Lessons Learned from 2024 Regulatory Inspections

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Objectives

- Understand the different regulatory agencies that conducted inspections last year
- Overview of 2024 Inspection Year with a focus on
  - Types of Inspections
  - Purpose of Inspections
  - Results & Reporting

Health Canada

HEALTH CANADA'S REGULATORY OPERATIONS AND ENFORCEMENT BRANCH (ROEB) – CLINICAL TRIAL COMPLIANCE PROGRAM (CTCP)

- Health Canada
  - **Regulatory Operations and Enforcement Branch (ROEB)**
    - a. Medical Devices and Clinical Compliance
    - b. Clinical Compliance, Border Operations and Canada Vigilance
    - c. Clinical Trial and Biological Product Compliance
      - i. Biological Product Compliance
      - ii. Clinical Trial and Biological Product Compliance
      - iii. **Clinical Trial Compliance (CTC)**
- Health Canada may inspect **Sponsors, clinical trial sites**, Contract Research Organizations (CROs) and Site Management Organizations (SMOs). The ROEB Inspectorate conducts approximately 80 inspections each year across Canada (goal is up to 2% of all Canadian clinical trial sites per year). Inspections are conducted during the active phase of a clinical trial or after the completion of a clinical trial. [1]

Health Canada – Types of Inspections

Sponsor System-Based Inspection

Often referred to as system-based inspections. [2]

2 systems are chosen as the focus of the inspection (i.e Safety, Pharmacovigilance, Monitoring, etc).

Health Canada Inspector will assess the compliance with the Food and Drugs Act and Part C, Division 5 and ICH GCP with particular focus on the systems and procedures that describe how the trial is conducted and monitored. [2]

Qualified Investigator Site Inspection

A qualified investigator (QI) inspection is conducted at one clinical trial site. A clinical trial site is defined as one trial led by one QI at once location (physical address)[2]

Health Canada will assess the compliance with the Food and Drugs Act and Part C, Division 5 and ICH GCP, as adopted by Health Canada.[2]

Sponsor Compliance Readiness Inspection

This inspection is scheduled at the beginning stages of the trial, to assess initial compliance and to evaluate the systems and procedures in place for the conduct and oversight of the clinical trial.

Health Canada – Types of Results

Qualified Investigator Site Inspection

- Observation risk rating[3]
  - Critical (Risk 1): situation that results in fatal, life threatening or unsafe conditions or trial data is compromised
  - Major (Risk 2): a result that may result in undue risk and/or could invalidate data
  - Minor (Risk 3): deficiency or deviation from the Regulations
- Overall rating[3]
  - Compliant: combination of major and minor observations
  - Non-Compliant: 1 or more observation classified as critical, will be informed prior to exit meeting

Sponsor System-Based Inspection

- No Overall Rating is provided, observations are rated.

Compliance Readiness Inspection

- No Overall Rating is provided

U.S Food & Drug Administration

The Food and Drug Administration (FDA) Bioresearch Monitoring (BIMO) program with the following objectives:

1. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical studies;

2. To verify the accuracy and reliability of clinical study data submitted to FDA in support of research or marketing applications; and

3. To assess compliance with FDA's regulations governing the conduct of clinical studies.

As part of the BIMO program, FDA's Office of Regulatory Affairs (ORA) conducts inspections of **clinical investigators, sponsors, sponsor-investigators**, monitors, contract research organizations (CROs), institutional review boards (IRBs), nonclinical (animal) laboratories, bioavailability and bioequivalence studies, post-marketing adverse drug experience reporting, and risk evaluation and mitigation strategies reporting, in support of preapproval, licensing, premarket and **marketing applications submitted to the Agency for products regulated by all FDA product centers** as part of the BIMO program, among other activities. [4]

U.S Food & Drug Administration – Types of Inspections

Clinical Investigator Inspection

Inspections involve evaluation of the clinical investigator's practices and procedures to determine compliance with applicable regulations. When the inspection occurs as a result of FDA's receipt of a marketing application or submission, it will include a comparison of the data submitted to FDA with source documents, or for animal drug studies, copies of source documents, and case report forms (CRFs). For surveillance inspections or for-cause inspections of ongoing studies, data comparison may only involve source documents and CRFs because data for ongoing studies may not be available. [5]

Sponsor Inspection

The primary focus of sponsor inspections is to evaluate the sponsor's practices and procedures to determine compliance with applicable regulations and adherence to good clinical practice standards to ensure subject protection and data quality and integrity. These inspections may include, but are not limited to, a review of the sponsor's practices and procedures related to clinical trial oversight, including activities such as site monitoring, vendor audits, training, and data collection, handling, and management. The inspectional focus is not to scientifically evaluate the results of the study or the quality of the protocol. [5]

*Inspections can be conducted by the FDA when the trial is being conducted under an Investigational New Drug (IND) application and/or data from your site has been submitted by the Manufacturer for a marketing application (per 21 CFR 312.120). [4]

U.S Food & Drug Administration – Types of Results

- **No Action Indicated**
  - No objectionable conditions or practices were found during an inspection or the significance of any objectionable conditions found does not justify further regulatory action.[5]
- **Voluntary Action Indicated (Form 483)**
  - Objectionable conditions or practices were found, but the Agency is not prepared to take or recommend any regulatory action since the objectionable conditions or practices do not meet the threshold for regulatory action. [5]
- **Official Action Indicated (Form 483)**
  - Objectionable conditions and/or practices were found, and regulatory action should be recommended. The scope, severity, or pattern of the violation(s) support findings that:
    1. Subjects under the care of the clinical investigator would be or have been exposed to an unreasonable and significant risk of illness or injury; or
    2. Subjects' rights, welfare, or safety would be or have been seriously compromised; or
    3. Data integrity or reliability is or has been compromised. [5]

2024 In Review

5 Regulatory Inspections

- Health Canada CRI (IIT)
- Health Canada QI GCP Inspection (Industry)
- FDA Sponsor Inspection (IIT)
- FDA Clinical Investigator Inspection (IIT)
- FDA Clinical Investigator Inspection (Industry)

Health Canada Compliance Readiness Inspection (IIT)

Type of Inspection:

- Investigator Initiated
- 1 Inspector
- Remote Inspection (3 days)

Focus:

- Comprehensive Good Clinical Practice Inspection
  - Training and Essential Documents
  - Investigational Product Accountability
  - Safety Reporting
  - Qualified Investigator Oversight

Health Canada Compliance Readiness Inspection (IIT)

Results (No Observations)

- No written feedback or rating is provided
- Overall positive feedback for preparedness, especially the filing structure
- Small discussion points:
  - One equipment calibration appeared out of date
  - No training available for QI/Sub-I training on Investigator Brochure
  - No evidence of electronic data capture system training

Health Canada Compliance Readiness Inspection (IIT)

Next Steps & Response:

- Closing Letter is sent within few days of closing meeting (no written observations)
- No additional action is required but correcting any observations is highly recommended

Health Canada Qualified Investigator Inspection (Industry)

Type of Inspection:

- Industry Sponsored
- 1 Inspector
- Hybrid Inspection (3 days onsite, 3 planned remote days extended by 3 additional remote days)

Focus:

- Comprehensive Good Clinical Practice Inspection
  - Training and Essential Documents
  - Source Data Verification
  - Investigational Product Accountability
  - Safety Reporting
  - Qualified Investigator Oversight

Health Canada Qualified Investigator Inspection (Industry)

Results (Non-Compliant and Intent to Suspend Letter Issued):

- 4 Critical Observation
  - Missing source records for eligibility criteria and baseline assessments (i.e physical exams)
  - Good documentation practices: back dating review of eligibility source records, labs, and safety documentation
    - Initial review completed in EMR but documented later on paper print out. Date added to indicate date of EMR review
  - Medical Decisions were inadequately documented
  - Inadequate monitoring of the trial

Health Canada Qualified Investigator Inspection (Industry)

Next Steps & Response:

- Observations are discussed at Closing Meeting
  - Exit Meeting scheduled within 15 business days of closing meeting
  - Draft Exit Notice is issued in advance to exit meeting
  - Final Exit Notice issued after exit meeting
  - Intent to Suspend Letter issued to the Sponsor
- Responses due within 30 calendar days of the issuance of the final Exit Notice
  - If responses are deemed adequate, the intent to suspend is lifted
  - If responses are deemed inadequate, a Suspension Letter is issued to the Sponsor until all observation responses are deemed acceptable by Health Canada.

FDA Sponsor Inspection (IIT)

Type of Inspection:

- Investigator Initiated Non-IND Study prompted by marketing application
- 1 Inspector, 2 members of the Centre from Drug Evaluation (CDER) also attended
- Onsite Inspection (5 days)

Focus:

- Verification of primary outcomes and process of assessment
- Electronic Data Capture System
- Audit trails
- Trial Master File

FDA Sponsor Inspection (IIT)

Results (No Action Indicated, Discussion points only)

Discussion Items

- Audit trail was deficient in the “what” and “why” of data change
  - Inspector was unable to verify the changes made to an EDC
  - No Form 483 issued as this was an academic trial, not conducted under IND
- Some Protocol deviations (out of window assessments) were not captured in deviation logs
- Some inconsistency in methods to assess a primary outcome
- Inspector was impressed with the level of documentation (i.e data management, SOPs) in the TMF.

FDA Clinical Investigator Inspection (IIT)

Type of Inspection:

- Investigator-Initiated Non-IND Study prompted by marketing application
- 1 Inspector present
- Onsite Inspection (5 days)

Focus:

- Deferred consent process
- SAE collection
- Accuracy of registry data
- Dosing assignment and compliance
- 10% patient records reviewed (34)
- 50% death records reviewed (23)

FDA Clinical Investigator Inspection (IIT)

Results (No Action Indicated, Discussion points only)

Discussion Items:

- 1 late SAE
- Time discrepancy in electronic data capture system and data reported to FDA
  - Suspected due to a time zone discrepancy (MST-UAT) in the data extraction. All reports were consistently 6 hours different
- Deferred consent process was adequately described and consistently followed for all participants that were reviewed
- Registry event collection
  - All events of interest were collected by the inspector to verify registry events

Release of copies of the medical record (even redacted) to inspector is NOT permitted by AHS. Be sure to inform them in advance

FDA Clinical Investigator Inspection (Industry)

Type of Inspection:

- Industry Sponsored IND Study
- Surveillance Inspection (High enrolling site)
- 1 Inspector
- Onsite Inspection (5 days)

Focus:

- Comprehensive Good Clinical Practice Inspection
  - Sponsor and REB oversight
  - Monitoring and Follow up reports
  - Training records
  - Data verification and audit trails
    - 100% review of primary outcome measures
  - Investigational Product accountability
  - System functionality, disaster recovery, validation documentation

FDA Clinical Investigator Inspection (Industry)

Results (Form 483 Issued: Voluntary Action Indicated)

- Discussion items:
  - Good documentation practices: few instances of data scratched out or obscured
  - Informed consent documentation (completeness, correct version)
  - Unreported Adverse Event
  - Unreported Concomitant medication
- Observation: Voluntary Action Indicated
  - Failure to report SAE to Sponsor within required timelines
    - 5/6 were not reported within expected 24 hours
      - 3 SAEs were occurred as part of the same event and reported at the 26th hour
      - Since it resulted in death it raised the significance of the deficiency and raised to the level of an observation
      - The observed trend is another contribution factor that raised this to level of observation

FDA Clinical Investigator Inspection (Industry)

Next Steps & Response

- Form is issued at closing meeting
  - Response to be provided (voluntarily) with 15 calendar days from issuance
    - Response should include a Corrective and Preventative Action Plan (CAPA)
  - Response is sent to the Centre for Drug Evaluation with copy to Inspector and is included in the report

References & Helpful Links

1. N2 Guidance for Health Canada Inspections
2. POL-0030: Compliance and enforcement approach and inspection strategy for clinical trials of drugs involving human subjects
3. Risk classification guide for observations related to inspections of clinical trials of human drugs (GUI-0043): Assigning risk to an observation
4. Food and Drug Administration Compliance Program Chapter 48 – Bioresearch Monitoring. 7348.810. Sponsors and Contract Research Organizations
5. Food and Drug Administration Compliance Program Chapter 48 – Bioresearch Monitoring. 7348.811. Clinical Investigators and Sponsor-Investigators

Questions?

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