Session 4: Agency Updates: Policies, Guidances, and Initiatives

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
February 14, 2024 – 1:20 – 2:05 PM

Moderator: **Emily Gebbia, JD**
Associate Director of Regulatory Development | OSI | OC
CDER | FDA

Stephen Vinter, BSc, Cchem
Head of Compliance Team 1 | MHRA

Hocine Abid, MD, MBA
National Manager | ROEB | HC

MHRA Updates

Stephen Vinter
Head Compliance Team 1
Healthcare Quality and Access
MHRA

A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
February 13, 2024

Medicines & Healthcare products Regulatory Agency

Health Canada Santé Canada

Overview

MHRA initiatives and current plans.

Decision making…

Decision Making

- Capability
- Data
- Technology
- Collaboration

MHRA Compliance Strategy

Capability

A workforce with new skills and a pipeline of talent:

- Training
- Tools
- Effective use of data
- Recruitment

Data

Optimal use of data and intelligence:

- Inspection planning
- Inspection conduct
- Our own performance

Technology

Using technology as an enabler to our work:

- On inspection (data visualisation & Hardware)
- Use of data (e.g. Artificial Intelligence)

Collaboration

Collaborating with partners and stakeholders both domestically and internationally:

- Preventing non-compliance by upstream engagement
- Partnerships
- Outcome Based Cooperative Regulation

Collaboration

Outcome Based Cooperative Regulation

Enabling organisations to opt for basing their activities around demonstration that they can be trusted.

(An Introduction to Outcome Based Cooperative Regulation: Professor Christopher Hodges)

Summary

The MHRA will continue to evolve our approaches to harness new ideas and technology.

- Capability
- Data
- Technology
- Collaboration

MHRA Copyright information

Innovating Innovative Innovation

Emily S. Gebbia
Associate Director of Regulatory Development
Office of Scientific Investigations
CDER | US FDA

A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
February 13, 2024

Overview

- Provide context for efforts to encourage innovation
- Highlight FDA guidance on clinical trial innovation
- Discuss barriers to and opportunities for increasing innovation

The Innovation Imperative

What hasn't changed

- Need to protect participants' rights, safety, and welfare
- Need to ensure data quality and integrity

What has changed?

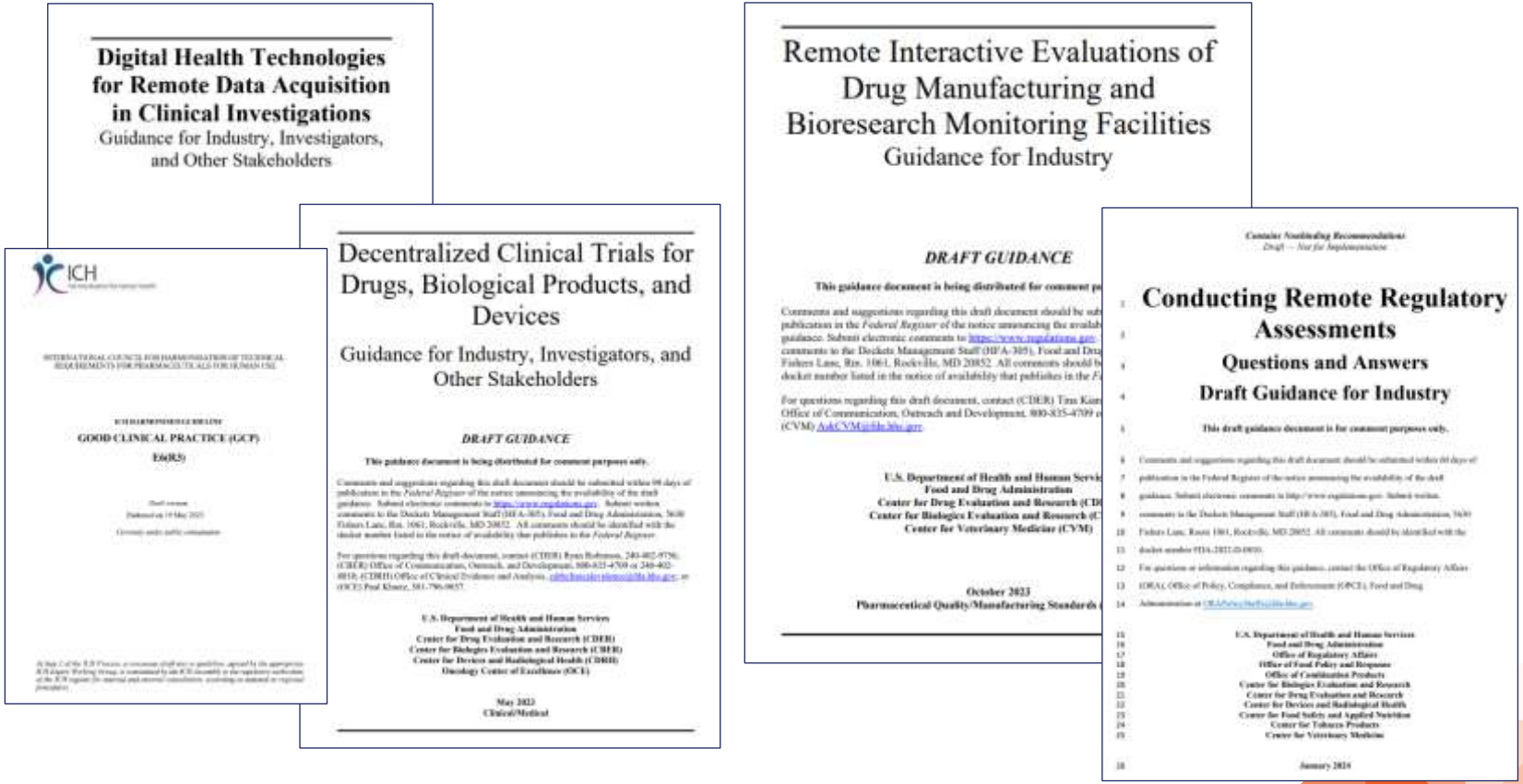
- Technological advances
- Cost and complexity of trials
- Emphasis on diversity, equity, and inclusion

Legislation and Innovation

Existing efforts to encourage innovation bolstered by recent legislation

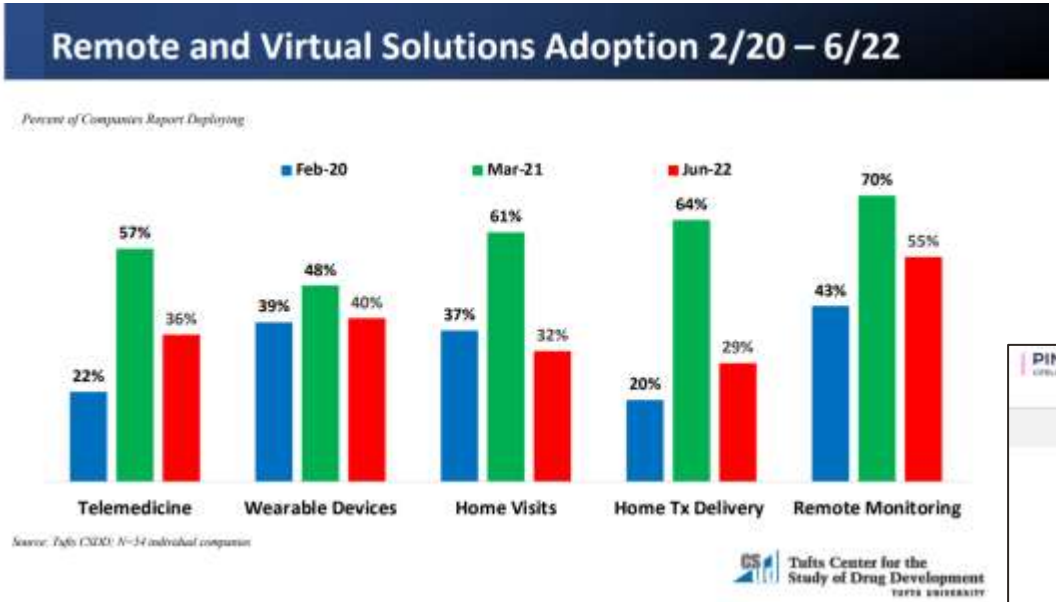
Selected FDORA Provisions	
3612	Adds inspection provision specific to BIMO
3611	Extends authority to request records in advance or in lieu of inspection to BIMO inspected entities
3605	Requires public meeting on mitigation of disruption to clinical studies and updated guidance
3606	Requires guidance on DCTs
3607	Requires guidance on use of DHTs and use of “seamless, concurrent, and other innovative clinical trial designs”

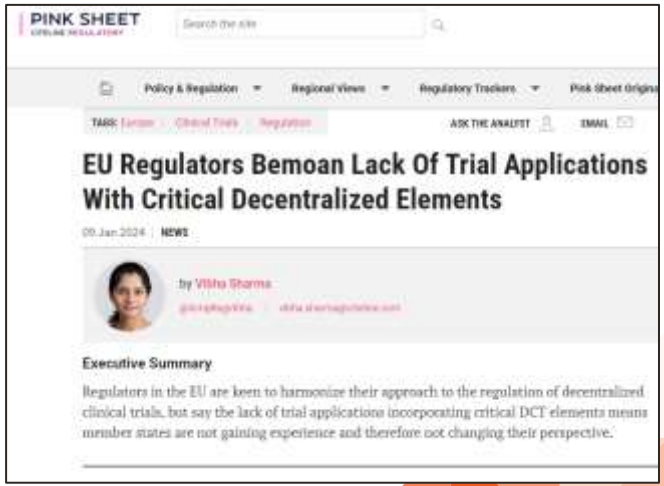
FDA Guidance Supporting Innovation



MORE FDA Guidance Supporting Innovation

And Yet . . .


Remote and Virtual Solutions Adoption 2/20 – 6/22
Percent of Companies Report Deploying
Feb-20
Mar-21
Jun-22
22%
57%
36%
39%
48%
40%
37%
61%
32%
20%
64%
29%
43%
70%
55%
Telemedicine
Wearable Devices
Home Visits
Home Tx Delivery
Remote Monitoring
Source: Tufts CSDD: N=34 individual companies
Tufts Center for the Study of Drug Development


PINK SHEET
Policy & Regulation
Regional Views
Regulatory Trackers
ASK THE ANALYST
EMAIL
EU Regulators Bemoan Lack Of Trial Applications With Critical Decentralized Elements
09 Jan 2024 | NEWS
by Vibha Sharma
Executive Summary
Regulators in the EU are keen to harmonize their approach to the regulation of decentralized clinical trials, but say the lack of trial applications incorporating critical DCT elements means member states are not gaining experience and therefore not changing their perspective.

Barriers

"[O]ur research found a significant distinction between the commonly perceived barriers to innovation and the actual obstacles, which are often more rooted in tradition than regulation."

Caraleigh Holverson, *Overcoming Barriers to Adoption for Innovations in Policy: Reflections from the Innovation Toolkit*

Actual Barriers

*Skepticism (based on experience)

*Risk aversion (as a structural constraint)

*Status quo defenders (with something to lose)

Opportunities

Examples of FDA's Center for Drug Evaluation and Research efforts related to clinical trial innovation efforts include (but are not limited to):

Key Programs	Key Activities
Complex Innovative Trial Designs (CID)	• Developing efforts to enhance use of simpler trials that could more easily be integrated into clinical practice (often called "point-of-care trials")
Model-Informed Drug Development (MIDD)	• Guidance on implementing decentralized clinical trial (DCT) designs
Real-World Evidence (RWE)	• Artificial intelligence and machine learning in the drug development lifecycle
Rare Disease Endpoint Advancement (RDEA)	• Efforts to improve enrollment of participants from underrepresented populations, including racial and ethnic groups, through innovative clinical trials
Patient-Focused Drug Development (PFDD)	• International harmonization efforts related to innovative clinical trial design and conduct
Digital Health Technologies (DHTs)	• Public-private partnerships and other external collaborations
Drug Development Tool Qualification	

Enhancing Adoption of Innovative Clinical Trial Approaches

To understand the state of innovation in clinical trial design and conduct, CDER is gathering information from internal and external stakeholders on the barriers and facilitators to incorporating innovative clinical trial approaches in drug development programs.

We are looking for your perspectives via comments to our public docket FDA-2023-N-4489 and/or participation in a public workshop hosted in partnership with the Duke Margolis Center for Health Policy on March 19 and 20, 2024.

We look forward to your Participation!

For more information please contact:

Food & Drug Administration
Kevin Bugin
Deputy Director of Operations
Kevin.Bugin@fda.hhs.gov

Duke Margolis
Luke Durocher
Senior Events & Marketing Manager
margolisevents@duke.edu

Post public comment by April 19, 2024

LINK

Register for March 19-20, 2024 public workshop

LINK

Virtual and in-person (DC) options available

Resources

- Consolidated Appropriations Act, 2023
- Public Meeting: Mitigating Clinical Study Disruptions During Disasters and Public Health Emergencies
- ICH Harmonized Guideline Good Clinical Practice (GCP) E6(R3), Draft
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations
- Decentralized Clinical Trials for Drugs, Biological Products, and Devices
- Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities
- Conducting Remote Regulatory Assessments Questions and Answers
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
- Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies
- A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers
- Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers
- CDER Docket and Public Workshop: *Enhancing Adoption of Innovative Clinical Trial Approaches*
- CDER Complex Innovative Trial Design Meeting Program
- Model-Informed Drug Development Paired Meeting Program
- Advancing Real-World Evidence Program
- Rare Disease Endpoint Advancement Pilot Program
- CDER Patient-Focused Drug Development
- Digital Health Technologies (DHTs) for Drug Development
- Drug Development Tool (DDT) Qualification Programs

U.S. FOOD & DRUG ADMINISTRATION

Health Canada's Clinical Trial Compliance Program Policies, Guidance documents and Initiatives

Hocine Abid, MD, MBA
National Manager
Clinical Trial Compliance Program

A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop

Health Canada Santé Canada

Medicines & Healthcare products Regulatory Agency

Overview

- Health Canada's Clinical Trial Compliance Program: Mandate, R&Rs, Scope and Activities.
- Canada's Clinical Trial Regulatory Framework.
- Key Guidance Documents for Stakeholders.

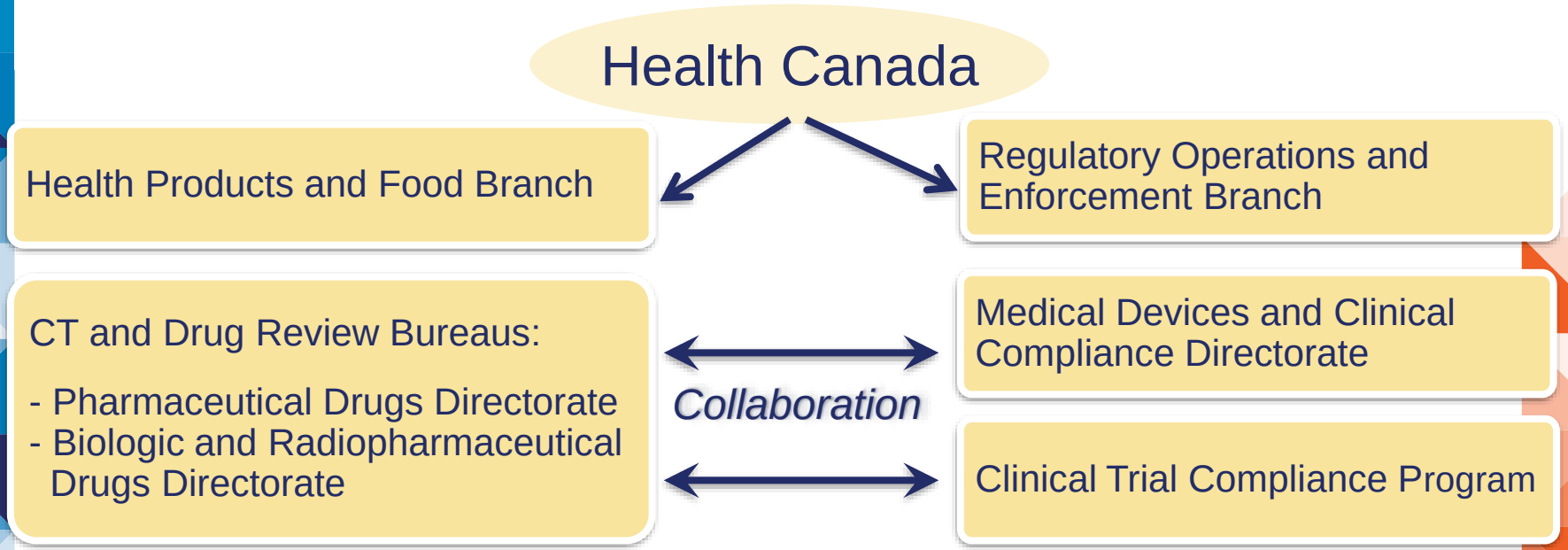
Clinical Trial Compliance Program Mandate

- Promotes & verifies compliance of drug clinical trials against Canada's *Food and Drugs Act* (*FDA*) and its associated Regulations (*particularly, Part C, Division 5 of the Food and Drug Regulations: "Drugs for Clinical Trials Involving Human Subjects" which includes the principles of Good Clinical Practices):*

  - To protect participants enrolled in Clinical Trials (CT) and
  - Increase the confidence in the reliability of the clinical data collected and subsequently submitted to Health Canada.

- Authority to inspect: Section 23 of Canada's FDA.

Oversight: HC's Roles & Responsibilities



- Drug Market Authorisations
- CT Authorization: No Objection Letter
- Clinical Trial Application
- CTA-Amendment and Notification
- Adverse Event reporting
- Suspension, cancellation

- Compliance inspection
- Guidance development
- Compliance promotion
- Suspension, cancellation

Health Canada's Clinical Trial Compliance Program: Scope and Activities

- Inspection of active trials at qualified investigator sites
- For-cause inspection: compliance verification
- Compliance promotion: publication of guidance documents, training and information sessions
- Inspection of Sponsor/CRO/SMO (risk-based)
- Bioequivalence trials inspection (clinical and lab sites)
- Data Integrity inspection of pivotal clinical trials
- Compliance readiness inspection
- International collaboration/coordination

Canada's CT Regulatory Framework

- **Canada's Food and Drugs Act:**
  - **Authority to inspect under Section 23. Article :** 23 (1) Subject to subsection (1.1), an inspector may at any reasonable time enter **any place** where the inspector believes on reasonable grounds any **article** to which this Act or the regulations apply is manufactured, prepared, preserved, packaged or stored.

- **Food and Drug Regulations (FDR), Part C, Div.5: "Drugs for CT Involving Human Subjects"**
  - Came into force on Sep. 1, 2001. Includes the requirements for GCP
  - Does NOT apply to CT using Natural Health Products or Medical Devices.

- **Clinical Trials for Medical Devices and Drugs Relating to COVID-19 Regulations.**

- ***Future (initiative): Canada is modernizing its Clinical Trial Regulations.***

Key HC CT Guidance Documents

Where to find them :

Health Canada- Drugs and health products - **Compliance and enforcement -** Drug and health products - Good Clinical Practices

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

Health Canada - **Applications and Submissions** Drug Products - Guidance Documents: Clinical Trials

- https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials.html

GUI-0100: “Guidance document, Part C, Division 5 of the Food and Drug Regulations”

https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/guidance-drugs-clinical-trials-human-subjects-gui-0100.html

To understand and comply with Part C, Division 5 of the Food and Drug Regulations (FDR):

- **<u>Sections 1-4</u>: Purpose, Scope, Introduction, Implementation Guidance**
- **<u>Section 5:</u> Regulations & Interpretation**
  - Section of Regulations in a box
  - Interpretation with references made to pertinent sections of ICH E6(R2)
  - Examples of observations cited under each section of the Regulations
- **Appendices: Glossary and References**

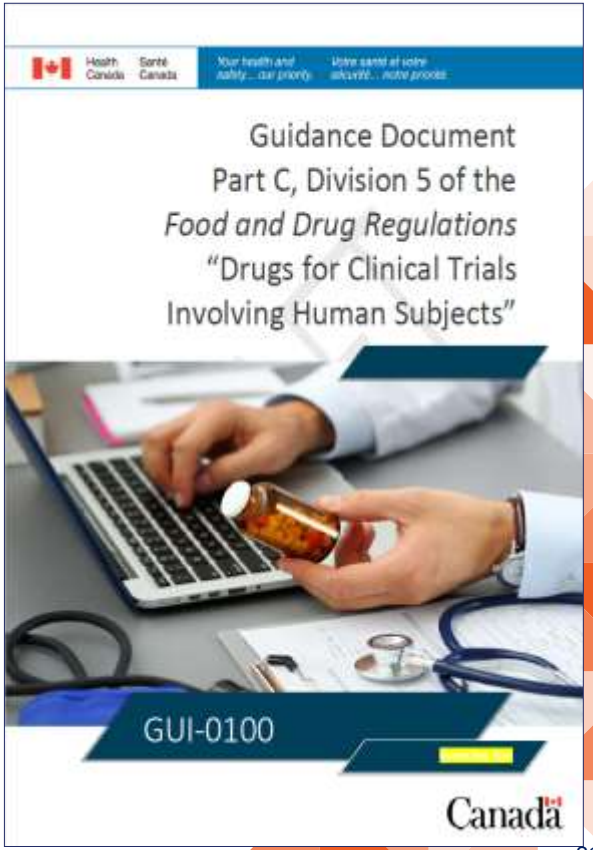


Table of contents

5.1 Interpretation

C.05.001

The definitions outlined in this section are available in Appendix A.

5.2 Application

C.05.002

(1) Subject to subsection (2), this Division applies to the sale or importation of drugs to be used for the purposes of clinical trials involving human subjects.

(2) Except for paragraph C.05.003(a), subsections C.05.006(2) and (3), paragraphs C.05.010(a) to (i), section C.05.011, subsections C.05.012(1) and (2), paragraphs C.05.012(3)(a) to (d) and (f) to (h), subsection C.05.012(4) and sections C.05.013, C.05.016 and C.05.017, this Division does not apply to the sale or importation of a drug for the purposes of a clinical trial authorized under subsection C.05.006(2).

Interpretation

The Regulations apply to the sale and importation of drugs to be used in clinical trials involving humans that are conducted in Canada. As per section C.05.002, no person can sell or import (refer to Glossary (terms) for definitions of sell and import) a drug for the purposes of a clinical trial involving humans **unless authorized** (refer to section 5.6 Authorization). For Phase IV clinical trials, limited provisions of Part C, Division 5 apply which are set out in subsection C.05.002(2) and described below.

Phase IV clinical trials include those trials that involve the use of:

- a new drug that has been issued a notice of compliance (NOC) under subsection C.08.004(1) of the Regulations, if the clinical trial is in respect of a purpose or condition of use for which the NOC was issued; or

C.05.010(d)

(d) For each clinical trial site, the approval of a research ethics board is obtained before the clinical trial begins at the site;

Interpretation

Health Canada's relevant regulations do include certain requirements related to REBs, but Health Canada does not have jurisdiction over how REBs conduct their operations or establish SOPs. The regulatory obligations to obtain the REB approval are the responsibility of the sponsor.

The REB membership is defined in section C.05.001 of the Regulations [refer to Appendix A] and may be reviewed during the inspection, as required.

Health Canada recommends that REBs overseeing clinical trials in Canada operate according to well established and recognized standards such as the ICH E6, the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2 2022)*, and provincially established standards.

Section 3 of ICH E6 describes the responsibilities, composition and operations of REBs. The responsibility of a REB is to protect the rights, safety, and well-being of all human subjects. An REB should pay special attention to trials that may include vulnerable human subjects (elderly, children, mentally ill, prisoners, etc.). This section also lists the documents that should be provided to an REB in order to obtain ethics approval to conduct a clinical trial.

An REB should review and document a proposed clinical trial within a reasonable time and will document its views in writing, clearly identifying the trial, the documents reviewed and the dates for approval or disapproval (ICH E6, 3.1.2).

When and if approval is given, an REB should conduct periodic reviews of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at a minimum, at least once per year (that is a trial that is considered to be high risk to a human subject will be reviewed more often to ensure that the highest standards are in place to ensure the human subject's safety) (ICH E6, 3.1.4). An REB should follow its established and documented procedures as per ICH E6 section 3.3.

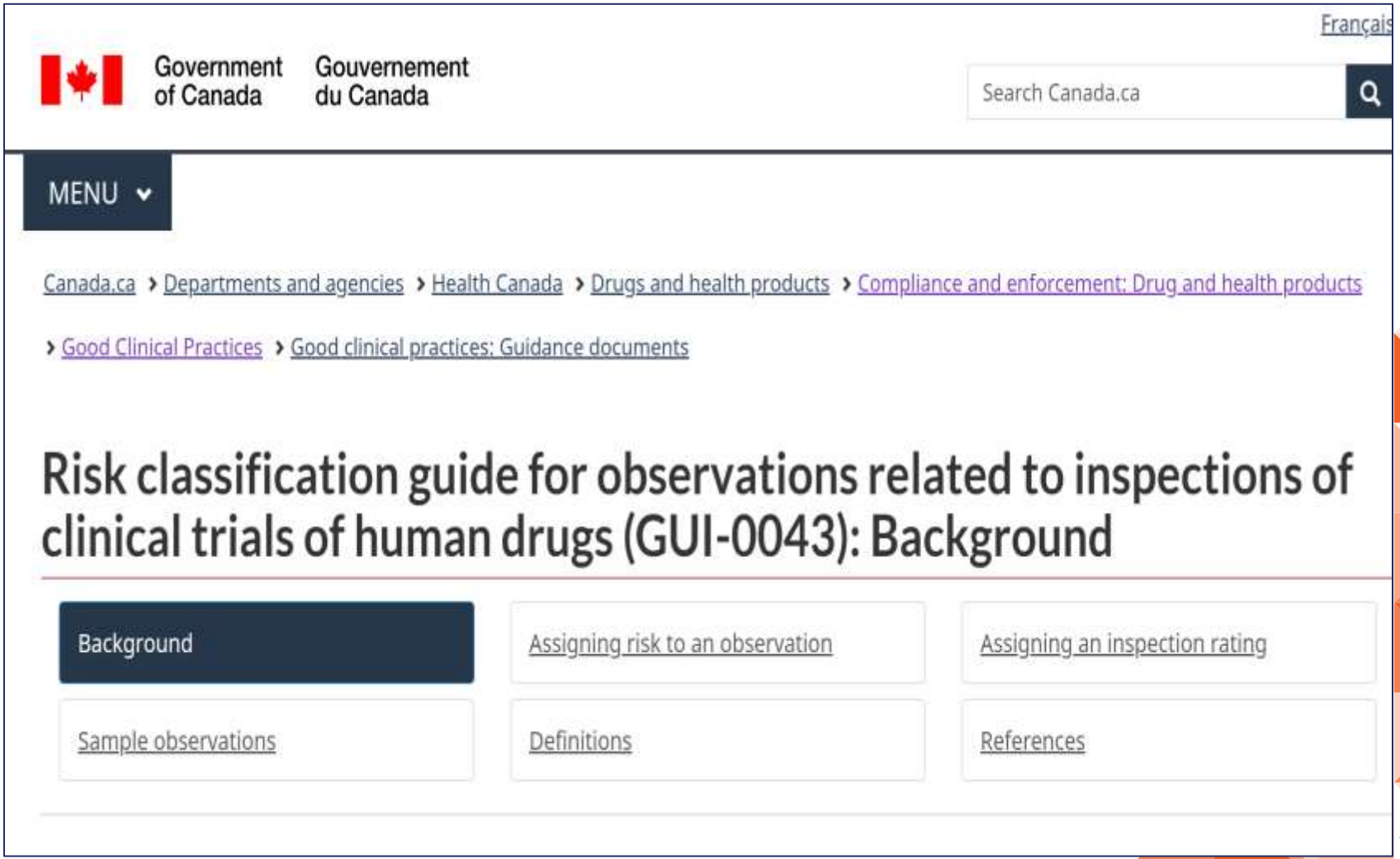
Examples of observations typically cited under this section of the Regulations include:

- The sponsor did not get the approval of the REB before the clinical trial began at the clinical trial site.
- The sponsor did not get approval from the REB before a protocol amendment was implemented at the clinical trial site.

GUI-0043: Risk Classification Guide For Observations Related to CT Inspections

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

- This Guide provides clarity and transparency,
- describes how inspectors classify observations according to risk,
- describes the process for assigning an overall rating to an inspection,
- promotes consistency in the assignment of risk rating to observations & overall inspection rating, and
- provides examples of risk-rated observations.


Français
Government of Canada
Gouvernement du Canada
Search Canada.ca
MENU
Canada.ca › Departments and agencies › Health Canada › Drugs and health products › Compliance and enforcement: Drug and health products › Good Clinical Practices › Good clinical practices: Guidance documents
Risk classification guide for observations related to inspections of clinical trials of human drugs (GUI-0043): Background
Background
Assigning risk to an observation
Assigning an inspection rating
Sample observations
Definitions
References

Risk classification guide for observations related to inspections of clinical trials of human drugs (GUI-0043): Assigning an inspection rating

Background | Assigning risk to an observation | Assigning an inspection rating
Sample observations | Definitions | References

Once all the observations have been rated, the inspector will assign an overall rating of "C" or "NC", when applicable:

- "C" (Compliant): the regulated party has demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* (Act) and its Regulations
- "NC" (Non-compliant): the regulated party has not demonstrated that the activities it conducts are in compliance with the Act and its Regulations

Both "C" and "NC" ratings require corrective and preventive actions (CAPAs) for cited observations.

Critical observations (risk 1)

If 1 or more observations are classified as **critical** (risk 1), the inspector will inform the regulated party before the exit meeting. They will be informed that this will likely result in an overall **"NC"** rating. This may result in additional compliance and enforcement actions.

Health Canada will ask for an action plan that outlines the corrective measures to be taken as well as the time frame for implementing these measures.

If there is a potential immediate health risk (potential injury) to a clinical trial subject or other person (as per section C.05.017 of the Regulations), the inspector will request an evaluation to confirm the risk from the Pharmaceutical Drugs Directorate (PDD) or Biologic and Radiopharmaceutical Drugs Directorate (BRDD). Enforcement actions will be taken as required to achieve compliance in accordance with the Compliance and enforcement policy for health products (POL-0001).

Major observations (risk 2)

In most cases, the inspector will assign a **"C"** rating to observations classified as **major** (risk 2). However, the inspector could assign an **"NC"** rating in the following situations:

- the nature and/or extent of the major observations indicate that the clinical trial is not being conducted with sufficient controls
- repetition of most major observations reported during previous inspections, indicating the corrective actions submitted were not implemented or adequate preventive actions were not put in place in a timely manner to avoid recurrence of these deviations

C.05.010(b) observation

The clinical trial was not always conducted according to the protocol.

Risk 1 (critical) example:

- The inclusion and exclusion criteria outlined in the protocol were not followed, which resulted in the randomization of participants who should have been excluded. This created undue risk to the participants.

Risk 2 (major) examples:

- The study visits by the QI were not conducted as per the protocol requirements.
- The participant had multiple test samples collected during the clinical trial that were not required by the protocol and to which they did not consent.
- Clinical samples were not always collected, handled and stored in accordance with the requirements in the protocol and associated lab manual.
- It was not always demonstrated that:
  - the clinical trial was conducted in accordance with the protocol and
  - the sponsor and/or REB (as required) were notified of the protocol deviations

Risk 3 (minor) example:

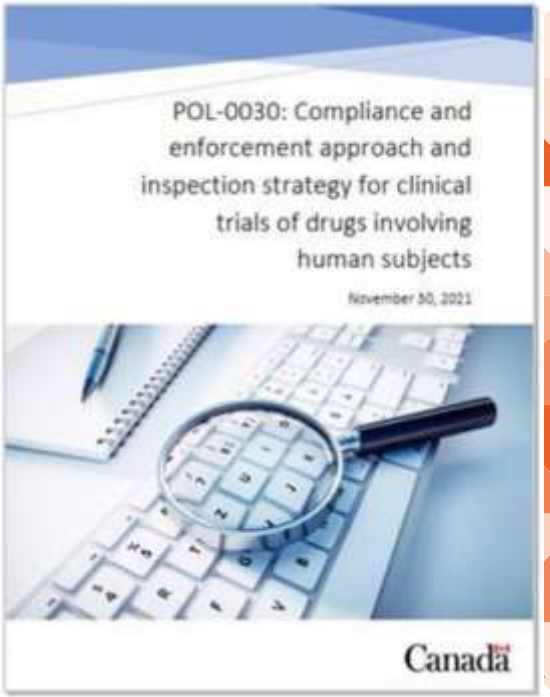
- Multiple participants had study visits that were outside of the visit window outlined in the protocol. These were not documented as protocol deviations.

Other important sources of information

POL-0030: C&E approach and inspection strategy for Clinical Trials of drugs involving human subjects

http://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/inspection-strategy-clinical-trials.html

- To inform stakeholders about Canada's national compliance and enforcement approach and CT inspection strategy.
- Describes the inspection process used to verify compliance with the Act & the Regulations of the activities related to the conduct of clinical trials performed by a regulated party at a Canadian site.

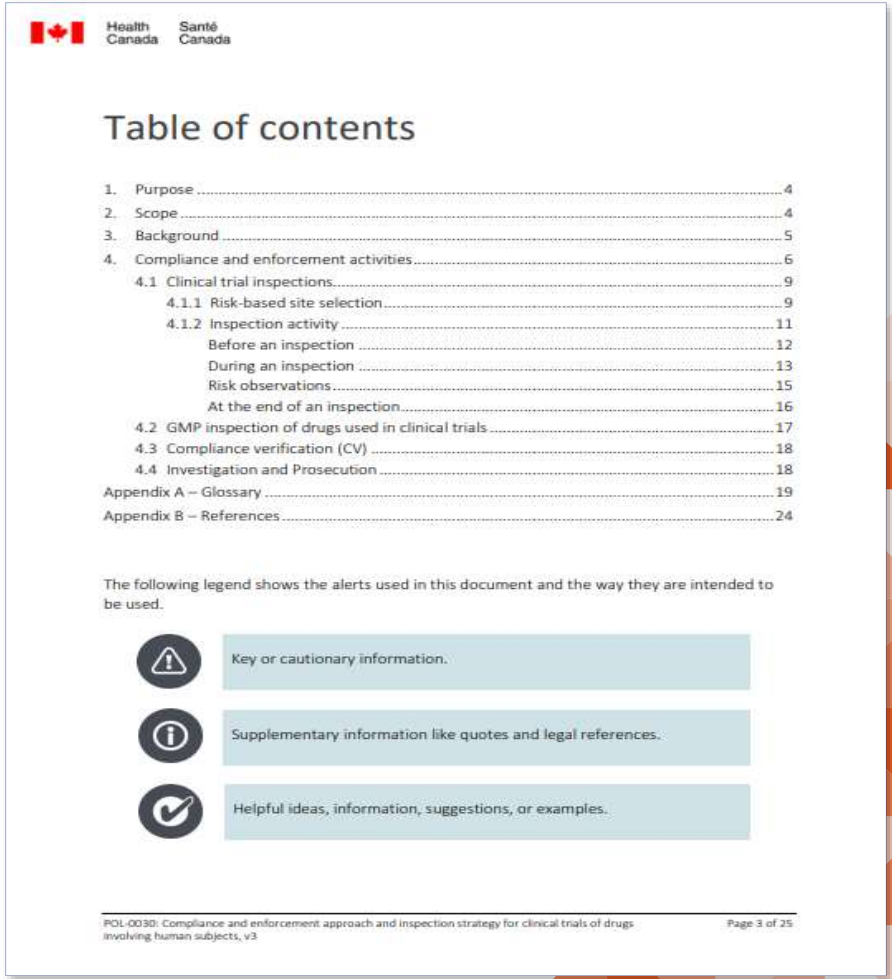


POL-0030 Contents:

1. Purpose
2. Scope
3. Background
4. Compliance & enforcement activities
   - 4.1 Clinical trial inspections
     - 4.1.1 Risk-based site selection
     - 4.1.2 Inspection activity
       - ➢ Before an inspection
       - ➢ During an inspection
       - ➢ Risk observations
       - ➢ At the end of an inspection
   - 4.2 GMP inspection of CT drugs
   - 4.3 Compliance verification (CV)
   - 4.4 Investigation and Prosecution

Appendix A – Glossary

Appendix B – References



Health Canada Santé Canada

Table of contents

The following legend shows the alerts used in this document and the way they are intended to be used.

Key or cautionary information.

Supplementary information like quotes and legal references.

Helpful ideas, information, suggestions, or examples.

POL-0030 refers to Health Canada's overarching Framework and Policies

Compliance & Enforcement (C&E) Framework	C&E Policy for Health Products (POL-0001)	Collection & Retention of Records Policy (POL-0140)
HC's Roles & Responsibilities, actions and tools, guiding principles and decision factors.	C&E approach for health products regulated under the Food and Drugs Act and its Regulations.	Handling of all records obtained by inspectors during C&E activities in person or remotely.

Other Key Guidance Documents

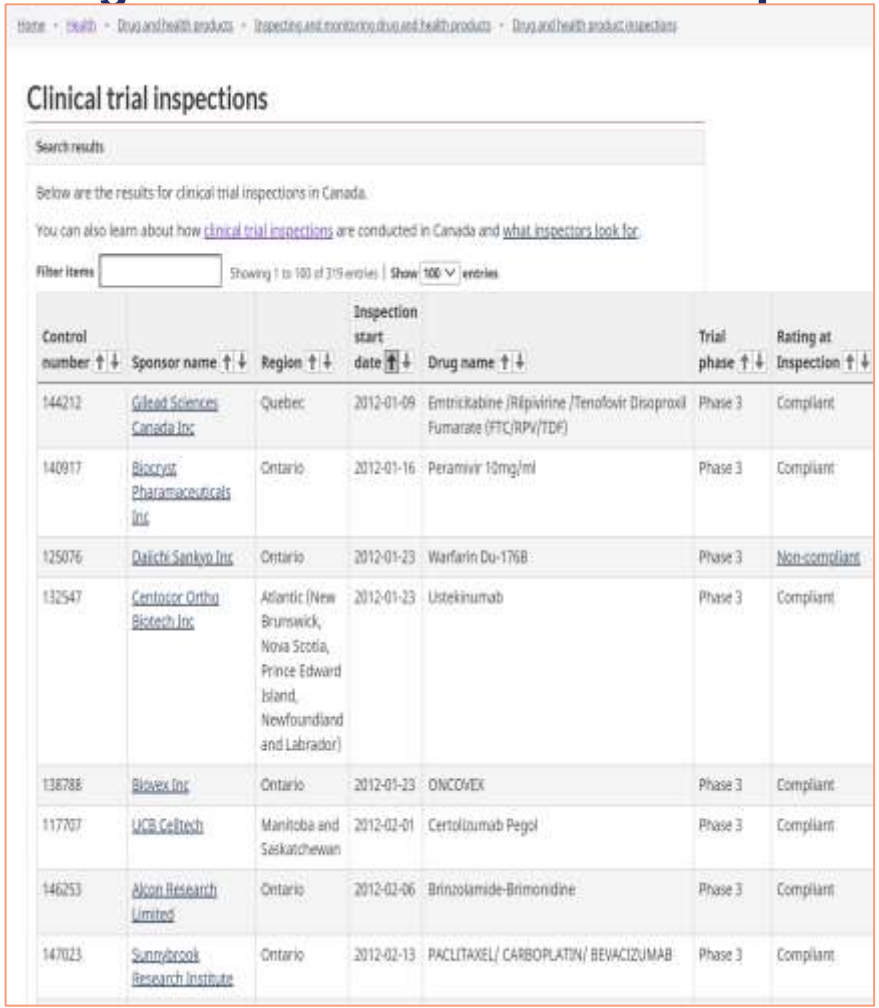
- Importing and exporting health products for commercial use (GUI-0117)
  https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/importation-exportation/commercial-use-health-products-guidance/document.html
- Annex 13 to the Good Manufacturing Practices Guidelines: Drugs Used in Clinical Trials (GUI-0036)
  www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/annex-13-good-manufacturing-practices-guidelines-drugs-clinical-trials-0036.html
- Guidance Document For Clinical Trial Sponsors: Clinical Trial Application (CTA)
  https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html

The drug and health products inspections database

https://www.canada.ca/en/health-canada/services/inspecting-monitoring-drug-health-products/drug-health-product-inspections.html

- List of Inspections and their outcomes since 2012.
  - **Inspection outcomes: Non-Compliant or Compliant.**
- **Initial Inspection Deficiencies** posted within 3 days of the inspection.
- **Inspection Report Cards** posted within 30 days of the inspection.
- HC regulatory actions taken (**suspension or cancellation** as an example).

Drug and Health Products Inspections Database



Home • Health • Drug and health products • Inspecting and monitoring drug and health products • Drug and health product inspections

Clinical trial inspections

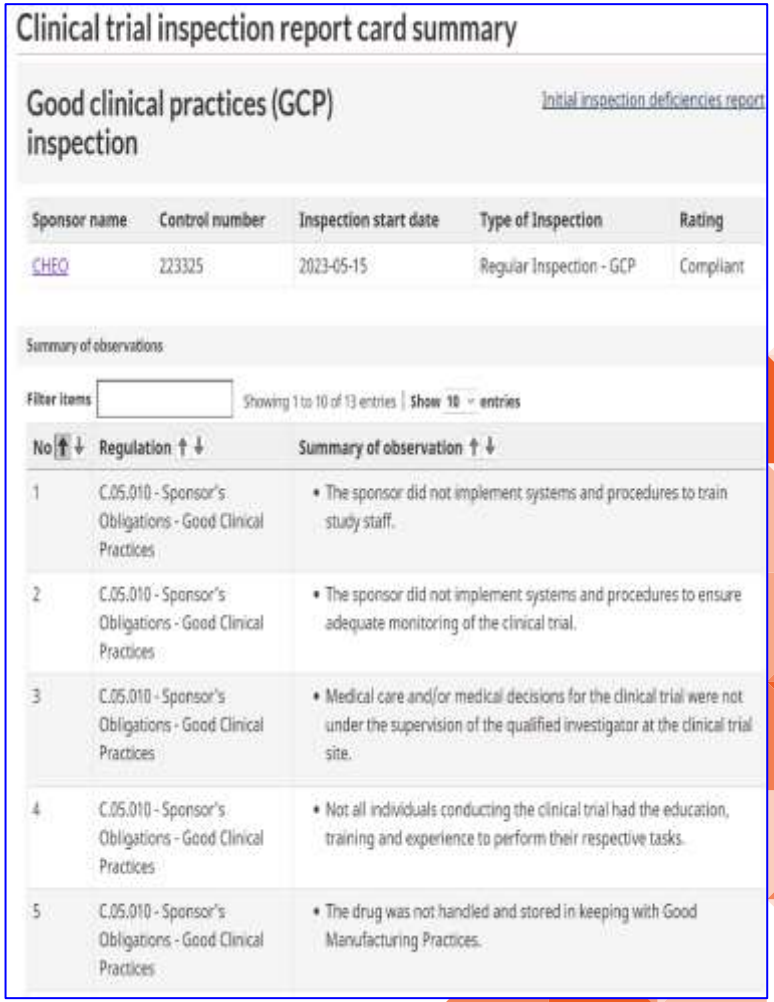
Search results

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.

Filter items | Showing 1 to 100 of 319 entries | Show 100 entries

Control number	Sponsor name	Region	Inspection start date	Drug name	Trial phase	Rating at Inspection
144212	Gilead Sciences Canada Inc	Quebec	2012-01-09	Emtricitabine /Rilpivirine /Tenofovir Disoproxil Fumarate (FTC/RPV/TDF)	Phase 3	Compliant
140917	Biocryst Pharmaceuticals Inc	Ontario	2012-01-16	Peramivir 10mg/ml	Phase 3	Compliant
125076	Daiichi Sankyo Inc	Ontario	2012-01-23	Warfarin Du-176B	Phase 3	Non-compliant
132547	Centocor Ortho Biotech Inc	Atlantic (New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	2012-01-23	Ustekinumab	Phase 3	Compliant
138788	Biovex Inc	Ontario	2012-01-23	ONCOVEX	Phase 3	Compliant
117707	UCB Celltech	Manitoba and Saskatchewan	2012-02-01	Certolizumab Pegol	Phase 3	Compliant
146253	Alcon Research Limited	Ontario	2012-02-06	Brinzolamide-Brimonidine	Phase 3	Compliant
147023	Sunnybrook Research Institute	Ontario	2012-02-13	PACLITAXEL/ CARBOPLATIN/ BEVACIZUMAB	Phase 3	Compliant



Clinical trial inspection report card summary

Good clinical practices (GCP) inspection

Initial inspection deficiencies report

Sponsor name	Control number	Inspection start date	Type of Inspection	Rating
CHEO	223325	2023-05-15	Regular Inspection - GCP	Compliant

Summary of observations

Filter items | Showing 1 to 10 of 13 entries | Show 10 entries

No	Regulation	Summary of observation
1	C.05.010 - Sponsor's Obligations - Good Clinical Practices	• The sponsor did not implement systems and procedures to train study staff.
2	C.05.010 - Sponsor's Obligations - Good Clinical Practices	• The sponsor did not implement systems and procedures to ensure adequate monitoring of the clinical trial.
3	C.05.010 - Sponsor's Obligations - Good Clinical Practices	• Medical care and/or medical decisions for the clinical trial were not under the supervision of the qualified investigator at the clinical trial site.
4	C.05.010 - Sponsor's Obligations - Good Clinical Practices	• Not all individuals conducting the clinical trial had the education, training and experience to perform their respective tasks.
5	C.05.010 - Sponsor's Obligations - Good Clinical Practices	• The drug was not handled and stored in keeping with Good Manufacturing Practices.

Questions?

Clinical Trial Compliance Program E-mail:
GCP_BPC@hc-sc.gc.ca

All guidance documents and further information are available online at: www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html