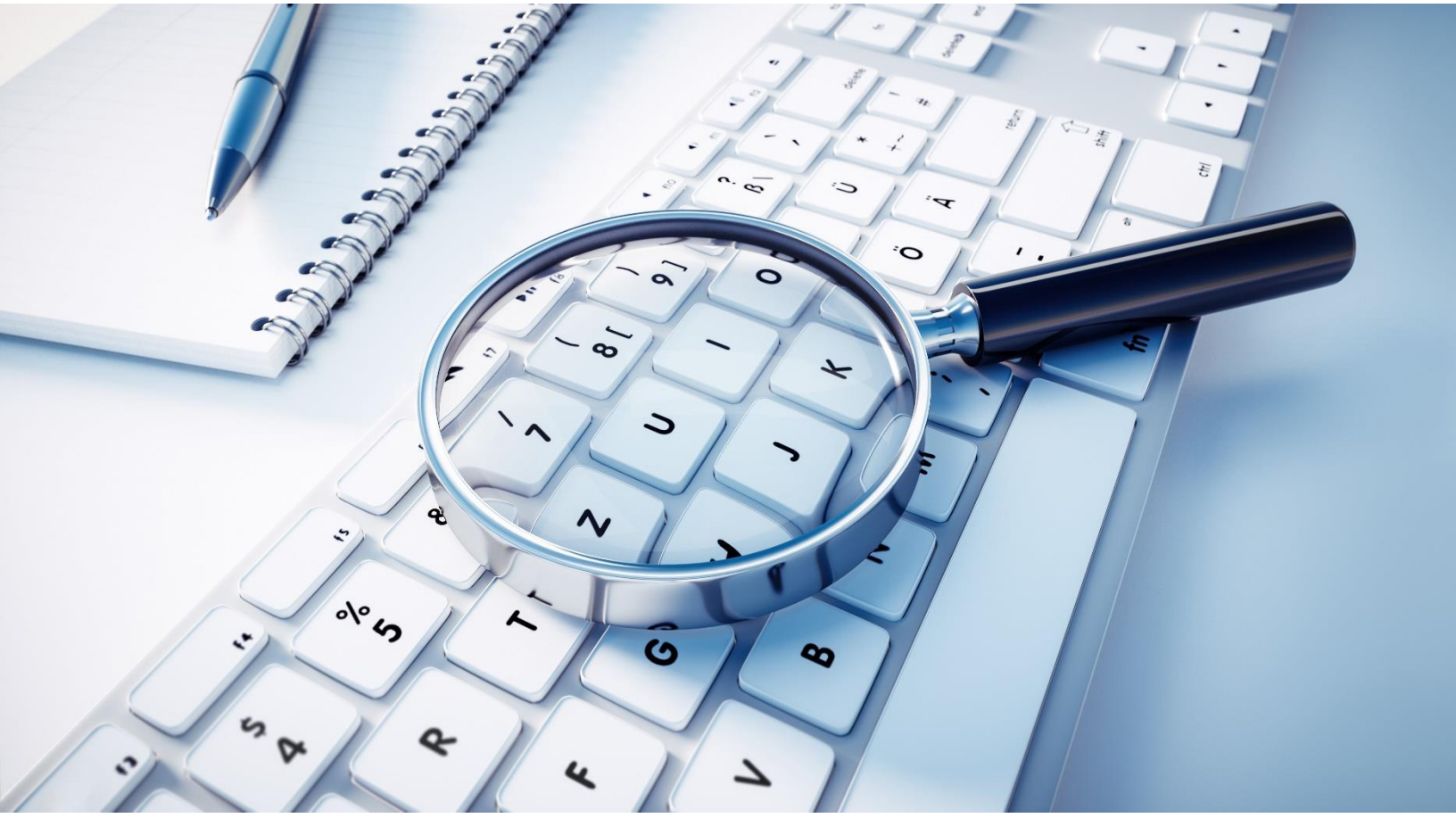
POL-0030: Compliance and enforcement approach and inspection strategy for clinical trials of drugs involving human subjects

November 30, 2021



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Disclaimer

This document does not constitute legislation. In the event of any inconsistency or conflict between the legislation and this document, the legislation takes precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the legislation and the applicable administrative policies.

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.

1. Purpose

The purpose of this policy is to inform all stakeholders involved in clinical trials about Health Canada's national compliance and enforcement (C&E) approach and inspection strategy for clinical trials of drugs involving human subjects regulated under:

- the *Food and Drugs Act* (the Act), and
- Part C, Division 5 "Drugs for Clinical Trials Involving Human Subjects" of the *Food and Drug Regulations* (the Regulations)

Refer to Appendix A – Glossary for the definition of "inspection" and other terms used in this document.

This document also briefly describes the inspection process used to assess whether the activities performed by a regulated party involved in the conduct of clinical trials of drugs in human subjects in Canada are in compliance with the Act and Part C, Division 5 of the Regulations.

The Act and the Regulations allow us to:

- monitor the sale and importation of drugs used in clinical trials in Canada
- enforce good clinical practices (GCP)
- take action(s) to protect the health, safety and rights of trial participants

2. Scope

This policy applies to you if you are a party involved in the conduct of clinical trials of drugs in human subjects in Canada.

Regulated parties that may be subject to clinical trial inspections by Health Canada include:

- sponsor
- qualified investigator (QI)
- contract research organization (CRO), including CRO specialized in bioequivalence (BE) trials

- site management organization (SMO)
- any other party involved in the conduct of a clinical trial

The Regulations clearly establish that the sponsor has the overall responsibility of conducting a clinical trial involving drugs in human subjects. In Canada, a sponsor may delegate any or all trial-related duties to other parties (e.g. CROs, SMOs) and as such, these parties may be inspected by Health Canada. However, sponsors remain accountable in all respects for the trial data's quality and integrity, and participant safety.

The Regulations do not differentiate between a commercial and a non-commercial sponsor (e.g. sponsor-investigator) and as such, the same requirements apply.

This document covers the following clinical trials of drugs conducted in humans in Canada:

- phases I to IV
- commercial or academic
- ongoing or completed
- involving pharmaceuticals, biologics, gene therapies, cell therapies, blood products, vaccines and radiopharmaceuticals for human use

This document does **not** apply to inspections of:

- clinical trials/investigational testing involving medical devices
- clinical trials involving natural health products (NHPs)
- observational studies, which do not include drug intervention

3. Background

Part C, Division 5 "Drugs for Clinical Trials Involving Human Subjects" of the Regulations, came into force on September 1, 2001. Regulatory activities conducted by Health Canada's Regulatory Operations and Enforcement Branch (ROEB) include inspections and other C&E activities (e.g. compliance verifications (CVs) and investigations) to assess compliance with the Act and the Regulations. These activities are conducted by Health Canada under the authority of section 23 of the Act. Health Canada inspectors are designated under subsection 22(1) of the Act.

Collaboration with all stakeholders involved in the conduct of clinical trials is essential to ensure compliance with the Act and the Regulations, including the requirement to comply with GCP. Part C, Division 5 of the Regulations provides for flexibility to follow international GCP standards in order to satisfy the requirements of the Regulations.

In May 1997, Health Canada adopted the *International Conference on Harmonization (ICH) E6(R1): Good Clinical Practice Consolidated Guideline* (ICH E6). ICH E6(R1) was amended in November 2016 to ICH E6(R2) to enhance sponsor oversight and management of clinical trials and to improve standards for electronic records and essential documents related to clinical trial data. The *ICH Guidance Document: Good Clinical Practice: Integrated Addendum to E6(R1), ICH Topic E6(R2)* (hyperlink to Health Canada's *Notice – Release of ICH E6(R2): Good Clinical Practice*) was fully adopted by Health Canada as of April 3, 2019.

In June 2019, the Act was amended to add sections 3.1 to 3.3 pertaining to clinical trials, including that "no person shall conduct a clinical trial in respect of a drug, device or prescribed food for a special dietary purpose unless the person holds an authorization issued under the regulations that authorizes the conduct of the clinical trial" (section 3.1 of the Act).

On August 20, 2019, Health Canada published a new *Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" (GUI-0100)*, to provide guidance in the interpretation of Part C, Division 5 of the Regulations, and specifically in terms of its relationship to ICH E6 in the Canadian context.

4. Compliance and enforcement activities

As part of its regulatory responsibilities, Health Canada monitors compliance and undertakes enforcement activities. Compliance is assessed through inspections and other C&E activities such as CVs. Regulated parties have **mandatory** responsibilities under the Act. Any party conducting a regulated activity can be inspected. Foreign entities that conduct regulated activities in Canada, or in relation to a product sold, imported or advertised in Canada are also subject to Canadian law.

The main objective for the inspection of clinical trials of drugs involving human subjects is to verify compliance with the Act and Part C, Division 5 of the Regulations. This includes, but is not limited to the verification of:

- compliance with the generally accepted principles of GCP, referred to in section C.05.010 of the Regulations

- the level of protection of the rights and safety of the research subjects in the conduct of clinical trials of drugs for human use
- the validity and integrity of the data

Since September 1, 2001, all clinical trials are subject to Part C, Division 5 of the Regulations, and CVs are carried out in accordance with this Division. CVs of clinical trials involving any regulated party may be initiated when there are reasonable grounds to believe that non-compliance may have occurred or is occurring, and that enforcement measures may be necessary (e.g. complaints received regarding specific trials, reports of adverse drug reaction(s) (ADR), reports from other regulatory authorities).

During an inspection or a CV, a regulated party is required to provide all reasonable assistance and information necessary for the inspector to perform their duties. An inspector may request that a regulated party provide evidence that its facility, equipment, and practices and procedures meet the applicable requirements.

Regulated parties are expected to:

- understand the relevant Act and Regulations and their obligations
- ensure their products, activities, and processes comply with the applicable laws
- assist inspectors during an inspection as required by law

Obstruction of inspectors will not be tolerated. The inspection provisions in the Act exist, in part, to provide protection to Canadians and study participants who are vulnerable to the risks posed by health products and their advertising. Preventing an inspector from inspecting, or knowingly making any false or misleading statements orally or in writing while the inspector is engaged in carrying out their duties or functions under the Act or the associated Regulations is a violation of subsection 24(1) of the Act, and is subject to penalties.

Depending on the classification of the health product involved, and the election of the prosecutor to proceed summarily or on indictment, a violation of either subsection 24(1) or subsection 23(13) of the Act could result in a prosecution under section 31 or section 31.2 of the Act. If convicted, a person would be liable to pay fines ranging from $500 to $5,000,000, or a term of imprisonment ranging from three (3) months to two (2) years, or to both a fine and imprisonment.

Similarly, subsection 23(13) puts a duty on the owner, the person in charge, and any person found in a place entered by an inspector, to provide all reasonable assistance and to provide all information the inspector reasonably requires.

If an inspector believes that a person obstructed, hindered, lied, or failed to give all reasonable assistance to the inspector, the inspector may notify the person involved, and/or their management as applicable, in order to remedy the situation. As is always the case, further C&E action may be taken in accordance with Health Canada's *Compliance and enforcement policy for health products (POL-0001)*. For example, a clinical trial can be suspended or cancelled if a risk to the health and safety of Canadians is identified.

The *Compliance and enforcement policy framework* provides information about Health Canada's approach to C&E, including roles and responsibilities, actions and tools, guiding principles and decision factors.

Refer to the *Compliance and enforcement policy for health products (POL-0001)* for more information on Health Canada's national C&E approach for health products regulated under the Act and its Regulations.

Under the Act, the inspector has certain powers to verify compliance with the Act and Regulations, and to prevent non-compliance. For example, in accordance with subsection 22.1(1) of the Act, an inspector may order a person to provide any documents, information or samples specified by the inspector. This information is to be provided on or before the date and time, and at the place and in the manner specified by the inspector.

For more information on the legislative provisions for inspector orders as provided for under the Act, refer to the *Policy on inspector orders for health products (POL-0139)*.

According to subsection 31.2(1), and subject to section 31.4 of the Act, a person who contravenes any provision of the Act or the Regulations, as it involves a clinical trial that relates to a therapeutic product, is guilty of an offence and liable on conviction to the increased fines and penalties set out in sections 31.2 and 31.4 of the Act.

All records accessed and obtained by inspectors during C&E activities (e.g. inspections, CVs) either in person or remotely, are handled in accordance with Health Canada's *Policy on collection and retention of records related to health product compliance and enforcement (POL-0140)*.

4.1 Clinical trial inspections

4.1.1 Risk-based site selection

The Clinical Trial Compliance Program (CTCP) within the ROEB is responsible for clinical trial site selection for inspections, in collaboration with the Therapeutic Products Directorate (TPD) and the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) of the Health Products and Food Branch (HPFB) of Health Canada.

A risk-based approach is applied in the site selection process to minimize the potential health risks inherent to clinical trials involving human subjects. The selection of sites for inspection is based on a variety of criteria. These criteria are collectively considered in order to select sites throughout all levels of the drug assessment and regulatory approvals process.

The boxes below describe the criteria that may be considered by Health Canada when selecting regulated parties for inspection.

The **selection of sponsors, CROs (including CROs specialized in BE trials), and SMOs** for inspection is made according to a number of criteria which may include, but are not limited to the following (not necessarily in order of priority):

- type and degree of experience of sponsor, CROs and SMOs (e.g. commercial vs. non-commercial, new sponsor/CRO/SMO)
- anything that may jeopardize the validity and the integrity of the data submitted to Health Canada (ICH-GCP principles), such as protocol non-compliance, informed consent issues, inadequate ADR reporting, etc.
- level of risk to Canadians (e.g. therapeutic area, pivotal study included as part of a new, supplementary or abbreviated new drug submission; NDS, SNDS, ANDS)
- volume of activities, such as the number of clinical trials conducted by the regulated party
- compliance history (if applicable), including:
    - previous trial suspensions/cancellations

  - severity of deficiencies/deviations (e.g. risk 1 (critical), risk 2 (major), risk 3 (minor) observations)
  - quality systems affected by the deficiencies/deviations (e.g. safety, data management, monitoring and/or others)
- status of corrective actions and/or preventive actions (CAPA). For example, CAPA still pending, acceptable or not, or completed and implemented, if applicable
- number of subjects enrolled in the clinical trials
- number of serious unexpected adverse drug reactions (SUADRs) submitted to Health Canada
- type of tasks delegated to CRO(s) and/or SMO(s)
- other factors, such as complaints from internal/external sources
- other criteria as identified by TPD and/or BRDD (if applicable)

The **selection of clinical trials at QI sites** for inspection is based on specific aspects of the clinical trial and the site, such as, but not limited to the following (not necessarily in order of priority):

- type of sponsor (e.g. commercial vs. non-commercial)
- type of site (e.g. located at large institution vs. small clinic)
- geographic location (i.e. sites selected in all provinces across Canada)
- level of risk to Canadians (e.g. therapeutic area, pivotal study included as part of a NDS, SNDS, ANDS)
- type of investigational product (e.g. pharmaceutical vs. biologic)
- novel therapies, dosage form/route of administration of the investigational product
- complexity of the clinical trial design, including its subject population
- observations made during past inspections/inspection history of the QI and sponsor (if applicable)
- number of clinical trials conducted at the site

- number of active subjects enrolled at the clinical trial site
- number of serious adverse events (SAEs)/ADRs/SUADRs at the clinical trial site
- other factors, such as complaints from internal/external sources
- other criteria as identified by TPD and/or BRDD (if applicable)

4.1.2 Inspection activity

Sponsors, QIs, CROs, SMOs or any other party conducting a regulated activity under Part C, Division 5 of the Regulations may be subject to inspection by Health Canada. Inspections are performed to assess compliance with the Act and its associated Regulations (particularly, Part C, Division 5) and the recognized GCP, as adopted by Health Canada.

Inspections of different types of regulated parties (e.g. sponsor, QI, CRO, SMO) are conducted each year in Canada, and may include re-assessments and re-inspections. The total number of inspections in a given year may vary, depending on the complexity of the inspections conducted, and the time required for other C&E activities. An inspection can be conducted during the open phase of a clinical trial (active/ongoing), or after its completion (closed/completed), particularly if it is in support of a drug submission (e.g. NDS, SNDS, ANDS).

Inspections at QI sites, also referred to as clinical trial sites, allow for verification of source documents, including medical records, drug accountability, and drug storage conditions.

For the purposes of QI inspections by Health Canada, a clinical trial site is defined as one trial by one QI at one location (address).

A clinical trial may be conducted at one or multiple QI sites. For example, a multicenter clinical trial that is conducted at eight (8) different QI sites represents 8 potential inspections. Each site could be inspected for that specific trial.

Inspections at sponsors, CROs and/or SMOs, referred to as system-based inspections, allow for the verification of the systems and procedures that describe how the trial is conducted and monitored. For example, these inspections verify whether plans and standard operating procedures (SOPs) are adequate, and if they are followed and

updated as required. They also allow for the verification of the systems and procedures that describe the way clinical trial data is generated, modified, processed and reported. System-based inspections of sponsors, CROs and SMOs may involve or trigger inspection of QI sites.

Inspections at sponsors, CROs and/or SMOs follow a cyclical inspection approach where each sponsor, CRO and SMO is inspected periodically. The frequency of inspection takes into account risk factors and will generally be higher for less compliant parties, and lower for those entities who demonstrate greater compliance. The frequency of inspection may change if information is received about potential non-compliance depending on the nature and severity.

Additionally, other factors, as identified in section 4.1.1 above, may influence the frequency of inspections for a given regulated party, as they may affect the rights and safety of clinical trial subjects, or the evaluation of a drug submission.

An inspection may be conducted by a single inspector, or multiple inspectors, depending on the complexity of the inspection, or for other reasons as determined by Health Canada. Additionally, subsection 23(7) of the Act allows designated inspectors to be accompanied by any other individual the inspector believes is necessary to help them exercise their powers or perform their duties or functions. For example, ROEB may request that a clinical trial reviewer or other appropriate individual accompany the inspector(s) during the inspection, when their expertise is required.

For further information, refer to the *Policy on Individual(s) accompanying a health products inspector (POL-0141)*.

Before an inspection

In most cases, Health Canada gives notice before an inspection takes place in order to facilitate the organization of the inspection. An inspector contacts the regulated party to schedule the inspection. Health Canada may also request that the regulated party provide certain information or documents in advance to prepare for the upcoming inspection.

Subsection 23(3) of the Act allows a designated inspector to enter any place as described in subsection 23(1) by accessing it remotely by means of telecommunication. The same principles apply to inspections conducted remotely as they do to in-person inspections.

When entry to the place is in-person, the regulated party may or may not be given notice prior to the inspection. However, when entering remotely by telecommunication, the owner or person in charge will be given notice of the entry.

The *Policy on accessing the premises of a regulated party remotely to verify compliance (POL-0138)* provides additional information about conducting inspections, including CV activities, by means of telecommunication.

Inspectors may not give advance notice for an in-person inspection if:

- there is an immediate risk to the health and safety of the trial subject(s)
- this approach will better assess compliance with the Act and the Regulations

At the discretion of the inspector, a request for changing the date for a scheduled inspection may be acceptable, with a reasonable justification from the regulated party.

On average, an in-person inspection can be expected to take approximately **five (5) business days** (on-site), whereas a remote inspection (using telecommunication) may take up to **ten (10) business days**. However, more or less time may be required.

During an inspection

During an inspection, Health Canada inspectors will introduce themselves, present their identification, and will explain the purpose and scope of the inspection. The inspector(s) will review the regulated party's processes, records, documents and procedures. Health Canada inspections are consistent with internationally accepted practices, comparable with global regulatory counterparts.

During a **clinical trial inspection at a QI site** (on-site and/or remotely), Health Canada inspectors look carefully at many different areas to assess compliance with the Act and Part C, Division 5 of the Regulations, including, but not limited to, the following (not provided in any order of priority):

- review of the clinical trial site documentation (e.g. regulatory documents, ethics approval(s), delegation log, etc.), as per the established inspection plan

- verification that data have been accurately transcribed from source documents (e.g. original medical records) to case report forms (CRFs)
- participant care and informed consent
- staff qualification and training
- protocol/GCP compliance
- observed practices versus approved written procedures and regulatory requirements
- review of on-site/remote monitoring activities
- reporting of problems, such as serious adverse drug reactions (SADRs) and SUADRs
- manufacturing, handling and storage of the investigational drug(s) in accordance with the applicable good manufacturing practices (GMP), protocol and labelling requirements
- written agreements with sponsor and/or third parties (e.g. CRO, SMO, laboratories, drug supplier, storage)
- integrity of data and record keeping
- validation of electronic systems (e.g. electronic CRF, electronic subject diaries), if applicable
- adequacy of CAPA implemented, subsequent to the previous inspection(s), if applicable

During a **sponsor/CRO/SMO inspection** (on-site and/or remotely) by Health Canada, inspector(s) will review one, several or all of the following systems/items, but not limited to (not provided in any order of priority):

- organization and personnel
- quality systems
- training
- trial master file (TMF)/archiving
- monitoring
- protocol/GCP compliance

- project management
- regulatory and ethics approvals
- contracts and agreements
- pharmacovigilance/safety
- investigational drug(s) management
- computer system(s) validation
- data management and statistics
- study reports

The selection of the systems/items will depend on the scope of the inspection and will be established in the inspection plan provided to the regulated party.

Additional guidance to understand and comply with Part C, Division 5 of the Regulations, including GCP, and to help you prepare for a clinical trial inspection by Health Canada can be found here:

- *Guidance document: Part C, Division 5 of the Food and Drug Regulations: Drugs for Clinical Trials Involving Human Subjects (GUI-0100)*
- *International Council on Harmonization (ICH) Guidance Document: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)* (hyperlink to Health Canada's Notice)

Risk observations

Inspectors make "observations" when they identify deficiencies or deviations from the Regulations. Each observation is classified by level of risk:

- Critical (Risk 1)
- Major (Risk 2)
- Minor (Risk 3)

For more information on the rating of observations and the overall inspection rating, refer to the *Classification of observations made in the conduct of inspections of clinical trials (GUI-0043)*.

At the end of an inspection

At the end of an inspection, Health Canada presents the observations to the regulated party during an "Exit Meeting". This meeting provides the regulated party with the opportunity to ask for clarifications prior to the report being finalized. The "Final Inspection Exit Notice" (inspection report) is then issued to the regulated party. This document outlines any observations (deficiencies/deviations) noted by the inspector. Inspection reports are written in such a way as to protect the identity of clinical trial subjects.

The drug and health products inspections database (DHPID)

Shortly after the inspection, and before the "Final Inspection Exit Notice" is issued to the regulated party, Health Canada posts an initial inspection deficiency(ies) (IID) report online. This provides a preliminary overview of any initial deficiencies found during the inspection.

After the Exit Notice is issued, Heath Canada will post the inspection report card (IRC) to summarize the inspection observations and rating. These reports can be found on the *Drug and health products inspections database (DHPID)*.

Note that the results from the system-based inspections of sponsors, CROs and/or SMOs are not included in the DHPID at this time, but may be added in the future.

The regulated party must take corrective actions that address the observations in order to be in compliance with the Act and the Regulations. The regulated party may also need to create and implement a CAPA plan that includes target dates for completion. The timeline to respond to Health Canada and provide the CAPA is **thirty (30) calendar days** (or **60 calendar days** in case of a Notice of suspension), unless otherwise specified by the inspector.

For QI inspections, the "Final Inspection Exit Notice" gives the regulated party an overall inspection rating. This rating is based on the number/nature and risk level of observations at the time of the inspection:

- **Compliant (C)** – The regulated party has demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations. A "**C**" rating does not mean that there are no observations or corrective actions required.

- **Non-compliant (NC)** – The regulated party has not demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations.

In all cases of non-compliance (and for inspections in support of a drug submission), the results will be communicated to the relevant Health Canada review directorate (e.g. TPD, BRDD) with ROEB's recommendation to take appropriate C&E actions, as required:

- immediate suspension or "intent to suspend" the authorization to sell or import a drug for the purposes of a clinical trial (in its entirety or at a clinical trial site)
- assessment of the validity of the data submitted

Health Canada will take appropriate enforcement actions as required following an inspection, in accordance with Health Canada's *Compliance and enforcement policy for health products (POL-0001)*.

4.2 GMP inspection of drugs used in clinical trials

As per paragraph C.05.010(j) of the Regulations, every sponsor shall ensure that the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices (GMP) referred to in Divisions 2 to 4, except sections C.02.019, C.02.025 and C.02.026.

During a clinical trial (GCP) inspection, Health Canada inspectors will verify that the drugs used in clinical trials meet GMP requirements. For example, adequate evidence of GMP compliance would include:

- certificates of manufacture and certificates of analysis (CoA or batch certificates) for the lots of clinical trial material imported into Canada
- evidence of approved lot release by a qualified individual

GMP inspections are conducted separately from clinical trial (GCP) inspections, and will be in accordance with the regulations and policies pertaining to the manufacture and sale of drug products in Canada.

For additional information on GMP requirements for clinical trial drugs, refer to the *Guidance Document – Annex 13 to the Current Edition of the GMP Guidelines: Drugs Used in Clinical Trials (GUI-0036)*.

For more information on GMP inspections, refer to the *Good manufacturing practices inspection policy for drug establishments (POL-0011)*.

4.3 Compliance verification (CV)

Problems or concerns related to the performance of clinical trials may originate from:

- external sources, or referrals from other jurisdictions
- internal branch and departmental sources, such as TPD and BRDD

When a potential non-compliance or risk has been identified by Health Canada, CV activities will be conducted, as deemed necessary. This may include actions, such as information gathering via remote or on-site visits. Health Canada will take appropriate enforcement actions to address non-compliance and mitigate risk, in accordance with Health Canada's *Compliance and enforcement policy for health products (POL-0001)*.

4.4 Investigation and Prosecution

In certain circumstances, Health Canada may conduct an investigation into potential offences under the Act or make a referral to law enforcement.

An investigation involves collecting evidence under the authorities available in the Criminal Code of Canada (e.g. search warrant and production order). Priority will be given to contraventions by parties who demonstrate disregard for the legislative and regulatory requirements; who have a history of contravening the Act or who are engaging in activities that could cause serious harm (e.g. unlicensed activities, intentional avoidance of the law or sale of unapproved products).

Health Canada may refer the results of its investigation to the Public Prosecution Service of Canada, recommending prosecution in relation to offences under the Act and the Criminal Code of Canada where applicable.

Refer to Health Canada's *Compliance and enforcement policy for health products (POL-0001)* for more information about investigation and prosecution.

Appendix A – Glossary

Acronyms and abbreviations

ADR: Adverse drug reaction

AE: Adverse event

ANDS: Abbreviated new drug submission

BE: Bioequivalence

BRDD: Biologic and Radiopharmaceutical Drugs Directorate

C: Compliant

CAPA: Corrective actions and preventive actions

C&E: Compliance and enforcement

CoA: Certificate of analysis

CRF: Case report form

CRO: Contract research organization

CTA: Clinical trial application

CTCP: Clinical Trial Compliance Program

CV: Compliance verification

DHPID: Drug and health products inspections database

GCP: Good clinical practices

GMP: Good manufacturing practices

GUI: Guide/Guidance document

HPFB: Health Products and Food Branch

ICH: International Conference on Harmonization

ICH E6: International Conference on Harmonization Guidance E6: Good Clinical Practice Consolidated Guideline

IID: Initial inspection deficiencies

IRC: Inspection report card

NC: Non-compliant

NDS: New drug submission

NHP: Natural health product

POL: Policy

QI: Qualified investigator

ROEB: Regulatory Operations and Enforcement Branch

SAE: Serious adverse event

SADR: Serious adverse drug reaction

SMO: Site management organization

SNDS: Supplemental new drug submission

SOP: Standard operating procedure

SUADR: Serious unexpected adverse drug reaction

TMF: Trial master file

TPD: Therapeutic Products Directorate

Terms

These definitions explain how terms are used in this document. If there is a conflict with a definition in the *Food and Drugs Act* or associated regulations, the definition in the Act or regulations prevails. Definitions quoted from other documents are identified in brackets at the end of the definition.

Adverse drug reaction (ADR): means any noxious and unintended response to a drug that is caused by the administration of any dose of the drug. (*réaction indésirable à une drogue*) (C.05.001)

Adverse event (AE): means any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and includes an adverse drug reaction. (*incident thérapeutique*) (C.05.001)

Clinical trial: means an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamics effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug. (*essai clinique*) (C.05.001)

Consistent with Section 2 of the *Food and Drugs Act*, a clinical trial is defined as a study, involving human subjects, for the purpose of discovering or verifying the effects of a drug, a device or a food for a special dietary purpose.

Compliance: The state of conformity of a regulated party (including a corporation, institution, individual or other legal entity) or a product with a legislative or regulatory requirement. (*conformité*) (POL-0001)

Compliance verification: Actions taken to verify compliance in response to information regarding known or suspected non-compliance with the applicable requirements of the *Food and Drugs Act* and its associated Regulations. This includes actions such as information gathering via either off-site or on-site visits. (*vérification de la conformité*)

Contract research organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. (*organisme de recherche sous contrat*) (ICH E6 1.20)

Drug: means a drug for human use that is to be tested in a clinical trial. (*drogue*) (C.05.001)

Enforcement: Actions that may be taken to compel or induce compliance in order to mitigate the risk identified by non-compliance with the Act and its associated regulations. (*application de la loi*) (POL-0001)

Good clinical practices (GCP): means generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons, and the good clinical practices referred to in section C.05.010. (*bonnes pratiques cliniques*) (C.05.001)

Import: means to import a drug into Canada for the purpose of sale in a clinical trial. (*importer*) (C.05.001)

Importer: The sponsor or person designated by the sponsor who is responsible for the import of the drug into Canada for the purpose of sale in a clinical trial. Individual investigators at the clinical trial sites in Canada may serve as Canadian Importers. (*importateur*) (*Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*)

Inspection: Monitoring and assessment against the applicable requirements of the *Food and Drugs Act* and its regulations. Inspections are routinely conducted based on risk to assess compliance. (*inspection*)

Inspector: Any person designated as an inspector under section 22 of the *Food and Drugs Act*. (*inspecteur*)

Investigation: Actions taken to gather evidence to support case referral for potential prosecution regarding specific violations of the *Food and Drugs Act* and its associated regulations. This includes activities carried out under the Criminal Code, such as taking witness statements and executing search warrants. (*enquête*)

Observation: A deficiency or deviation from Part C, Division 5 of the Regulations noted by an inspector during a clinical trial inspection that is confirmed in writing in the Final Inspection Exit Notice. The observations are classified as "critical" (risk 1), "major" (risk 2) or "minor" (risk 3). (*observation*)

Observational study: A type of study where the investigators do not manipulate the use of, or deliver, an intervention (e.g. do not assign subjects to treatment and control groups) nor collect samples from subjects that are outside of routine care, but only observe subjects who are (and sometimes subjects who, as a basis of comparison, are not) exposed to the intervention, and interpret the outcomes. (*étude d'observation*)

Qualified investigator (QI): means the person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

(a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and

(b) in any other case, a physician and a member in good standing of a professional medical association. (*chercheur qualifié*) (C.05.001)

Re-assessment: A follow-up inspection carried out in situations where the regulated party was assigned an overall "C" rating on the previous inspection but the number or type of observations contained in the previous Inspection Exit Notice are such that corrective action is required within a timely manner. The inspection is focused on, but not restricted to, those requirements of the Act and its associated regulations where observations were made. (*réévaluation*)

Re-inspection: A follow-up inspection carried out in response to the assignment of a non-compliant ("NC") rating. The inspection is focused on, but not restricted to, those regulatory requirements where observations were made. (*ré-inspection*)

Sell: includes offer for sale, expose for sale, and have in possession for sale and distribute, whether or not the distribution is made for consideration. (*vente*) (section 2 of the *Food and Drugs Act*)

The definition is broad in scope, and includes dispensing of drugs to subjects by physicians.

Serious adverse drug reaction (SADR): means an adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death. (*réaction indésirable grave à une drogue*) (C.05.001)

Serious unexpected adverse drug reaction (SUADR): means a serious adverse drug reaction (SADR) that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug. (*réaction indésirable grave et imprévue à une drogue*) (C.05.001)

Site or trial site: The location(s) where trial-related activities are actually conducted. (*lieu ou lieu de l'essai*) (ICH E6, 1.59)

Health Canada's interpretation is one site equals one trial by one QI at one location (address).

Site management organization (SMO): is an organization that manages research at clinical trial establishments. (*organisme de gestion d'établissements*)

Sponsor: means an individual, corporate body, institution or organization that conducts a clinical trial. (*promoteur*) (C.05.001)

Therapeutic product: means a drug or device or any combination of drugs and devices, but does not include a natural health product within the meaning of the *Natural Health Products Regulations.* (*produit thérapeutique*) (section 2 of the *Food and Drugs Act*)

Appendix B – References

Web addresses were accurate at the time of publication of this document.

Legislation

Food and Drugs Act
laws-lois.justice.gc.ca/eng/acts/f-27/

Food and Drug Regulations
laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/

Quality documents

Policies

POL-0001: Compliance and enforcement policy for health products
www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/policies-standards/compliance-enforcement-policy-0001.html

POL-0011: Good manufacturing practices inspection policy for drug establishments
www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/policies-standards/inspection-policy-canadian-drug-establishments.html

POL-0138: Policy on accessing the premises of a regulated party remotely to verify compliance
www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/policy-accessing-premises-regulated-party-remotely-verify-compliance.html

POL-0139: Policy on inspector orders for health products
www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/policy-inspector-orders-health-products.html

POL-0140: Policy on collection and retention of records related to health product compliance and enforcement
www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/policy-collection-retention-records-health-product-compliance-enforcement.html

POL-0141: Policy on Individual(s) accompanying a health products inspector
www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/policy-individual-accompanying-health-products-inspector.html

Guidance documents

GUI-0036: Guidance Document – Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines Drugs Used in Clinical Trials
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

GUI-0043: Classification of observations made in the conduct of inspections 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

GUI-0100: Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects"
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

Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html

Web pages/Associated documents

Compliance and enforcement policy framework
www.canada.ca/en/health-canada/corporate/mandate/regulatory-role/what-health-canada-does-as-regulator/compliance-enforcement-framework.html

Drug and health products inspections database (DHPID)
www.canada.ca/en/health-canada/services/inspecting-monitoring-drug-health-products/drug-health-product-inspections.html

International Council for Harmonisation (ICH) Guidance Document: Good Clinical Practice: Integrated Addendum to E6(R1) ICH Topic E6(R2) (hyperlink to Health Canada's *Notice – Release of ICH E6(R2): Good Clinical Practice*)
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