Health Canada Santé Canada

Your Health and Safety... Our priority

Votre santé et votre Securité… notre priorité

Health Canada's GCP Compliance Program

Association of Clinical Research Professionals Canadian Chapter

Via Webinar
December 5, 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.

Health Products and Food Branch Inspectorate

L'Inspectorat de la Direction générale des produits de santé et des aliments

Overview

- Organizational structure
- Regulatory framework
- Inspection process
- Common GCP issues and observations
- Available guidance
- Program updates

Clinical Trial Oversight

Health Canada

Therapeutic Products Directorate (TPD) and Biologics and Genetic Therapies Directorate (BGTD)

- CTA
- CTA-A, CTA-N
- AE Reporting

Communication

Inspectorate

- Coordination

Communication

Regions

- Inspections
- Compliance verifications and investigations

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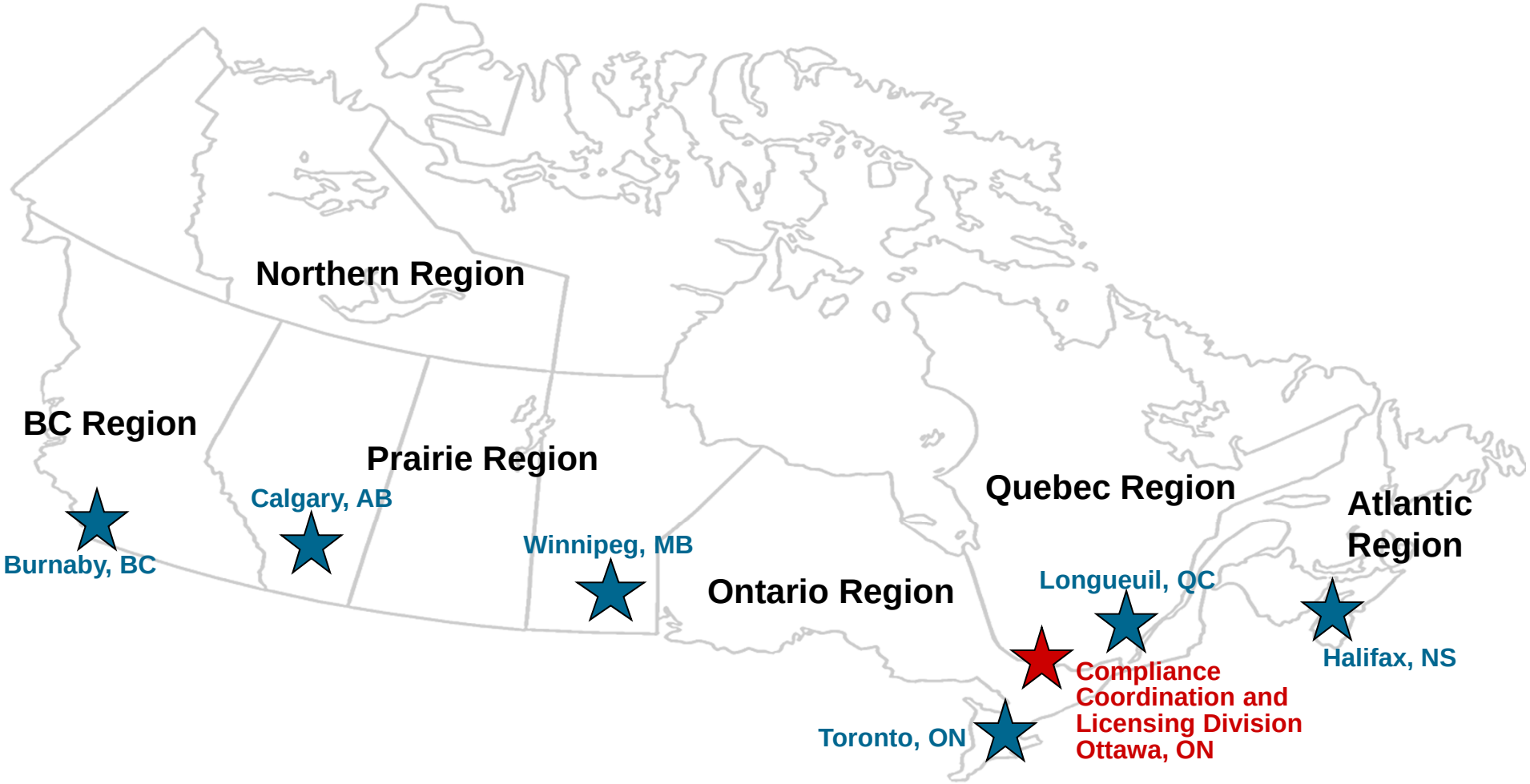
Inspection Program



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Clinical Trials Regulatory Framework

Food and Drugs Act (FDA)

- Authority to inspect under Section 23 of the *Food and Drugs Act*
- POL-0001 *Compliance and Enforcement Policy*

Food and Drug Regulations (FDR), Division 5 "Drugs for Clinical Trials Involving Human Subjects"

- Came into force on September 1, 2001
- Includes the requirement for good clinical practices
- Does not apply to Natural Health Products or Medical Devices (other regulations apply)

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International Conference on Harmonisation (ICH) E6

ICH Topic E6, “Good Clinical Practice: Consolidated Guidance” was adopted by Health Canada in 1997

- Supports and further describes the good clinical practices required by the *Food and Drug Regulations*
- An international, ethical, and scientific standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials
- Consistent with the Declaration of Helsinki
- Internationally adopted in order to increase confidence that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

Inspection Program

Main objectives of clinical trial inspections:

- Protection of subjects enrolled in clinical trials;
- Increase confidence that the data collected and subsequently submitted to Health Canada is valid; and
- Verify compliance to Division 5 of the *FDR* which includes the principles of Good Clinical Practices (GCP).

Inspection Strategy

Inspection Strategy for Clinical Trials (POL-0030)

- Average time of 5 days per inspection;
- 1 or 2 inspectors per inspection;
- Inspections are scheduled and announced
  - The notification occurs a minimum of 5 days before the inspection is conducted;
  - The notification is also sent to the sponsor.
- Unannounced inspections may be conducted when deemed necessary.

Inspection Process

How an inspection proceeds:

- Opening meeting
  - Introduction of participants (site, sponsor, HC)
  - Explanation of scope and purpose
  - Collection of site information
  - Inspection logistics/schedule
- Site tour
  - Patient areas
  - Drug storage
  - Record storage
  - Pharmacy
  - Laboratory

Inspection Process

Inspection procedure cont'd…

- Interviews
- Review of documentation
  - HC authorization/correspondence
  - REB approvals/correspondence
  - Informed consent
    - Procedure
    - Contents
    - REB approval
    - 100% check for signature
- Ongoing identification of observations throughout the inspection

Inspection Process

Inspection procedure cont'd…

- Closing meeting
  - Review of scope and purpose
  - Explanation of risk ratings
  - Presentation of observations and overall inspection compliance rating
  - Discussion of inspection and observations
  - Review of process and timelines for:
    - Issuance of draft exit notice and exit interview
    - Issuance of final exit notice
    - Sponsor's response to exit notice with corrective actions
    - Informal dispute mechanism
  - Other discussion, questions and answers

Inspection Process

What is reviewed during an inspection:

- Adherence to protocol
- Adherence to other procedures
- Training
- Drug quality
- Drug accountability and disposition
- Adverse event reporting
- Verification of source data reported on Case Report Forms (CRFs)

Inspection Report

Inspection Exit Notice is prepared

- Includes information such as:
  - Site profile
  - Officials
  - Product used in the trial
  - Protocol title/number
- Observations are recorded and assigned a risk in accordance with *Guide-0043 : Classification of Observations Made in the Conduct of Clinical Trials*
- Observations are categorized according to **risk**:
  - Critical (Risk 1)
  - Major (Risk 2)
  - Minor (Risk 3)

Inspection Report

Risk Ratings of Observations

- *Risk 1 observations:*
  - Clinical trial not authorized, as required and in accordance with Division 5 of the *Food and Drug Regulations.*
  - Evidence of fraud such as “fabricating” subjects, falsification of study data.
  - Misrepresentation or falsification of data submitted to obtain authorization to conduct clinical trials.
- *Risk 2 observations:*
  - Failure to report a REB that previously refused to approve a trial.
  - Informed consent not obtained from subjects before enrolment in the trial or after major amendments to the ICF.
- *Risk 3 observations:*
  - Date for the commencement of a clinical trial was earlier than that stated in the application.

Inspection Report

An overall rating is assigned to the inspection:

- ***Compliant ("C") rating:*** Only minor and major (depending on the case) observations are reported.
- ***Non-compliant ("NC") rating:*** One or many critical observations, or repetition of major observations reported during a previous inspection; may result in suspension of the trial.

Common Sponsor-Investigator Issues

- Typically stem from lack of awareness or understanding of the regulatory requirements
- Recognized that resources may be an issue
- Challenges inherent in working within a large, multi-unit organization, aspects over which the sponsor-investigator may not always have direct control
- Underlying principle in systems implemented should always be reduction of risk and quality

Site/Investigator selection and training

- Sponsor must ensure that sites are adequately resourced and equipped to properly conduct the study protocol (staff, facilities, equipment, etc.)
- Sponsor is responsible for ensuring that investigators and their staff receive adequate and appropriate training on the protocol and are educated with respect to applicable regulatory requirements.
- Sponsor is responsible for ensuring that all sites have processes and procedures in place to assure that the trial is conducted in accordance with GCP.

Labelling

- The sponsor is responsible for ensuring that study drug is labelled in accordance with C.05.011, including (in both official languages):
  - a statement indicating that the drug is an investigational drug to be used only by a qualified investigator
  - the name, number or identifying mark of the drug
  - the expiration date of the drug
  - the recommended storage conditions for the drug
  - the lot number of the drug
  - the name and address of the sponsor
  - the protocol code or identification

Drug handling, storage, accountability

- Sponsor is responsible for ensuring that the study drug gets from source to sites under conditions which will not compromise safety and effectiveness, and which is in accordance with the drug's stability profile and the study protocol.
- Sponsor is responsible for ensuring that sites properly handle and store the drug under conditions which are secure/segregated/temperature appropriate as applicable.
- Sponsor is responsible for ensuring that import requirements pertaining to the product and the sites are met.
- Sponsor is responsible for ensuring that emergency unblinding procedures are in place, as applicable.

Systems and Procedures

Common deficiencies observed under C.05.010(c):

There was no written procedure to describe, or the procedure did not adequately address:

- Informed consent process;
- Record retention – when, where and how to archive research files;
- AE reporting;
- Handling of the drug;
- Emergency procedures in the event of power failure for the drug storage.

Systems and Procedures

Common deficiencies observed under C.05.010(c):

- There was no maintenance/calibration program in place for the equipment used in the clinical trial (e.g. centrifuge, ECG, body mass scale)
- At the time of the inspection there was no documentation available to demonstrate that … had been validated (e.g., electronic trial data system)

Systems and Procedures

Common deficiencies observed under C.05.010(c):

- No monitoring had been conducted to date at …
- Monitoring at this site is not adequate to assure that the trial is conducted in accordance with good clinical practices and the study protocol.
- The sponsor does not have a documented procedure for monitoring.

Systems and Procedures: Monitoring

- Adequate monitoring of a trial is essential.
- Section 5.18 of ICH E6: GCP provides detailed guidance with respect to monitoring.
- Frequency and scope of monitoring should be risk-based, taking into consideration:
    - objective
    - purpose
    - design
    - complexity
    - blinding
    - size, and
    - endpoints of the trial

Systems and Procedures: Monitoring

- For on-site or off-site monitoring, monitors and QIs should follow a sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.
- For qualified investigator sponsored studies conducted by a group of physicians at different sites, it is the physician identified as the sponsor on the CTA who is required to monitor the trial at all investigative sites and verify that:
  - The requirements of Division 5 of the *Food and Drug Regulations* are met at each site and,
  - The trial is conducted according to the principles good clinical practices of ICH E6: GCP.

Records

Examples of deficiencies observed:

- C.05.012(1) Records

"There was no procedure or documentation available to demonstrate what study records would be maintained by the site, what personnel were authorized to access the records, measures to assure that records are kept in a secure location which maintains their integrity and confidentiality, and that records would be kept for 25 years."

Records

- Retention of study records for 25 years is required for all studies which have been issued an NOL, or for which a CTA-A has been filed since September 1, 2001.
- Sponsors are required to record, handle, maintain and store all information that pertains to their activities in a way that allows complete and accurate reporting as well as its interpretation and verification.
- Information should be recorded in a way that allows to establish that the clinical trial is conducted in accordance with GCP and the *Regulations.*
- All records should be readily available and located in Canada (refer to section 8 of ICH E6: GCP for guidance on maintenance by sponsor/site).

Training

- Regulations require that each individual involved in the conduct of the clinical trial is qualified by education, training and experience to perform his or her respective tasks.
- Delivery, content, manner of documentation, and frequency of training not specified in *Regulations.*
- Acceptable documentation of training may include:
  - Meeting minutes (including attendees)
  - Slide decks to reflect content
  - Sign off sheets for protocols/IB/work instructions/SOPs

Other Requirements: Drugs and NHPs

- Other drug/NHP products used in the study (e.g. symptom/side effect relief, rescue medications) which are not investigational or included under the NOL must be authorized for sale in Canada.
  - Drug products must have a valid DIN and be used within their approved indication/population.
  - Natural health products (NHPs) must have an NPN, DIN-HM, or EN and be used within their approved indication/population.

Other Requirements: Medical Devices

- Medical devices used in a clinical trial must be licensed (as applicable) for use in Canada.
- Common examples include pregnancy test kits, digital thermometers, blood pressure monitors, ECGs.
- The sponsor is responsible for ensuring that devices provided to Canadian sites meet all applicable Canadian requirements.
- To verify that a device is licensed in Canada, visit www.mdall.ca

GCP Current Guidance

- Guide-0043 *Classification of observations made in the conduct of inspections of clinical trials*
- Guide-0068 *Guidance for Records Related to Clinical Trials*
- Guide-0036 *Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines Drugs Used in Clinical Trials*
- *Good Clinical Practice: Consolidated Guideline, International Conference on Harmonization (ICH) Topic E6*

Program Initiatives

- Release of Summary Report of Inspections of Clinical Trials Conducted from April 2004 to March 2011 (March 28, 2012)
- GCP Information Sessions (“GCP Roadshow”) – Seven sessions in six cities across Canada during November 2010
- Stakeholder mailing list for new documents and program news
- GCP pre-inspection package was developed which includes:
  - Frequently Asked Questions
  - Checklists
  - Feedback Form
- The following vanity url was created: www.healthcanada.gc.ca/gcp
- Inspection Strategy is under review
- GCP Interpretive Guidance document is in development

Questions?

E-mail: GCP_BPC@hc-sc.gc.ca

Further information available online at:

Health Canada → Drugs and Health Products →
Compliance and Enforcement → Good Clinical Practices

www.healthcanada.gc.ca/gcp

www.santecanada.gc.ca/bpc

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Thank you!

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Health Canada