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To: Associations, Pharmaceutical Sponsors, Clinical Research Investigators, Research Ethics Board and all other interested parties,

I am pleased to inform you that Health Canada has revised the guidance document entitled “Classification of Observations made in the conduct of inspections of clinical trials”, which is now available on Health Canada’s Compliance and Enforcement website under “[What’s New](#)”.

The revisions are based on the comments received as a result of the publication of the original Guide-0043 on the Inspectorate website on October 20, 2006. All comments were carefully assessed and analysed. Several main issues were identified. The rationale for the decisions made respecting the issues identified by stakeholders is summarized and annexed to the revised Guide.

This guide is in effect as the date of this letter. Inquiries about this document can be addressed in writing to the GCP Coordinator, Good Clinical Practices Compliance Unit, by telephone at 613-952-8173, by fax 613-952-9805 or by e-mail at: GCP_BPC@hc-sc.gc.ca.

Yours truly,

Original signed by

Kim Dix for
Diana Dowthwaite
Director General

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

Classification of observations made in the conduct of inspections of clinical trials

Guide-0043

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October 23, 2006
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Disclaimer

This document does not constitute part of the Food and Drugs Act (Act) or the Food and Drugs Regulations (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.

Ce document est aussi disponible en français.

FOREWORD

This guidance document represents Health Canada's Health Products and Food Branch Inspectorate (Inspectorate) current stance on this topic. Guidance documents are administrative instruments that are meant to provide assistance to stakeholders including the industry and health care professionals on how to comply with the policies and governing Acts and Regulations.

Administrative instruments allow for flexibility in approach, as they have no force in law. Alternate approaches to those described in this document *may be* acceptable provided that the approach satisfies applicable Acts and Regulations. Alternate approaches must be discussed with the relevant Inspectorate authorities in order to ensure that applicable statutory or regulatory requirements have been met.

Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance document, in order to allow Health Canada to adequately assess the safety, efficacy or quality of a health product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are documented.

This guidance document should be read in conjunction with the relevant Acts, Regulations, policies, guidelines and any other requirements.

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1.0 PURPOSE

The purpose of this guide is to:

- help classify the level of severity of deviations noted as observations during inspections of clinical trials with drugs for human use.
- ensure uniformity in the assignment of ratings of observations among Inspectors of the Health Products and Food Branch (HPFB) Inspectorate.
- inform Sponsors, Qualified Investigators, Research Ethics Boards, Contract Research Organizations, Site Management Organizations and others involved or interested in the conduct of clinical trials, of conditions that HPFBI considers unacceptable.

2.0 BACKGROUND

In the conduct of inspections of clinical trials, compliance is assessed against Part C, Division 5 of the *Food and Drug Regulations*, “Drugs for Clinical Trials Involving Human Subjects”. Inspectors will note all deviations as observations in the inspection exit notice.

For each observation made, a classification, based on the severity of the deviation is assigned by the Inspector using this document as a guide. Once all the observations have been rated, all the information will be taken into account in assigning an overall rating of “C” or “NC” whereby:

“C” (Compliant) at the time of the inspection, the regulated party has demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations

Disclaimer: - A C rating does not mean that there are no observations or corrective actions required.

“NC” (Non compliant) at the time of the inspection, the regulated party has not demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations.

Objectionable conditions are defined as a situation that leads to fatal, life threatening or unsafe conditions for subjects enrolled in a clinical trial, including but not limited to, the conduct of unauthorized trials, adulteration, misrepresentation and falsification of records.

Actions recommended as the result of the assignment of a “NC” rating may range from the requirement for the sponsor to undertake and implement immediate corrective measures, up to the suspension or cancellation by Health Canada of the authorization to conduct a clinical trial. Therefore, situations involving an “NC” rating need to be unambiguous and directly supported by the applicable regulations.

3.0 SCOPE

This Guide covers all clinical trials subject to Part C, Division 5 of the *Food and Drug Regulations*.

The intent of this Guide is to help classify the severity of observations noted during inspections of clinical trials. Overall, the evaluation will commensurate with the nature and extent of the deviations (i.e. severity). The specific examples provided in this document would apply to specific inspected parties. Situations involving fraud, misrepresentation or falsification of source data or records linked with clinical trials will result in a “NC” rating.

Inspections may be conducted at the facilities of the Sponsors, Qualified Investigators (clinical trial sites), Sponsor-Investigators, Research Ethics Boards, and Contract Research Organizations. Inspections can also be conducted at facilities of Site Management Organizations, Testing Laboratories, and any other sites conducting tasks under the scope of a clinical trial subjected to the Regulations.

The inspection strategy applies to all clinical trials involving human subjects, as defined in Division 5 of the *Food and Drug Regulations*. Inspections are performed using these Regulations, which integrate good clinical practices (GCP) as described by the *International Conference on Harmonization*, Guidance document E6 (Tripartite Agreement), adopted by Health Canada.

The main objective of inspections of clinical trials is to ensure that sponsors conduct clinical trials in accordance with the Regulations. This includes, but is not limited to, conducting clinical trials in accordance with the approved protocol, that the data generated are accurate, that subjects enrolled in clinical trials are not subjected to undue risks, and that the trial is conducted in accordance with the generally accepted principles of good clinical practices (GCP-ICH).

The appendices attached to this document provide examples of observations, listed in decreasing level of severity. Please note that the list of observations in each appendix is not **exhaustive** and additional observations may be added if and when appropriate.

4.0 DEFINITIONS

The following definitions are provided to complement those already available in either Division 5 of the *Food and Drug Regulations* “Drugs for Clinical Trials Involving Human Subjects”, the Inspectorate’s Compliance and Enforcement Policy (POL-0001), or the Inspection Strategy for Clinical Trials.

Observation

A deficiency or deviation from Division 5 noted by an Inspector during the inspection of a clinical trial that is confirmed in writing in the exit notice. Each observation is attached to the inspection summary in the Inspection Reporting System. The observations are classified as “critical” (risk 1), “major” (risk 2) or “minor” (risk 3).

Critical observation

An observation describing a situation that results in fatal, life threatening or unsafe conditions for subjects enrolled in a clinical trial. It presents an immediate or latent undue risk to the rights, health and safety of subjects. The conduct of unauthorized trials, adulteration, misrepresentation and falsification of records are also critical observations.

Appendix 1 is a list of observations that are considered critical.

Major observation

An observation describing a marked deviation or deficiency, other than a critical one, that may result in undue health risks to the clinical trial subjects, in other persons or could invalidate the data.

Appendix 2 is a list of observations that are considered as major (risk 2). Major observations may be reclassified as critical (risk 1), depending on the nature and the extent of the deviation. For example, widespread or systemic deficiencies, such as a lack of evidence that informed consent was obtained from most of the subjects enrolled in a trial or marked deviations from the inclusion/exclusion criteria that endanger the health and safety of subjects, could result in a “critical” classification, whereas an isolated departure, such as the lack of a signed informed consent form from a single subject, would be classified as a “major” classification. Observations classified as major may be upgraded to critical when accompanied with an arrow up sign (↑), depending on the quantity and/or nature of the deviations.

Note: In all situations, when a major observation is reclassified as a critical observation, a justification will be provided to the site inspected.

Minor observation

An observation that is classified as not critical or major, but which indicates a deficiency and/or deviation from Division 5.

Appendix 3 contains a list of minor observations.

5.0 GUIDE

5.1 Critical (Risk 1) observations:

If one or more critical observations are noted during an inspection, the situation will be immediately brought to the attention of the Sponsor, Qualified Investigator (clinical trial site), Research Ethics Board, and/or

Contract Research Organization as applicable. They are duly informed that this will likely result in the attribution of a “NC” rating.

In these cases, the Inspector will discuss the appropriate course of action with his/her superior, the Compliance and Enforcement Coordination Division (CECD), and the Therapeutic Products

Directorate (TPD) and/or Biologics and Genetic Therapies Directorate (BGTD). An action plan specifying the corrective measures to be taken as well as the time frame necessary to implement these actions will be requested. When the resulting situation presents an immediate potential health hazard to the subjects, a health hazard evaluation will be requested of the TPD and/or BGTD. Enforcement actions will be taken as required; including but not limited to; seizure and/or voluntary detention of products, suspension or cancellation of the clinical trial authorization.

5.2 Major (Risk 2) observations:

When an inspection generates observations classified as major, a “C” rating will be assigned in most situations. However, a “NC” rating could be assigned to the site inspected in the following situations:

- When the major observations indicate that the clinical trial is not conducted with sufficient controls.
- Repetition of most major observations reported during previous inspections, revealing that the corrective actions submitted were not implemented, or adequate preventative actions were not put in place in a timely manner to avoid recurrence of these deviations.

5.3 Minor (Risk 3) observations:

A “C” rating will be assigned in all situations when minor observations are noted.

REFERENCES:

1. *Food and Drug Regulations*
2. ICH Guidance E6: Good Clinical Practices: Consolidated guideline
3. Health Products and Food Branch Inspectorate Compliance and Enforcement Policy, POL-0001
4. Inspection Strategy for Clinical Trials
5. Summary Report of the Inspections of Clinical Trials Conducted in 2003 / 2004

APPENDIX 1

Critical (Risk 1) observations

C.05.003 Prohibition

- Clinical trial not authorized, as required and in accordance with Division 5 of the *Food and Drug Regulations*.
- Sponsor imported drugs for the purpose of conducting clinical trials without having received authorization from Health Canada prior to importation.

C.05.004 General

- Use of a prohibited substance without having received prior authorization.

C.05.005 Application for Authorization

- Misrepresentation or falsification of data submitted to obtain authorization to conduct clinical trials.

C.05.006 Authorization

- Clinical trial ongoing after authorization suspended or cancelled.
- Importation of a clinical trial drug when authorization is suspended or cancelled.

C.05.008 Amendment

- Information contained in the application for amendment falsified, misleading, or deceptive.
- Failure to notify Health Canada after amendments were implemented in cases where the clinical trial endangered the health of trial subject or other person.
- Failure to stop a clinical trial during a suspension or cancellation.

C.05.010 Good Clinical Practices

- Evidence of fraud such as “fabricating” subjects, falsification of study data.

C.05.011 Labelling

- Statement/s on label is/are false or misleading.

C.05.012 Records

- Sponsor withholding data (e.g.: for purpose of deception).
- No records of serious adverse drug reactions which occurred inside and/or outside Canada.
- No records in respect of the use of a drug in a clinical trial.
- No records with respect to the enrolment of clinical trial subjects.

C.05.013 Additional Information and Samples

- Providing false, misleading or deceptive samples of the drug or additional information relevant to the drug or the clinical trial.

APPENDIX 2

Major (Risk 2) observations

C.05.001 Interpretation

- Voting members of the Research Ethics Board (REB) were not independent of the Qualified Investigator and/or the sponsor of the clinical trial. (↑)
- Approvals of clinical trials without a quorum of members with the required representation.
- Major changes to previously approved protocols that increase health risks to subjects, were given expedited approval only.
- REB membership did not include a minimum of 5 members or REB membership was not composed of a majority of Canadian citizens or permanent residents.
- REB membership did not include all of the representative expertise required by the regulations.
- REB did not have written procedures in accordance with Good Clinical Practices.
- REB approval of the clinical trial not conducted as per their written operating procedures.
- REB did not maintain adequate written minutes of meetings.
- REB did not consider the qualifications of qualified investigators before approving trials.
- REB did not conduct periodic reviews of continuing clinical trials.

C.05.005 Application for Authorization

- Information contained in the application was incomplete or incorrect. (↑)
- Failure to report a REB that previously refused to approve a trial. (↑)

C.05.006 Authorization

- Failure to disclose all Canadian clinical trial sites to Health Canada.
- Failure to provide all necessary information, not previously provided in the application, prior to the sale or importation of a drug at a clinical trial site.

C.05.007 Notification

- Failure to notify Health Canada when changes made to the chemistry and manufacturing information or to the approved protocol.

C.05.008 Amendment

- Implementation of an amendment not subject to subsection C.05.008 (4) without obtaining authorization or before the end of the 30 day default period. (↑)
- Failure to disclose a previous REB refusal.
- Failure to implement an amendment at a clinical trial site. (↑)
- Failure to provide the Minister within 15 days with information regarding an immediate amendment to the protocol.

C.05.010 Good Clinical Practices

- Qualified Investigator does not have the qualifications to conduct the clinical trial. (↑)
- Medical care and decisions related to the trial are not under the supervision of the Qualified Investigator. (↑)
- Failure to obtain REB approval of the protocol or the informed consent forms prior to initiation of a clinical trial. (↑)
- Protocols not amended, informed consents not amended, and/or subjects not advised/re-consented when information becomes available regarding health and safety concerns, or use of the clinical trial drug which endanger the health of the clinical trial subject or other person. (↑)
- Failure to obtain REB approval prior to implementation of amendments to protocol or informed consents forms. (↑)
- Informed consent not obtained from subjects before enrolment in the trial or after major amendments to the informed consent form. (↑)
- Informed consents not administered properly or not signed and dated. (↑)
- Inadequate source data to substantiate clinical trial results. (↑)
- Clinical trial was not conducted in accordance with the protocol. (↑)
- Sponsor did not notify the Qualified Investigator of serious unexpected adverse drug reactions that occurred at other sites. (↑)
- Qualified Investigator did not notify the sponsor and/or REB in a timely manner of serious unexpected adverse drug reaction. (↑)
- No procedures in place for reporting new safety information to the Qualified Investigator.
- Significant clinical endpoint data not collected on time, not correctly recorded, or not accurately transcribed/transferred to case report forms. (↑)
- Inadequate systems in place for drug accountability.
- Storage or handling controls in place for drugs were inadequate.
- Source data was not verified for quality, completeness and integrity.
- Systems and procedures that assure the quality of every aspect of the clinical trial were not implemented.

- The informed consent did not contain all of the required information. (↑)
- Inadequate monitoring of the clinical trial site by the sponsor.
- Individuals involved in the conduct of the clinical trial are not qualified by education, training or experience to perform their respective tasks.
- Incomplete documentation of protocol deviation.
- Lack of documentation that Sponsor was informed of protocol deviations.

C.05.012 Records

- No security procedures in place for electronic records or electronic signatures.
- The electronic data system was not validated.
- Sponsor has no or incomplete records of all adverse events which occurred inside or outside Canada. (↑)
- Incomplete records respecting the enrolment of clinical trial subjects.
- Incomplete records concerning shipment, receipt, use, disposition, return or destruction of the drug. (↑)
- Quantities of drug not accounted for through the various stages of shipment, receipt, disposition, return or destruction of the lot of the drug. (↑)

- No signed/dated qualified investigator undertaking for each clinical trial site prior to the commencement of his/her responsibilities.
- Copies of the protocol/amendments and informed consents approved by the REB not retained for each clinical trial site.
- Absence of REB attestation for each clinical trial site stating that it has reviewed and approved the protocol, the informed consent and that it functions in compliance with GCP. (↑)
- No edit trails for changes to electronic records, to identify who made the changes or when.
- No provisions for retention of records for 25 years.
- Incomplete records in respect of the use of a drug in a clinical trial.

C.05.014 Serious Unexpected Adverse Drug Reaction Reporting

- Sponsor failed to report serious and unexpected adverse drug reactions to Health Canada. (↑)
- Sponsor did not comply with the prescribed timeline for reports of fatal or life threatening adverse drug reactions.
- Sponsor did not submit, within the prescribed timeline, an assessment of the importance and implication of any findings made.

C.05.015 Discontinuance of a Clinical Trial

- Sponsor did not inform Health Canada that the clinical trial was discontinued in its entirety or at a clinical trial site within 15 days after the date of the discontinuance.
- Sponsor did not provide Health Canada with the reasons for the discontinuance and its impact on the proposed or ongoing clinical trials.
- Sponsor did not inform all qualified investigators of the discontinuance of a trial, the reason for the discontinuation or did not advise them in writing.
- Sponsor did not stop the sale/importation of the drug as of the date of the discontinuance.
- Sponsor, after having discontinued a clinical trial, resumed selling or importing the drug without having submitted the required information to Health Canada.
- Clinical trial ongoing at one or more sites after Sponsor stated that the trial was discontinued at those sites. (1)

APPENDIX 3

Minor (Risk 3) observations

C.05.005 Application for Authorization

- Sponsor did not maintain copies of previous investigator's brochures pertaining to the clinical trial drug.
- Date for the commencement of a clinical trial at one or more trial sites was earlier than that stated in the application.

C.05.007 Notification

- Delay in written notification by the sponsor within fifteen days after the date of the change that requires notification.

C.05.010 Good Clinical Practices

- Delegation of tasks incomplete, signature log incomplete.
- Correction of data not initialled and/or dated.
- Minor errors in transcribing data from source documents to case report forms.
- Drug is not manufactured, handled or stored in accordance with the applicable good manufacturing practices. (↑)
- Source data stored in unsecured location.

C.05.011 Labelling

- Labelling of the products not complying with requirements of the Regulations. (↑)

APPENDIX 4

Summary of main comments received subsequent to web posting on December 29, 2006.

Over 304 comments were received as a result of the publication of Guide 0043 *Classification of observations made in the conduct of inspections of clinical trials* on the Inspectorate website on December 29, 2006. All comments received were carefully assessed. The analysis of comments identified several main issues. The rationale for the decisions made respecting the issues identified by stakeholders is summarized below. Some comments which were outside the scope of this guide may be addressed in a future FAQ document.

Issue #1: Several comments were received regarding Division 5 of the *Food and Drug Regulations* “Drugs for Clinical Trials Involving Human Subjects”(Regulations)

Your comments regarding Division 5 will be passed to the clinical trials regulatory review group.

With the introduction of the 2001 regulatory framework for clinical trials, Health Canada committed to a comprehensive review of the framework within three to five years. In response to this commitment, Health Canada launched a public e-consultation in June 2006 and held a stakeholder workshop in March 2007.

Results from the 2006 electronic consultation and the 2007 stakeholder workshop will help inform the development of short, medium and long-term measures to strengthen the regulatory framework for clinical trials. Additional consultations will be undertaken by the Branch as necessary as we move forward on this initiative, including through the Canada Gazette process if regulatory amendments are being considered.

We invite you to visit the [Review of the Regulatory Framework for Clinical Trials](#) on the web to obtain more information as we progress on this initiative.

We also invite you to continue providing your views and suggestions on ways to improve the clinical trials regulatory framework for the future by using the following:

E-mail address: clinical_trials_regulatory_review@hc-sc.gc.ca

Issue #2: Several comments referred to the Inspection Process

The inspection process is covered in the [Inspection Strategy for clinical trials](#). The review of the inspection strategy is subject to a regular review according to the Quality System in place. This review should be undertaken by April 2008. We will take your comments in consideration during the next review to make the process more transparent. Some of your comments also may be addressed in a FAQ document.

Issue #3: A number of comments were received regarding transparency of our program

Transparency is one of the guiding principles governing the Inspectorate in the application of the Acts and Regulations under its mandate. The Inspectorate is aware of the need to improve communication with stakeholders.

Consistent with and in the spirit of the *Privacy* and *Access to Information* Acts, the Inspectorate makes information on compliance and enforcement activities available to the public. For instance, the [Compliance and Enforcement Policy](#) is a public document:

The Inspectorate recognizes that some of its decisions may be disputed by regulated parties. In the interest of transparency and fairness, the Inspectorate has implemented internal appeal processes to facilitate the resolution of contentious issues that arise in making some of its decisions. The Inspectorate will, however, ensure such internal appeals do not compromise its compliance and enforcement activities.

Issue #4: Many expressed concern regarding specificity of observations

The intent of this guide is to help classify the severity of observations noted during inspections of clinical trials. Overall, the evaluation will commensurate with the nature and extent of the deviations (i.e. severity). The specific examples provided in this document would apply to specific inspected parties and should be interpreted case by case.

The appendices attached to this document provide examples of observations, listed in decreasing level of severity. Please note that the list of observations in each appendix **is not exhaustive** and that additional observations may be added if and when appropriate.

Observations classified as major may be upgraded to critical when accompanied with an arrow up sign (↑), depending on the quantity and/or nature of the deviations.

Issue #5: Many comments were received regarding the definitions

The definitions included in the guide are provided to complement those already available in the *Regulations*, the Inspectorate's [Compliance and Enforcement Policy](#), or the [Inspection Strategy for Clinical Trials](#).

Do not hesitate to communicate with the GCP Coordinator for any questions or details by e-mail:

GCP_BPC@hc-sc.gc.ca

Thank you for your participation.