GCP Compliance in Canada: Division 5 and Other Requirements

Association of Clinical Research Professionals (ACRP)

Via Webinar
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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.

Overview

- Organizational Overview, Roles and Responsibilities
- Regulatory Framework
- GCP Inspections and Statistics
- Recent Compliance Issues and FAQs
- Program Updates

Objectives

Following this presentation, participants should be able to:

- Describe how Health Canada regulates clinical trials in Canada, including its regulatory framework and inspection program.
- Identify common compliance issues and apply considerations to mitigate them.
- Discuss recent GCP Compliance Program initiatives and updates.

Roles and Responsibilities

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
- Investigations

Structure

*Partial Structure

Health Canada

Health Products and Food Branch (HPFB)

HPFB Inspectorate

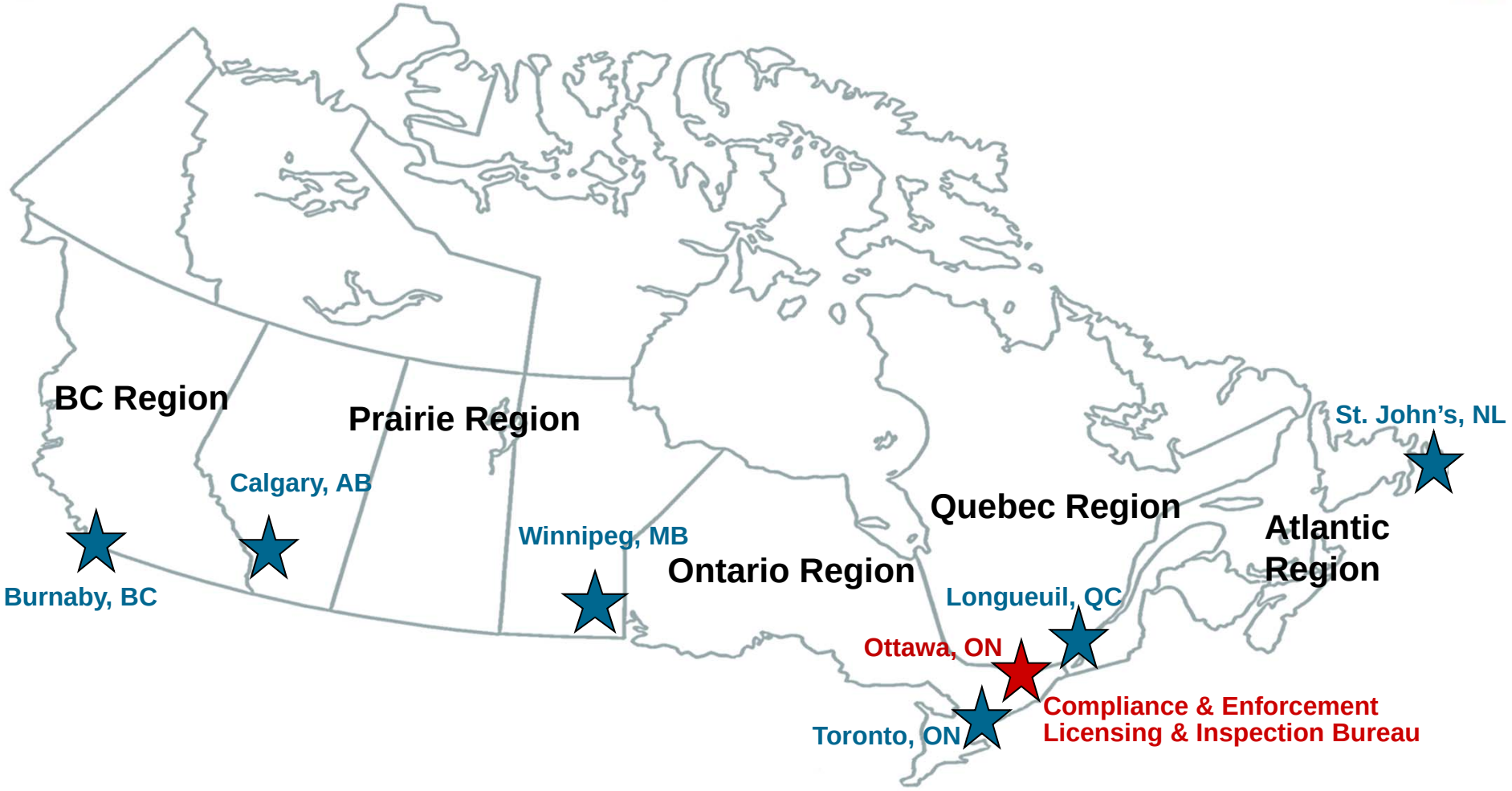
Good Clinical Practices Compliance Unit

Regions and Programs Bureau (RAPB)

Regional Offices

Halifax, Nova Scotia
Longueuil, Quebec
Toronto, Ontario
Winnipeg, Manitoba
Edmonton, Alberta
Burnaby, British Columbia

Clinical Trial Oversight



Regulatory Framework

Clinical Trials Regulatory Framework

Food and Drugs Act

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

Food and Drug Regulations, Division 5

"Drugs for Clinical Trials Involving Human Subjects"

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

Clinical Trials Regulatory Framework

Food and Drug Regulations (FDR)

- Requirements apply to marketed drugs used in the study (but not included under the NOL)

Natural Health Products Regulations (NHPR)

- Requirements apply to natural health products used in the study (which are not the investigational product)

Medical Devices Regulations (MDR)

- Requirements apply to medical devices imported/sold as part of a drug clinical trial
- Medical devices used in drug clinical trials must be licensed
- Devices under study are subject to the submission of an Investigational Testing Application

Clinical Trial Inspections

Clinical Trial Inspections

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

Selection of Sites for Inspection

- Studies for inspection are selected based on variety of risk-based criteria, including:
  - the phase in the drug development process
  - the complexity of the clinical trial design
  - subject population
  - novel therapies/dosage forms
  - significant or frequent reports of adverse events
  - notices from sponsors of protocol deviations
  - other factors
- Collaboration between the directorates who review CTAs and the Inspectorate in identifying studies for inspection

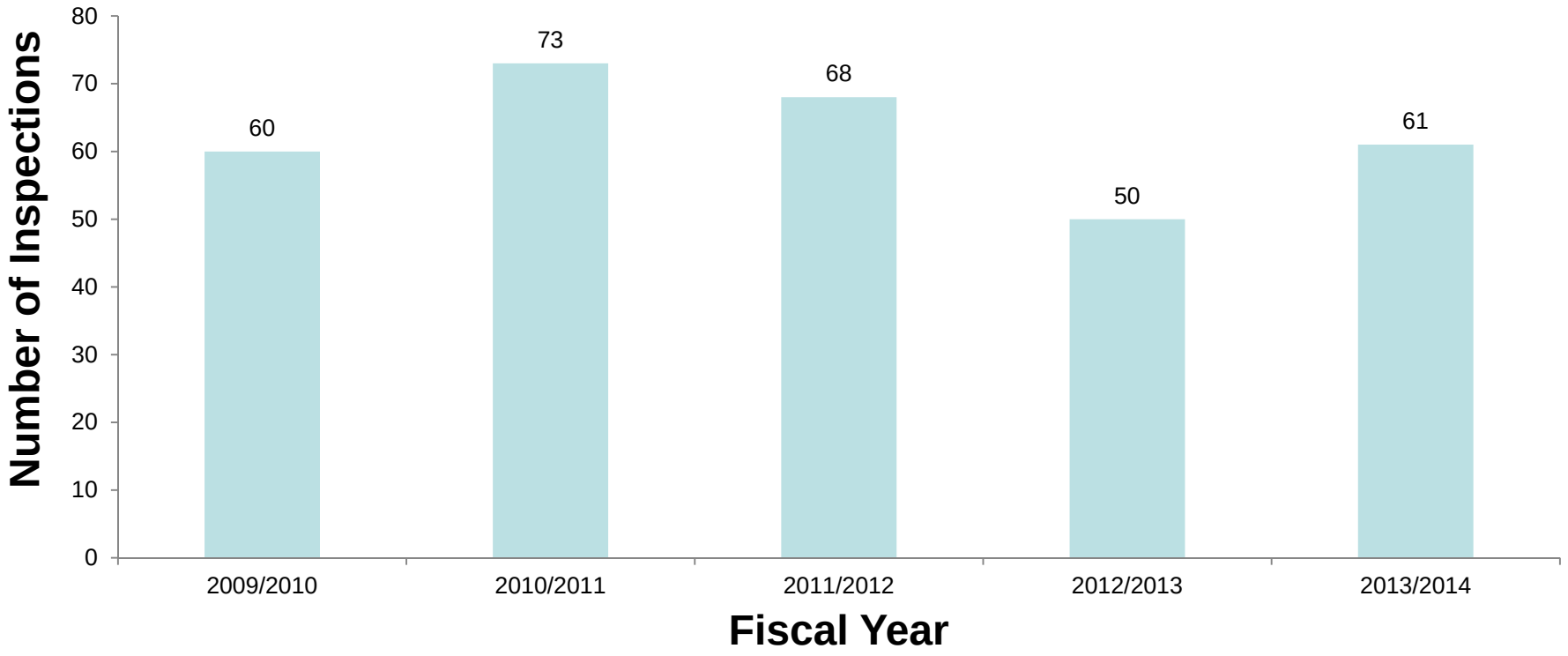
Selection of Sites for Inspection

- From lists of identified studies, the Inspectorate requests site information from sponsors, including:
  - location of each site
  - name of each qualified investigator
  - status of the study (not yet enrolling subjects, dosing, in follow up, closed)
  - number of subjects enrolled, active and withdrawn
  - number of SAEs
  - parties involved (e.g., SMO, CRO, etc.)

Selection of Sites for Inspection

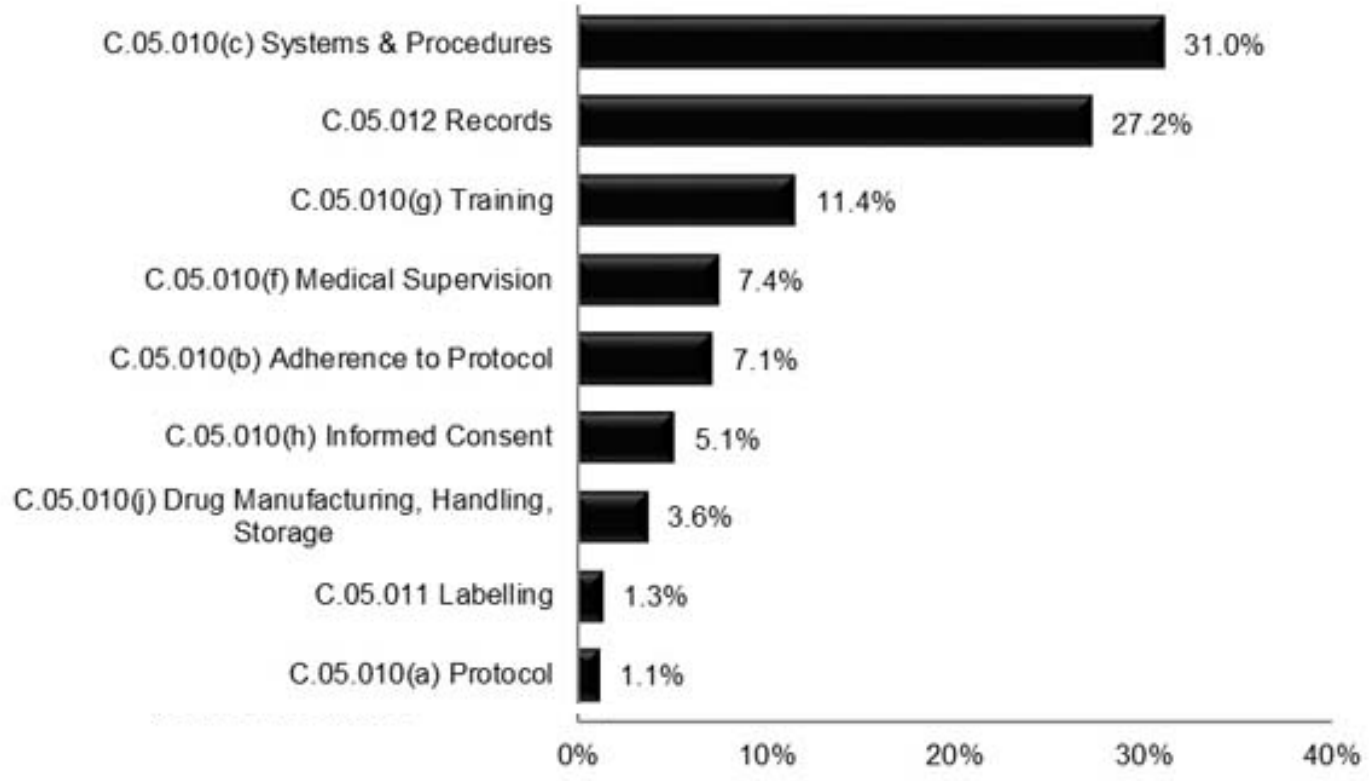
- The Inspectorate then uses additional criteria to make the final selection of sites for inspection, including:
  - type of site (e.g., located at large institution vs. small clinic)
  - geographic location (i.e., sites selected throughout region)
  - number of clinical trials conducted at the site
  - regional concerns / priorities
  - required follow-up regarding a given regulated party
  - inspection history of QI and sponsor

Inspection Program Statistics



Regulatory Sections Cited Most Frequently

During FY 2013/2014, observations were most frequently cited against the following Division 5 sections:



Non-Compliance

- Of the 61 inspections conducted during FY 2013/2014, five (5) received a Non-compliant rating.

- In the cases where a "NC" rating was assigned, the Inspectorate took action, including requiring the inspected parties to immediately correct the deficiencies, and recommending to the Health Canada directorate which issued the authorization, TPD or BGTD, that the authorization to conduct the inspected study be suspended or cancelled.

Compliance Issues and FAQs

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
    - design
    - complexity
    - blinding
    - size
    - endpoints of the trial

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 of good clinical practices of ICH E6: GCP.

Maintenance/Calibration of Equipment

- Regular and proper maintenance of equipment used in a study is critical to patient safety and the integrity of data collected in a clinical trial.
- Maintenance and calibration of equipment is considered to be a requirement under Division 5 and documentation of this must be available upon inspection.
- Documentation may include (but not limited to):
  - Routine calibration records and procedures
  - Maintenance and repair records
  - Equipment manuals

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 or DIN-HM and be used within their approved indication/population.

Other Requirements: Medical Devices

- Medical devices used in a clinical trial must be licensed (Class 2, 3, and 4) for use in Canada.
- Common examples include pregnancy test kits, digital thermometers, blood pressure monitors, ECGs.
- Class I devices must be manufactured or imported by a licensed establishment.
- 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

Labelling

- Labels are required to include the required information in both English and French.
- The definition of a label permits that some information may accompany the drug as a package insert, or affixed to the secondary container.
- Identification/traceability must be maintained via a lot number, barcode, or other identifier, and this must be affixed to the primary container.
- Blinding must be protected whichever system is used.

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

Training

- In general, staff involved in the study are expected to have documented training on those aspects of the study for which they have been delegated responsibilities.
- Study staff, commensurate with their involvement in clinical research, should be knowledgeable of good clinical practices and Canadian regulatory requirements.
- Frequency of “refresher” training should be in accordance with an individual’s involvement in clinical research and ongoing familiarity with the requirements.

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 demonstrates that the clinical trial is conducted in accordance with GCP and the *Regulations.*
- All records (including electronic records) should be readily available and located in Canada (refer to section 8 of ICH E6: GCP for guidance on maintenance by sponsor/site).

Electronic Records

- Sponsors are referred to ICH E6 Section 5.5.3 for guidance on management of electronic records.
- Study records may be transferred to electronic media storage, preferably at the completion of a trial, and only if the:
  - Corrections to the original data are clearly captured in the secondary medium.
  - Person performing the transfer attests (signs and dates an attestation) that the secondary documents are true copies of their respective primary documents.
  - Transfer process is fully validated.
- When transferring to a secondary medium, standards, such as those developed by the Canadian General Standard Board, or equivalent, should be used.

Validation of Electronic Systems

- Any electronic system used to capture, process, manage and/or archive clinical trial information should be adequately validated and evidence of validation should be readily available to Health Canada's Inspectors.
- Documentation of the system design specifications and a validation plan based on those should be developed.
- The validation plan should include:
  - Objectives and scope
  - Nature of and time at which validation activities should be performed
  - Personnel delegated for the conduct of the validation
  - Security measures
  - Main features of the system including the mode of interaction with other systems and procedures

Service Providers

- Sponsors are ultimately responsible for the conduct of clinical trials they initiate in Canada.
- This includes responsibility for the activities of third parties, such as site management organizations (SMOs), contract research organizations (CROs), laboratories, document retention services, etc., they contract to support trial activities.
- Delegated activities must be clearly articulated in written agreements.
- The sponsor must ensure that delegated third party service providers conduct regulated clinical trial activities in compliance with all applicable regulatory requirements and good clinical practices.

Submission of Trial Site Information

- C.05.05(c)(ix) requires that every sponsor submit, for each clinical trial application,

  "for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the qualified investigator if known at the time of the application"

- C.05.06(1)(d) requires that this information must be submitted before the sale or importation of the drug at a clinical trial site if it was not submitted in respect of that clinical trial site at the time of submitting the application.

Clinical Trial Site Information (CTSI) Forms

- Health Canada has a form to facilitate the submission of clinical trial site information, via fax (to BGTD and TPD) or email to TPD (preferred).

- All CTSI forms, whether accompanying a Clinical Trial Application (CTA) or an Amendment (CTA-A), or sent independently of a CTA or CTA-A, must be sent directly to the applicable Directorate.

- The CTSI template can be found on Health Canada's website:

  http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctsif_dldcf-eng.php

Shipping and Transportation

- The sponsor is responsible for ensuring that the clinical trial is conducted in accordance with GCP; this includes controlling the factors which affect the quality of an investigational product (IP) during its storage and transportation.
- Systems must be in place for the monitoring, storage conditions, transportation and disposition of investigational products.
- Regardless of the agreements in place for the importation of the product, the sponsor ultimately bears responsibility for the correct handling and storage of the product to be used in the clinical trial.

Shipping and Transportation

- The sponsor must ensure that investigational product is transported in a manner that ensures the products will be maintained within an acceptable temperature range as defined in the approved labeling and supported by stability data.

- This may include shipment temperature monitoring, route mapping studies, and/or other additional transport studies to demonstrate adherence to labeled storage conditions.

Importation

- Investigational product may be imported and shipped directly to clinical trial sites.
- Site name and address on Clinical Trial Site Information (CTSI) form should match that on the shipping documentation.
- Shipments of imported study drugs should include a copy of the NOL.

Importation

- If additional drugs (e.g., comparator, concomitant and rescue medications) are being imported for the purpose of the clinical trial, a list of these drugs should be provided using the Summary of Additional Drugs Form (SOAD).
- The SOAD may be replicated to capture all additional drugs to be imported to facilitate processing at the Port of Entry.
- If this information is not known at the time of application, or changes after the CTA is authorized, sponsors may submit a SOAD to the appropriate review directorate as a CTA-N.

Program Updates

Guidance for CT Sponsors

- New *Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications* was published in May 2013
  - revised based on stakeholder consultation processes
  - consistent with the new Common Technical Document (CTD) format
  - includes application requirements for comparative bioavailability trials and filing requirements for the importation of clinical trial supplies
  - clarifications to amendment and notification requirements, study termination and closure criteria, application and review processes, and adverse drug reaction reporting criteria as well as format requirements
- Guide is available on Health Canada's website:
  http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php

Transparency

- Two initiatives have recently been implemented as part of Health Canada's openness and transparency agenda to fulfill commitments made in response to recommendations made by the Office of the Auditor General in the OAG Pharma Audit tabled in November 2011.

1) Posting of annual summary clinical trial inspection reports

(*Inspectorate Program Annual Inspection Summary Report 2013/2014* was posted to HC website on August 29, 2014)

2) Launch of Clinical Trials Database

(http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php)

Clinical Trials Database

- Health Canada's Clinical Trials Database was launched in May 2013.
- Provides a public listing of specific information relating to phase I, II and III clinical trials in patients.
- The database is not a registry, but is managed by Health Canada and provides a source of information about authorized Canadian clinical trials involving human pharmaceutical and biological drugs.
- The database lists trials that were authorized by Health Canada starting April 1, 2013. The database will be populated with information about each clinical trial after Health Canada issues its No Objection Letter (NOL).

Canada Vigilance E-reporting

- Electronic reporting of adverse drug reactions (ADR) is currently in production with some sponsors operating a gateway.

- Sponsors who have an established connection with the Canada Vigilance Production stream should submit their ADR reports only once through the Canada Vigilance gateway; reports no longer need to be sent in duplicate to multiple directorates: TPD, BGTD, MHPD and/or NHPD.

- For sponsors who have not yet established this connection, they should continue submitting their reports by fax or by mail to all the appropriate directorates.

Canada Vigilance E-reporting

- Scope includes pharmaceutical drugs, biologics, radiopharmaceutical drugs and natural health products

- For more information on E-reporting, contact the Trading Partner Management Office (TPMO):
  TPMO_BGPC@hc-sc.gc.ca

- Additional guidance on adverse event reporting for drugs used in clinical trial can be found on Health Canada's website:
  http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.php

International Activities

- Health Canada maintains relationships with numerous other regulatory authorities, including EMA, MHRA, and US FDA as well as:
  - Participates in inspection training initiatives, meetings, and discussions on specific issues
  - Attends international conferences to share and promote awareness of Canadian regulatory requirements for clinical trials
  - Attends inspections in Canada conducted by foreign regulators when possible

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

Thank you!

Camille Proulx

Compliance Officer

Good Clinical Practices (GCP) Compliance Unit

Health Products and Food Branch Inspectorate

Health Canada