Records to be maintained for 25 years		
Total:	292		113	39%	152	52%	27	9%			

The four main types of regulatory deviations noted during 2003 / 2004 inspections are, in decreasing frequency, displayed in table 3:

Table 3. Overall frequency of general classification of deficiencies made during inspections.

	Regulations	General classification of deficiency	% of total
1	C.05.012	Inadequate records	28%
2	C.05.010(c)	Insufficient quality systems	23%
3	C.05.010(h)	Inadequate process for informing, obtaining and maintaining informed consents from subjects	20%
4	C.05.010(a) and C.05.010(b)	Deviations from the research protocol	10%

Almost all inspections conducted resulted in a "C" rating. In many instances, corrective actions were implemented immediately.

Each of these four main type of deficiencies will be analysed sequentially for inspections at sites of Qualified Investigators sponsored by commercial sponsors (5.1), followed by inspections at sites of Qualified Investigators sponsored by non commercial sponsors (5.2) and finally the Research Ethics Boards (5.3). Each of these categories will list the type of deficiency in decreasing frequency and include examples of observations made by Inspectors.

5.1 INSPECTIONS AT SITES OF QUALIFIED INVESTIGATORS SPONSORED BY COMMERCIAL SPONSORS

Records C.05.012

The highest number of observations made with respect to the 23 trials supported by commercial sponsors were deficiencies in the accuracy and maintenance of records. Of a total of 113 deficiencies noted at the sites of Qualified Investigators, 38, or 34% related to deficient records.

The Regulations set out specific requirements to ensure that all clinical trial information is recorded, handled and stored in a manner that allows for complete and accurate reporting. This requirement applies to every record created in the conduct of a clinical trial. This includes for example, signed undertakings by Qualified Investigators to conduct a trial in accordance with good clinical practice; results of laboratory analyses; documents issued by the Research Ethics Board; and other records needed to support evidence of compliance with the approved protocol, the *Regulations* and good clinical practices. Source documents, often referred to as "first time entry" documents, are those to be maintained for the prescribed period of retention and should be kept in a secure location and accessible for inspection. When data is captured in an electronic manner, evidence of control of the use of these tools as well as evidence of the validation are required. Two examples of these deficiencies are:

Example #1: *The monitor's letter from the visit of August 2003 had been reviewed and stated that the doctor discontinued a patient for lack of efficacy of the treatment, however, there was no source documentation that this patient had been withdrawn from study August 6, 2003 due to lack of efficacy.*

Example #2: *The original Informed Consent form for patient --- was not available for review. A copy was kept in the files.*

In accordance with good clinical practices, signed, original consent forms (not a copy) are to be retained by Qualified Investigators, and a copy is to be provided to subjects. (Reference GCP; section 4.8.11 and 8.3.2)

5.1.2 Informed Consent - C.05.010(h)

A total of 25 observations were made at sites of clinical trials sponsored by commercial sponsors relating to deficiencies in the informed consent process. Research Ethics Boards are responsible for the review and approval of informed consent forms as well as all other information provided to subjects. Sponsors, Qualified Investigators and Research Ethics Boards should help promote compliance with informed consent process requirements by adopting and adhering to written standard operating procedures covering all aspects of the informed consent process, including how to inform, obtain and maintain the informed consent of subjects.

Following are a number of observations noted:

Example #3: *There is no written procedure specific for this trial that specifies who, how and when written informed consents are obtained and explained.*

Example #4: *The signature page (page 7 of 7) of one of the informed consents that had been reviewed was not attached to the previous 6 pages, it did not specify the actual study that they were signing for, each page had not been initialled nor did the signature page refer to all pages of the informed consent having been read.*

In cases of multiple page informed consent forms, every page of the form must be signed or initialled by the subject to confirm that he/she understands the content form of the consent and the agreement to participate in the clinical trial.

5.1.3 Systems and procedures - C.05.010(c)

The third highest number of observations related to the use of quality systems and procedures needed 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. The procedures should be approved and revised on a regular basis by Qualified staff. Training on these systems and procedures is an integral element verified during inspection. Examples of such observations include:

Example #5: *There was no written Standard Operating Procedures on the criteria to be used in the classification of adverse drug reactions and the reporting time limits for reporting to the Research Ethics*

Board the Serious Adverse Drug Reactions and the Serious and Unexpected Adverse Drug Reactions, and to Health Canada the Serious and Unexpected Adverse Drug Reactions.

Example #6: *There was no requirement to respond to the letters issued by the monitors at each visit stating the corrective actions that were taken to any noted observations.*

Overall, 23 observations out of a total of 113, or 20% of all observations related to this sub-section of the regulations.

5.1.4 Protocol - C.05.010(a) and C.05.010(b)

Clinical trial protocols should clearly describe the objective, design, methodology and organization of the clinical trial. Similar to the process of review and approval of the original protocol, any amendments to a protocol must be approved by a Research Ethics Board, in addition to being submitted to Health Canada before being implemented. A sponsor may modify immediately a protocol without securing an authorization only if the clinical trial or the use of the drug endangers the health of clinical trial subject. In such circumstances, the sponsor must provide the protocol amendment to Health Canada within 15 days of the amendment taking effect [C.05.008(4)].

Deviations from protocols or inadequate protocols at Qualified Investigator sites accounted for 11% of all observations. Examples of protocol deviations noted include:

Example # 7: *Subject 00000 was entered into the trial although she had not had the age 4-6 booster contrary to the protocol.*

Example #8: *The protocol for the clinical trial had a dosing chart for enzyme ABC which did not require rounding off. The pharmacy was calculating dosage to be delivered based on the subject's weight from the previous visit...*

5.2 INSPECTIONS AT SITES OF QUALIFIED INVESTIGATORS SPONSORED BY NON-COMMERCIAL SPONSORS

This category of clinical trials includes clinical trials that were sponsored by cooperative and non-commercial groups and by Qualified Investigators who have applied to conduct a clinical trial. An application to conduct a clinical trial is required, regardless of whether the sponsor is a commercial or a non-commercial sponsor.

5.2.1 Records - C.05.012

The highest number of observations made at clinical trial sites of the 22 clinical trials supported by non-commercial sponsors were deficiencies related to records both in terms of the accuracy of the records created and the maintenance of these records. Of the total of 152 deficiencies noted at these Qualified Investigator sites, 38, or 25% of all observation made at these sites were related to deficient records. Example of deficiencies include:

Example #9: *There was no documentation to indicate that the subjects enrolled in the trial met the inclusion / exclusion criteria. A Subject Eligibility Criteria form existed, but it was not completed...*

Example #10: *Subjects were assessed for inclusion / exclusion into the study, by the Study Coordinator: these records were not signed by the Qualified Investigator nor were they signed by the Study Coordinator who completed the records...*

Example #11: *Many records of the trial were noted in pencil or modified with correcting liquid...*

5.2.2 Systems and procedures - C.05.010(c)

The second highest number of observations related to the use of quality systems and procedures needed in the conduct of clinical trials. A total of 34 observations were made under this sub- section, representing 22% of all observations made at sites of Qualified Investigators of non- commercial trials. Relevant observations include:

Example #12: *Although documentation at this site indicates that there has been some central monitoring of the trial data, there has not been any on-site monitoring of this trial...*

Example #13: *There were no delegation forms explaining the functions delegated to the staff, including their signatures. There was no information as to who was acting on behalf of the Qualified Investigator in his absence...*

5.2.3 Informed Consent - C.05.010(h)

A total of 32 observations identified at sites of clinical trials sponsored by non-commercial sponsors related to the informed consent process, representing 21% of all observations made at non-commercial sites. The Research Ethics Board is responsible for the review and approval of the informed consent form as well as every information relayed to subjects. Cooperative groups / non-commercial sponsors as well as research institutions may take the initiative to institute policies that would ensure a high level of compliance to this critical element for the conduct of clinical trials.

The Qualified Investigator is responsible for the process used to explain to potential subjects the risks and anticipated benefits of participating in a clinical trial. This process should be well defined and supported with written standard operating procedures, including how to inform, obtain and maintain the informed consent of subjects, and to ensure consistency in the information provided to every subjects. Examples of such deficiency include:

Example #14: *There was no written Standard Operating Procedures for the process and responsibilities pertaining to obtaining Informed Consents so as to assure uniformity among the sub-investigators.*

Example #15: *The parents of subject number 000 signed version #3 of the informed consent form when the subject was enrolled, but there is no indication that version #4 of the informed consent, which was approved by the Research Ethics Board on February 4, 2004, has been signed by the subject's parents although the subject has visited the site since February 4, 2004. ... Version #4 of the informed consent form indicates that*

inflammation of the lungs and lung infections are a rare side effect of the study drug and this side effect is not indicated in version #3 that was signed by the subject's parents.

Example #16: *The Informed Consent form for the study ABC did not include a statement that Health Canada will be granted direct access to the subject's original medical records for verification.*

5.2.4 Protocol - C.05.010(a) and C.05.010(b)

Clinical trial protocols should clearly describe the objective, design, methodology and organization of the clinical trial. Once submitted, reviewed and approved by Health Canada and the respective Research Ethics Boards, deviations from the protocol should not occur unless it endangers the health of the clinical trial subject. It is only in such a situation that deviations are acceptable and in these instances, specific information relayed under subsection C.05.008(4) must be submitted to Health Canada within 15 days of the occurrence.

Deviation from protocols or inadequate protocol at Qualified Investigators sites accounted for 10% of all observations.

Example #17: *For subject #000 the validated psychological assessment tool to gauge patient and family acceptance of the study drug was not administered 30 days after discharge as required by the protocol. It was explained by the clinical research associate that the site has decided not to complete this assessment for any subjects...*

5.3 INSPECTIONS AT RESEARCH ETHICS BOARDS INVOLVED IN THE APPROVAL OF CLINICAL TRIALS INSPECTED

5.3.1 Systems and procedures - C.05.010(c)

Research Ethics Boards play a key role in protecting the rights, safety and well-being of human research subjects. The principal mandate of a Research Ethics Board is to approve and conduct periodic reviews of clinical trials. The regulations require that a Research Ethics Board not be affiliated with the sponsor, and also set out membership criteria. Protocol amendments, in accordance with subparagraph C.05.008(1)(*c*)(i) of the regulations, must also be reviewed and approved by a Research Ethics Board. Section 3 of the good clinical practice guidelines describe in detail the responsibilities of Research Ethics Boards; specify requirements for written procedures to which Research Ethics Boards should adhere; and note the range of documents/processes that should be subject to Research Ethics Board review (e.g., protocol, informed consent form, safety information, recruitment information, compensation to subjects).

Observations identified relating to Research Ethics Boards include:

Example #18: *The written terms of reference for the Research Ethics Board did not provide information as to how decisions would be made. It was not clear if a vote would be taken. Review of the approval for one recent study showed that the final decision regarding the protocol was achieved through consensus of the committee.*

Example # 19: *The written terms of reference for the membership of the Research Ethics Board did not specify that the majority of members must be Canadian citizens or permanent residents and both men and women must be represented. In addition, they did not specify that there must be one member whose primary experience and expertise is in a non-scientific discipline. ... the non-medical members could not be confirmed since their CVs were inaccessible.*

Protocol amendments, in accordance with subparagraph C.05.008(1)(*c*)(i) of the regulations require the approval of the amended protocols by the Research Ethics Board.

Example #20: *Although it was orally stated that major amendments to protocols may be referred to a full board review, according to the Research Ethics Board procedure, all amendments are approved solely by the associate chair...*

In accordance with sub-section C.05.010(h), the informed consent is to be obtained from every participant only after the risks and anticipated benefits to the subject's health have been explained. A key role of Research Ethics Boards is to review and approve the entire process to be used, including the advertising and recruitment material used, the actual consent form and the circumstances that will require a revision and re-consenting of subjects.

5.3.2 Records - C.05.012

As with Sponsors and Qualified Investigators, Research Ethics Boards must record, handle and store all information that pertains to their activities in a way that allows complete and accurate retrieval of records. These records should be kept in a secure location and for the prescribed period of time. A total of 6 observations were made related to this requirement, including the following:

Example # 21: *The approval letter issued by the Research Ethics Board did not state the version of the protocol, the amendment, the information to be provided to subjects.*

5.3.3 Membership of the Research Ethics Board - C.05.001

The Regulations provide specific minimum requirements for the membership of the Research Ethics Boards, including the expertise, the citizenship and the gender of members. Additional provincial and / or institutional requirements may also apply. When inspecting Research Ethics Boards, all applicable requirements are considered, although observations made by Inspectors are always based on deviations from the Regulations.

Out of 5 Research Ethics Boards inspected, 3 observations were made, including:

Example # 22: *The minutes of the Research Ethics Board meeting of ... 2003 did not indicate that a member with knowledge of Canadian laws and a member knowledgeable in ethics were present.*

6. OTHER PERTINENT INFORMATION

6.1 TIME REQUIRED FOR THE CONDUCT OF INSPECTIONS

The unique "horizontal" approach used in 2003 / 2004 required, overall, more time to complete. On average, approximately two weeks were required for Inspectors to prepare for these inspections, two weeks for the actual on-site inspections and over two weeks for the reporting and reviewing of corrective actions. All inspections were conducted by a team of two Inspectors.

7. CONCLUSIONS

The conduct of clinical trials is a shared responsibility among sponsors, whether commercial or non-commercial, Qualified Investigators, Research Ethics Boards, research institutions, human research subjects and Health Canada. The understanding, by all involved, of their respective roles and responsibilities is an important element to ensure that the best outcomes are achieved.

This document, the second annual summary report, is intended to increase awareness of regulatory requirements for the conduct of clinical trials by sponsors, Qualified Investigators, and Research Ethics Boards. It is hoped that providing examples, made anonymous, of a range of deficiencies noted during inspections will help promote greater compliance.

The nature and incidence of observations identified by the Inspectorate in 2003 / 2004 were comparable across clinical trials supported by commercial and non-commercial sponsors. Deficiencies related to records at Qualified Investigator sites were the most frequent observations, representing 28% of all observations. Second and third in terms of frequency were deficiencies related to inadequate systems / procedures and inadequate informed consent process. Between 20% and 23% of all observations were under these categories for Qualified Investigators conducting clinical trials under either commercial or non-commercial sponsorship.

With respect to Research Ethics Boards, 40% of observations related to regulatory deficiencies in systems and procedures; 15% related to inadequate records; and 11% related to deficiencies in membership.

Although inspections of clinical trials have only been conducted since 2002, the impetus for inspections in Canada has already been made clear with a two-fold focus:

1. The use of adequate quality systems and procedures for the proper conduct of clinical trials and,

2. The use of an adequate process for soliciting, obtaining and maintaining the informed consent of subjects.

Both elements will remain a priority as they are closely linked to the primary objective for the inspection of clinical trials, namely the protection of subjects enrolled in clinical trials.

Acknowledgement

The conduct of clinical trials requires dedication on the part of many health care professionals. The collaboration exhibited during inspections by Qualified Investigators, Sponsors and Research Ethics Boards, research institutions as well as the staff at the institutions during these inspections, is acknowledged.

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

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

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

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-Good Clinical Practices E6.
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/e6_e.pdf

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