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Clinical Trial Compliance Program

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Regulatory Operations and Enforcement Branch (ROEB)

N2 Regional Meeting
May 13th, 2019
Cullen Theatre, First Floor Conference Centre
St. Paul's Hospital, Vancouver, BC

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Overview

- Organizational Changes, Roles and Responsibilities
- Regulatory Framework
- Clinical Trial Inspections and Statistics
- Common Compliance Issues and FAQs
- Program Updates

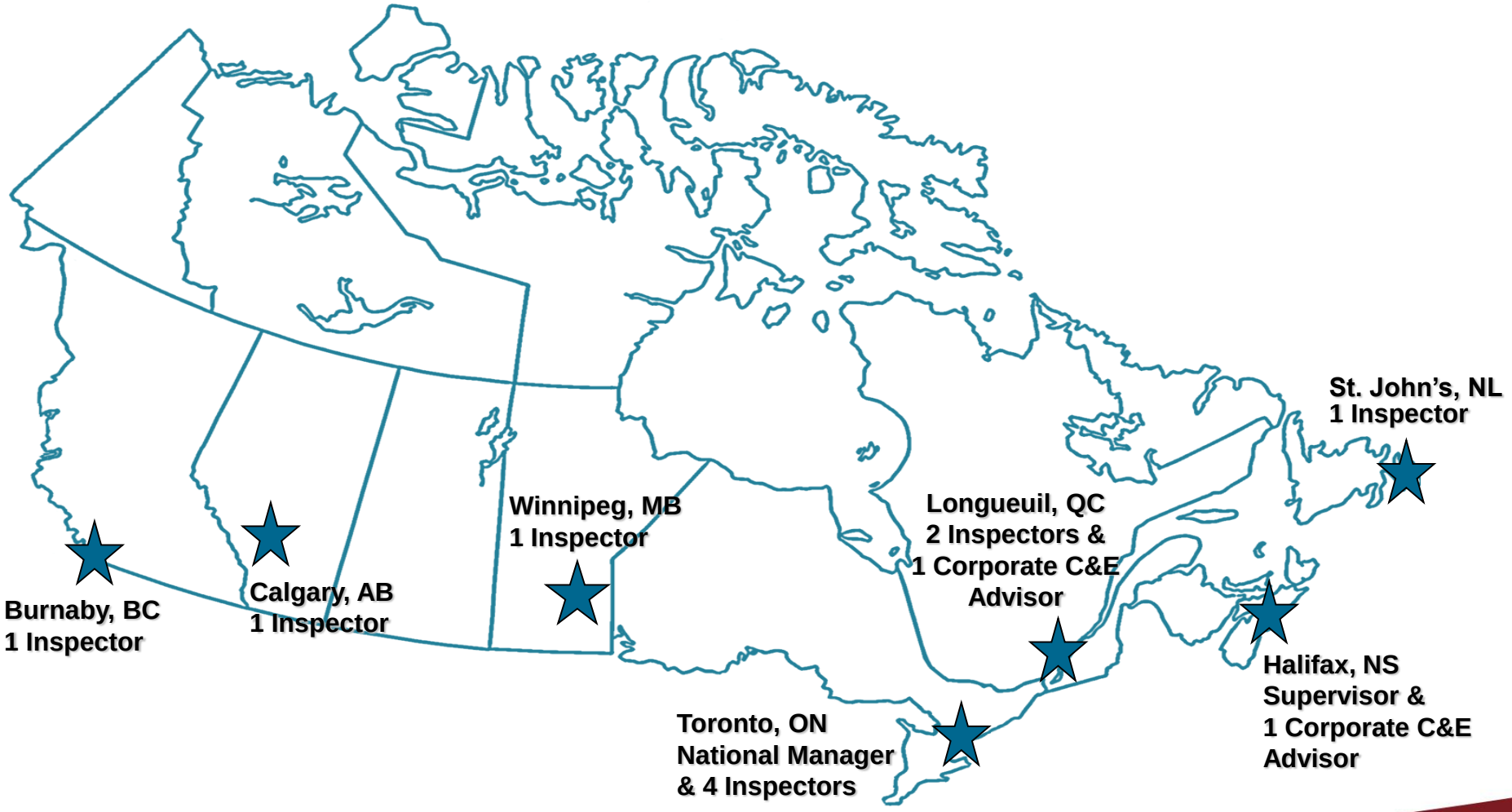
Regulatory Operations and Regions Branch (RORB) now Regulatory Operations and Enforcement Branch (ROEB)

- Created on April 2016 with 7 Directorates, 1000+ staff
- Merging of the Health Products and Food Branch Inspectorate (HPFB Inspectorate) with the Regions and Programs Bureau (RAPB)
- To strengthen accountability and simplify the delivery of health product compliance and enforcement programs
- Clarity of compliance and enforcement roles and responsibilities, one management structure, one budget, and more consistency in program delivery

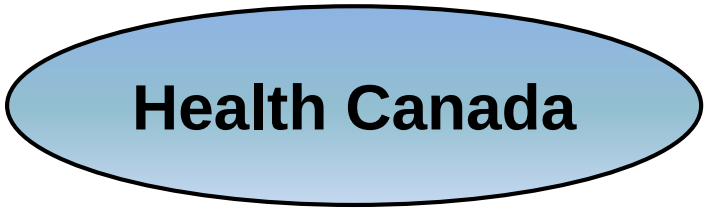
Clinical Trial Compliance Program

National Manager – Hocine Abid, Toronto, ON

Inspection Supervisor – TBD



Health Canada Roles and Responsibilities in Clinical Trial Oversight



Health Products and Food Branch (HPFB)

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

- Clinical Trial Application (CTA)
- CTA- Amendment (CTA-A), CTA-Notification (CTA-N)
- AE (Adverse Event) Reporting
- No Objection Letter (NOL), Suspension, Cancellation

Communication

Regulatory Operations and Enforcement Branch (ROEB)

Medical Devices and Clinical Compliance Directorate (MDCCD)

- Inspection
- Compliance Verification
- Investigation

Regulatory Framework

Regulatory Framework

Food and Drugs Act (FDA)

- Authority to inspect under Section 23 of the *FDA*

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

- Came into force on September 1, 2001
- Includes the requirements for Good Clinical Practices (GCP)
- Does NOT apply to Natural Health Product (NHP) Clinical Trials or Investigational Testing of Medical Devices (MD); other regulations apply

Clinical Trials Regulatory Framework

- **Overview of Part C, Division 5 of the *FDR:***
  - C.05.001 (Interpretation)
  - C.05.002 (Application)
  - C.05.003 (Prohibition)
  - C.05.005 (Application for Authorization)
  - C.05.006 (Authorization)
  - C.05.007 (Notification)
  - C.05.008 (Amendment)
  - C.05.009 (Additional Information and Samples)
  - C.05.010 (Sponsor's Obligations – GCP)
  - C.05.011 (Labelling)
  - C.05.012 (Records)
  - C.05.013 (Submission of Information and Samples)
  - C.05.014 (Serious Unexpected Adverse Drug Reactions)
  - C.05.015 (Discontinuance of a Clinical Trial)
  - C.05.016 & C.05.017 (Suspension and Cancellation)

Clinical Trial Inspections

Scope and Strategy of Clinical Trial (CT) Inspections

- Ongoing trials are planned / selected for inspection with the main objectives of patient safety and compliance (Part C, Division 5, GCP, integrity of data)

- Currently, CT Inspections are not pursuant to marketing authorization applications

- The inspection program focuses on:
  - Ongoing clinical trial sites
  - Qualified Investigator (QI) inspections
  - Mostly Phase II and III trials

- Pilot 2017/2018: broader coverage of clinical trials sector

Site / Studies Selection

- **Studies for inspection are selected based on variety of risk-based criteria, including (but not limited to):**
  - 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 (AEs)
  - notices from sponsors of protocol deviations
  - other factors
- **Collaboration between the Directorates (TPD/BGTD) who review CTAs and ROEB in identifying studies for inspection.**

Site / Studies Selection

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

Site / Studies Selection

- **ROEB staff then uses additional criteria to make the final selection of sites for inspection, including (but not limited to):**
  - 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

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

Inspection Report / Exit Notice

Observations & Risk Rating

- Deficiencies or deviations from Part C, Division 5 (of *FDR*) and GCPs are recorded as observations and assigned a risk in accordance with **Guide-0043: *Classification of Observations Made in the Conduct of Clinical Trials***

  www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/classification-observations-conduct-inspections-clinical-trials-guide-0043.html

- The observations are classified as:
  - Critical – Risk 1
  - Major – Risk 2
  - Minor – Risk 3

Inspection Report / Exit Notice

Inspection Rating

- **(C) Compliant:** At the time of the inspection, the regulated party has demonstrated that CT conduct is in compliance with the *Food and Drugs Act* and its associated Regulations.

  - (C) Compliant rating does not mean that there are no observations or corrective actions required.

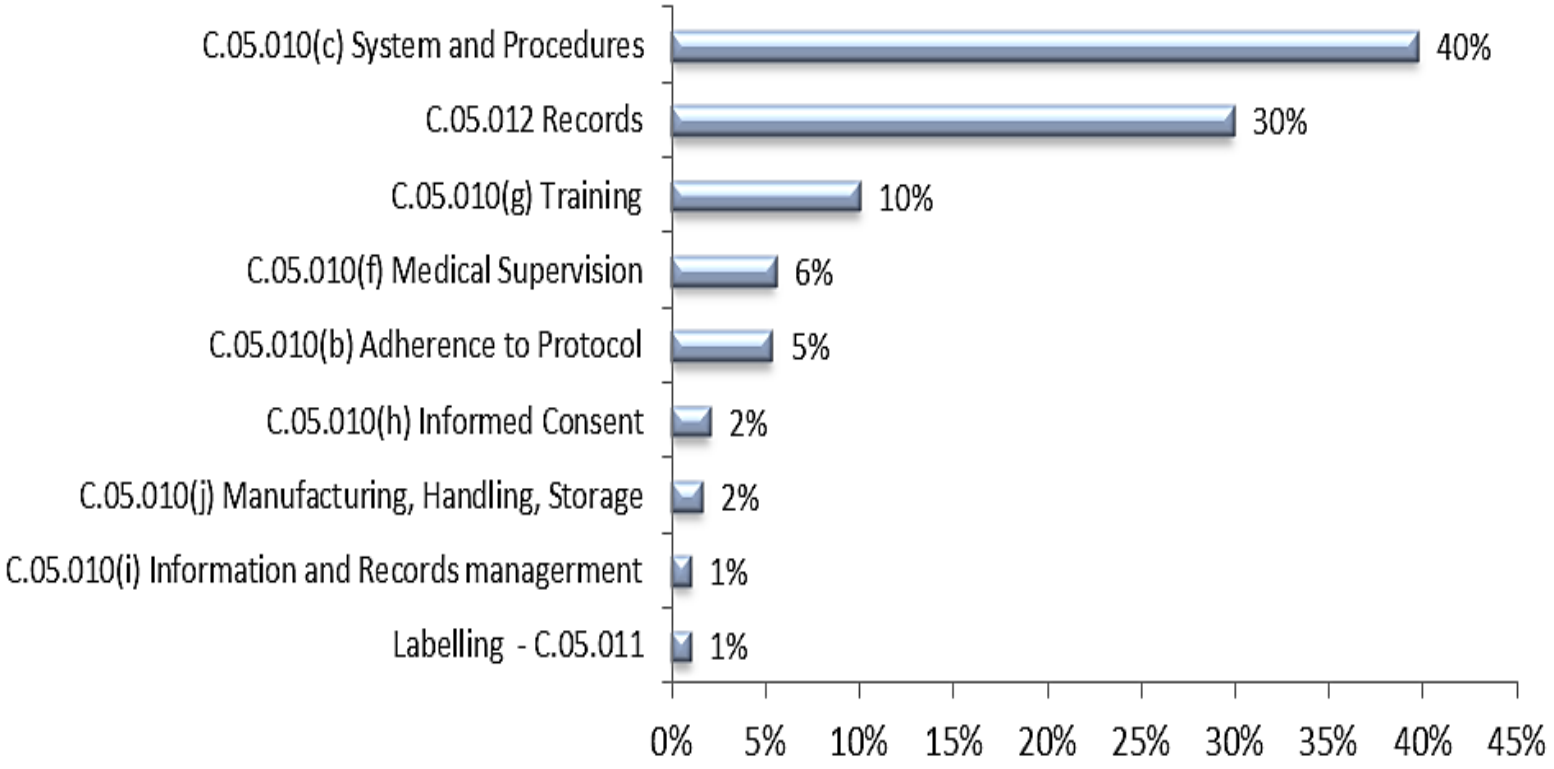
- **(NC) Non-Compliant:** At the time of the inspection, the regulated party has NOT demonstrated that CT conduct is in compliance with the *Food and Drugs Act* and its associated Regulations.

  Additional actions – intent to suspend, immediate suspension (trial at this site / trial at all Canadian sites / all CTs at this site), cancellation.

Common Compliance Issues and FAQs

Regulatory Sections Most Frequently Cited

During fiscal year 2015-2016, observations were most frequently cited against the following Part C, Division 5 sections:



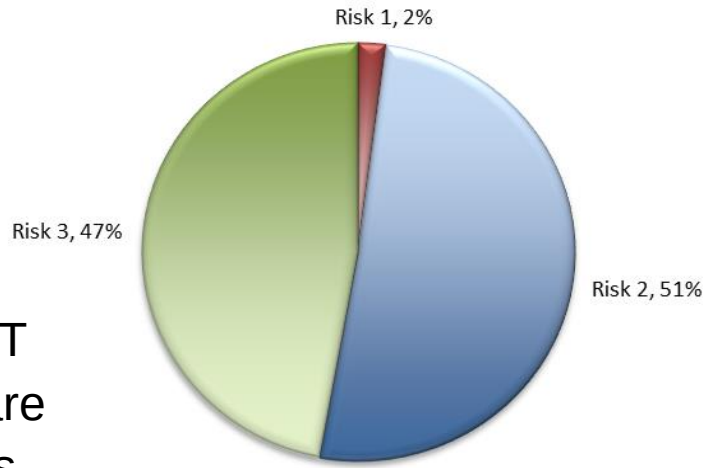
Risk Ratings of 2015-2016 Observations

- In 2015-2016, 488 observations were noted:
  - 2% (10 observations) were given a Risk 1 (critical) rating
  - 51% (248 observations) were given a Risk 2 (major) rating
  - 47% (230 observations) were given a Risk 3 (minor) rating

- Overall Compliance Rate 86%

- All Risk 1 observations were cited against section C.05.010.

This requires the sponsor to ensure, at each CT site, that medical care and medical decisions are under the supervision of a QI, and that systems and procedures are in place to ensure the quality of every aspect of the CT.



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.
- For on-site or off-site monitoring:
  - Monitors and QIs should follow a sponsor's established written SOP as well as those procedures that are specified by the sponsor for monitoring a specific trial.
- For QI 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 sites.

Other Requirements: Drugs, NHPs, Medical Devices

- Other products used in the study (e.g. symptom/side effect relief, rescue medications, medical devices) 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.
  - Medical devices used in a clinical trial must be licensed (Class 2, 3, and 4) for use in Canada www.mdall.ca

Labelling

- Labels are required to include the required information (see C.05.011) 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 CT 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 the Regulations.
  - Acceptable documentation of training may include:
    - Meeting minutes (including attendees)
    - Slide decks to reflect content
    - Sign off sheets for protocols / investigator's brochure (IB) / work instructions / SOPs
- 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 GCP 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.

Validation of Electronic Systems

- Sponsors are referred to ICH E6 Section 5.5.3 for guidance on management of electronic records.
- 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

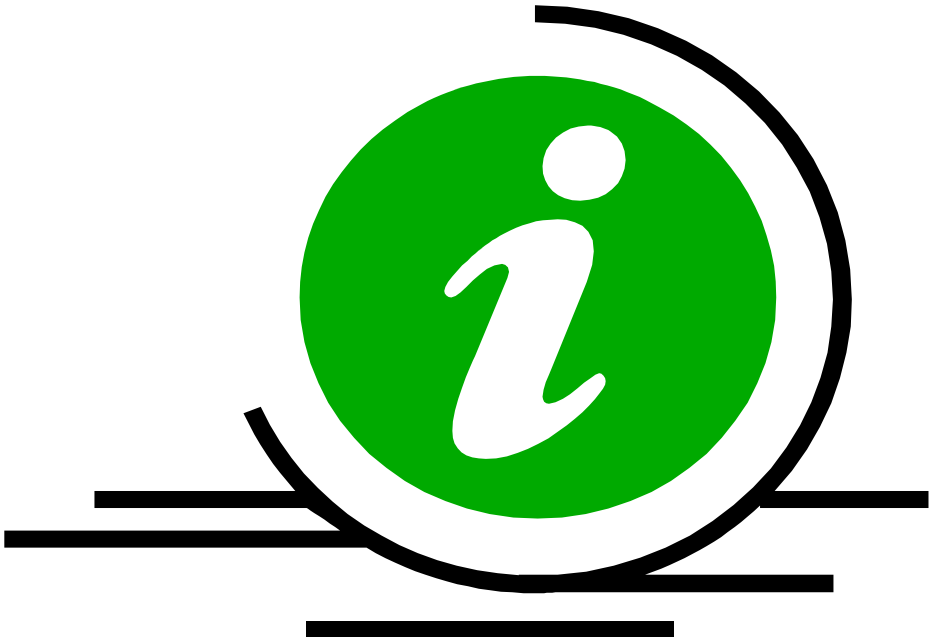
Service Providers

- **Sponsors** are ultimately responsible for the conduct of clinical trials they initiate in Canada.
    - ❖ You can contract out the activity, but not the responsibility!
- 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 GCP.

Importation

- Investigational product may be imported and shipped directly to CT sites.
  - Importers should be authorized by the sponsor. This information should be included in Appendix 1 of the HC/SC 3011 form. Appendix 1 may be replicated as many times as necessary to capture all 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 (and Appendix 1 of HC/SC 3011, if applicable).
  - If additional drugs (e.g. comparator, concomitant and rescue medications) are being imported for the purpose of the CT, 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



Health Canada Initiatives

- ***Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications***
  - Published in May 2013, available on Health Canada's website: www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html#a243

- **Health Canada's Clinical Trials Database**
  - Launched in May 2013, provides a public listing, not a registry.
  - The database lists trials that were authorized by Health Canada starting April 1, 2013: www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database.html

- **Canada Vigilance E-reporting**
  - Guidance on adverse event reporting for drugs used in clinical trial can be found on Health Canada's website: www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/clinical-safety-data-management-definitions-standards-expedited-reporting-topic.html

Transparency

- Several initiatives have been implemented as part of Health Canada's openness and transparency agenda

1) **Posting of Annual Inspection Summary Reports**
   www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/compliance-enforcement/inspectorate-program-annual-inspection-summary-report-2014-2015.html

2) **Launch of Clinical Trials Database**
   www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database.html

3) **Launch of Inspection Tracker: Drug Manufacturing Establishments 2015**
   www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/compliance-enforcement/inspection-tracker-drug-manufacturing-establishments.html

4) **Launch of Clinical Trial Inspection Cards 2015**
   www.healthycanadians.gc.ca/apps/gcp-bpc/index-en.html

Transparency – Clinical Trial Inspection Results

Clinical trial inspections

Clinical trials in Canada for human drugs must meet high safety standards. Canada inspects clinical trials to reduce the risks to people participating in the trials.

To learn more about the clinical trial inspections we conduct, you can visit about clinical trial inspections or browse these inspection results:

- Clinical trial inspections search results
- Non-compliant clinical trial inspections search results

You can also do your own search for clinical trial inspections. These results are updated regularly. Please note that the name of a drug could change over the course of a clinical trial.

Clinical trial search

Sponsor name:

Control number:

Region:

Drug name:

Trial phase:

Inspection start date: yyyy-mm-dd

Rating:

Submit Reset

Report a problem or mistake on this page

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Clinical trial inspections

Search results

Below are the results for clinical trial inspections in Canada.

You can also learn about how clinical trial inspections are conducted in Canada and what inspectors look for.

Showing 1 to 10 of 243 entries | Show 10 entries

Filter items

Control number	Sponsor name	Region	Inspection start date	Drug name	Trial phase	Rating
160296	Gilead Sciences Canada, Inc.	Ontario	2016-06-06	simtuzumab	Phase 2	Inspection in progress
190037	Bayer Inc.	Alberta	2016-06-06	Rivaroxaban (BAY 59-7939)	Phase 3	Inspection in progress
185883	Novo Nordisk Canada Inc.	Quebec	2016-05-25	Semaglutide	Phase 2	Inspection in progress
177174	GlaxoSmithKline Inc.	Ontario	2016-05-23	Pazopanib	Phase 2	Inspection in progress
187331	Cutanea Life Sciences Inc.	British Columbia	2016-05-16	Omiganan Topical Gel 1.6%	Phase 3	Compliant
174017	Pfizer Canada Inc.	Alberta	2016-05-09	Bococizumab (PF-04950615)	Phase 3	Compliant
140934	Children's Oncology Group	Atlantic (New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	2016-05-02	Oncaspar (pegaspargase)	Phase 3	Compliant

ICH E6(R2)

- Health Canada to look at implementation timelines, stakeholder engagement and training
- Health Canada and FDA Joint Public Consultation on ICH Guidelines for Registration of Pharmaceuticals for Human Use, April 2017
- The current target date for full implementation of the Integrated Addendum has been extended to April 1st, 2019 www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/good-clinical-practice-consolidated-guideline-topic.html
- **GUI-0100**: **"Guidance document – Part C, Division 5 of the FDR",** incorporating ICH E6(R2) Addendum, public consultation from Dec 15, 2017 to April 15, 2018, and should be finalised 2018-19 www.canada.ca/en/health-canada/programs/consultation-drugs-clinical-trials-involving-human-subjects.html

Clinical Trial Compliance Program Review

- Originally designed in 2002, Health Canada started a review of its Clinical Trial Compliance Program in 2016 (still underway)
- Program mandate remains the same (safety & compliance)
- Broad direction is to rebalance the mix of inspections to get broader coverage of phases of trials and players (sponsors, QIs, CROs, SMOs, etc.) in the clinical trials sector

Clinical Trial Compliance Program Review

- In fiscal year 2017-18, ROEB conducted pilot inspections (in addition to regular program inspections) to asses risks/benefits in the drug lifecycle.
- The following types of pilot inspections were conducted:
  - International inspection (x1) – closed trial for a site in a non-PIC/S country (in support of a submission)
  - Bioequivalence (x2) – trials or sites in Canada, trial open or closed
  - Sponsor (x2) – sites in Canada, trial open or closed
  - CRO (x2) – CRO systems or specific trials

Questions?

Clinical Trial Compliance Program

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

Further information available online at:

www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html