Clinical Trials and Safety Surveillance of Drugs in Development

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Overview

• Clinical Trials Regulations
• Clinical Trial Applications – filing requirements
• Pre-Market Safety Surveillance of Drugs in Development: Procedures Established
• Harmonization of ADR Reporting Requirements
• Future Considerations
Organizational Structure

Health Products and Food Branch

- Biologics & Genetic Therapies Directorate
  Biologics & Radiopharmaceuticals

- Therapeutic Products Directorate
  Pharmaceuticals

- Office of Clinical Trials
Office of Clinical Trials

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New Clinical Trials Regulations in 2001

CT regulatory amendments came into force in 2001 with two overarching objectives:

- to strengthen protections for human research participants
- to increase research and development investment in clinical trials in Canada
Objectives of the 2001 New Clinical Trials Regulations

• Shorten application review times without endangering health and safety

• Improve safety mechanisms for research subjects

• Regulator be more involved in clinical trials monitoring and follow-up

• Improve access to innovative therapies and advice from Canadian physicians with research expertise
2001 CT Regulatory Framework – Clinical Trial Applications (CTA)

• New authorization requirements for phase I, II and III clinical trials:
  □ 30 day default review period for clinical trial applications
    [C.05.006(1)(b)]
  □ 7 day target for bioequivalence and appropriate Phase I clinical trial applications

• Clear and transparent requirements for application amendments, notification, labelling, and record keeping

• Strengthened oversight of clinical trials by requiring REB review.
New Regulatory Framework – Patients Safety

• Reporting of serious unexpected adverse drug reactions

• Framework for inspection program for all clinical trials against generally accepted principles of Good Clinical Practices

• Clear Ministerial authority to refuse an application, suspend or cancel the sale of drugs for use in clinical trials in Canada
CTA: 30-day Default System

• Scope [C.05.002]
  □ clinical trials in Phase I, II and III
  □ applications for Phase IV trials are not required [DIN/NOC]
  □ clinical trial amendments [C.05.008]
  □ notifications [C.05.007]

• Application requirements the same for all sponsors [industry and independent investigators – C.05.005]
• Additional information must be submitted within 2 days [C.05.009]
CTA: 7-day Target System [policy]

• **Scope**
  - Bioequivalence
  - Phase I trials in healthy volunteers

• **Exemptions**
  - Phase I trials in patients

• **Sponsors must receive No Objection Letter prior to initiation of the trial**
Additional reporting requirements

• Prior to commencement of the clinical trial [C.05.006(1)(d)]

☐ information on clinical trial site and qualified investigator

☐ information on REB for each clinical trial site

☐ information on REB refusal if applicable

☐ proposed date for commencement of the clinical trial at each site
Research Ethics Boards

- Defined in the Regulations [C.05.001]
  - comprised of at least 5 members
  - majority of members must be Canadian citizens/permanent residents
  - required expertise includes: science, medicine, ethics, law and community member
- Functions must be carried out according to Good Clinical Practices [C.05.012(3)(h)]
- Approval of protocol and risk/benefit statement found in informed consent form must be obtained prior to the initiation of the trial at a site [C.05.005(d)]
- Refusal must be reported [C.05.005(d)]
Qualified Investigators

- Defined in the Regulations [C.05.001]
  - Physician or Dentist

- Conducts trial according to Good Clinical Practices [C.05.012(3)(f)]

- No more than one qualified investigator per site

- Qualified investigator is responsible to make medical decisions
Sponsor’s Obligations

• Good Clinical Practices [C.05.010]
• Labelling of Clinical Trial Supplies [C.05.011]
• Record keeping requirements [C.05.012]
  □ 25 year retention period
  □ Storage locations not specified
  □ Qualified Investigator Undertaking
  □ REB Attestation
• Information and Samples [C.05.013]
• ADR reporting [C.05.014]
Suspension and Cancellation

- **Suspension [C.05.016]**
  - reasonable grounds
  - written notice indicating applicable site[s]
  - 30 day window with the opportunity to be heard

- **Cancellation [C.05.017]**
  - safety concern
  - written notice indicating applicable site[s]
  - 60 day window
Review Process

- Pre-CTA meeting:
  - particularly useful for new active substances or applications that will include complex issues that may be new to Health Canada
- Filing of CTA
- Clinical Trial Site Information Form
- CTA amendments
- Notification
  - administrative changes to the protocol
  - discontinuation not related to safety
  - some Quality changes
Filing a CTA

• Regulatory requirements:
  - The CTA is composed of three parts (modules):
    - Module 1 - contains administrative and clinical information about the proposed trial
    - Module 2 - contains Quality (Chemistry and Manufacturing) information about the drug product(s) to be used in the proposed trial
    - Module 3 - contains additional supporting Quality information
Content of a CTA

- Drug Submission Application Form (HC/SC 3011)
- Information on Prior-related Applications
- Investigator's Brochure
- Protocol Synopsis (PSEAT-CTA) or Submission Rationale / Brief Summary of the Drug Product
- Study Protocol(s)
- Informed Consent Document(s)
- Clinical Trial Site Information
- Canadian Research Ethics Board(s) Refusals
- Foreign Refusals
Investigator-Initiated CTAs

• Requirements

☐ HPB 3011
☐ Investigator’s Brochure (or Product Monograph)
☐ rationale for proposed study
☐ Informed Consent
☐ Quality information, if drug not marketed in Canada
CTA-A Requirements

• copy of the amended Protocol,
  □ a copy of the most recently authorized protocol,
  □ a clear description of the proposed changes (i.e., original wording vs. revised wording),
  □ and a rationale for each proposed change.
• If the purpose of the amendment is to extend the duration of the study,
  □ a copy of the amended Investigator's Brochure or an addendum to the Investigator's Brochure must be provided [C.05.008 3b].
When to file a CTA-A

• Sponsors must file a Clinical CTA-A when the proposed changes to the protocol:
  ✓ affect the selection, the criteria for selection, monitoring, or dismissal of a clinical trial subject
  ✓ affect the evaluation of the clinical efficacy of the drug
  ✓ alter the risk to health of a clinical trial subject
  ✓ affect the safety evaluation of the drug
  ✓ extend the duration of the clinical trial
Notifications

• Requirements

☐ Administrative amendment

☐ Safety amendments that are implemented immediately
  – considered as an amendment subject to 30 day default
  – submit Clinical Trial Attestation
Continuous Assessment

• Premature discontinuation of trial
  - detailed rationale
  - impact on proposed/ongoing trials
  - confirm that distribution stopped, unused drug returned and investigators notified

• Serious and Unexpected ADRs to be faxed to appropriate Directorate
Continuous Assessment

- Other Expedited Reports include:
  - for expected serious ADRs, an increase in the rate of occurrence
  - significant hazard to patient – e.g., drug does not appear to be working in life-threatening disease
  - major safety finding from newly completed animal study
Safety Updates/IB updates

• Required on an annual basis, or as requested

• Processed as Notifications

☐ Investigator’s Brochure (IB) annually

☐ new IB should reflect all safety information

☐ global safety of drug
Clinical Trials Adverse Drugs Reactions Reporting Requirements
Division 5 of the Food and Drug Regulations
C.05.014

- During a clinical trial the sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada:
  - where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
  - where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information.
ICH E2A Guidance Document: Clinical Safety Data Management

All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications).
ADR Reports Received when a Drug is in Clinical Trials in Canada

• For a drug not marketed in Canada:
  - Canadian and international clinical trial ADR reports
  - International spontaneous reports if the drug is marketed elsewhere

• For a Drug marketed in Canada but back in clinical trials for a new indication:
  - Canadian and international clinical trial ADR reports
  - Canadian and international spontaneous reports
Definitions

ICH E6 GCP and ICH E2A
Adverse Events

Any untoward occurrence in a clinical trial subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment

includes ADR, abnormal laboratory finding, symptom, disease, worsening of symptoms
Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose

Where causal relationship between a medicinal product and an adverse event is at least a reasonable possibility

Reporting health care professional or the sponsor assess the causality (attributability):

possibly, certainly, definitely, probably, possibly or likely related or not related.

“plausible relationship”, “suspected causality”, “causal relationship cannot be ruled out”
Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational medicinal product). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.
Serious Adverse Drug Reaction

- Adverse events significant enough to lead to important changes in the dose, population, in the monitoring, consent forms...

- ICH agreed definition of a SADR:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization
  - results in persistent or significant disability/incapacity, or
  - is a congenital anomaly/birth defect
Minimum Criteria for Expedited Reporting

• All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs

• Currently, no standard international nomenclature for the degree of causality between a medicinal product and an event. Terms used: certainly, definitively, probably, possibly or likely related or not related. The expression “reasonable causal relationship” accepted by CIOMS VI
Safety Surveillance of Drugs in Development
Objectives

• Timely detection of adverse drug reactions while the drug is in development:
  □ first and foremost to protect human subjects participating in clinical trials
  □ To gain an understanding of the safety profile of the drug as early in its development as possible

• Risk Assessment and Risk Management:
  □ Evaluation of the nature and severity of risk associated with a product based on the safety information gathered
  □ Occurs throughout a product’s lifecycle
Goals

• To build the safety profile for each product from its first clinical trial in Canada to market authorization

• To provide a locus of support for the Clinical Trial Groups I and II as well to the Clinical Bureaus when a new drug application is submitted

• To create a centre of expertise for the assessment of pre-market pharmaceuticals that is better positioned to ensure the safety of Canadians in clinical trials and to identify safety issues on drugs in development
Drugs in Clinical Trials in Canada

• Per year, around 700 drugs are in clinical trials: this includes new drugs as well as marketed drugs back in clinical trials for a new indication

• The ADR Division receives a daily average up to 500 reports/day events from national and international sources, including ADR reports from clinical trials and post-market spontaneous reports
Repository of Safety Information and Database Management

- Adverse Drug Reactions reports are:
  - Received by fax or by courier.
  - Dated and triaged (fatal, non-fatal, clinical trials, spontaneous reports...)
  - Entered into the ADR database
  - Reports separated by indications and assigned to Assessment Officers

- CIOMS VI:
  In order to assure standardized signal detection and evaluation processes, data entry quality and completeness is paramount
Safety Signal Generation

- Review and analysis of each incoming ADR report
- Periodic review and analysis of aggregate data
- Look for trends or for any event of concern
- Review the Investigator’s Brochure and/or Product Monograph (if drug is marketed), to check if event is “labelled” if not:
  - Review preclinical and clinical studies on the drug as well as advisory documents from other governmental organizations (EMEA, FDA, etc)
  - Bring forward the event/signal and the supporting evidence for discussion to the ADR Division’s signal generation weekly meeting for decision analyses, plausibility assessment, etc
Weekly Pre-market Safety Signal Meetings

• Discuss the newly identified potential risk and its implication(s)
• Discuss the actions to be taken:
  □ Continuation of the routine monitoring
  □ Request further safety information from sponsor
  □ Protocol amendments:
    □ Changes to monitoring procedures
    □ Alteration of patient population (inclusion and exclusion criteria; changes in dose or dose schedule…)
  □ Revision to the Informed Consent Form
  □ Amendment to the Investigators’ Brochure or the Product Monograph if the drug is already marketed
  □ If serious safety issue: termination of the clinical trial
Safety Signals Assessment

The analysis will be done by:

- Controlling confounding factors (for example: case-series analysis; data extraction and selection, statistical analysis…)
- Integration of the safety information and risk assessment
- Review the Study Protocol and Informed Consent Form
- Recommendations for risk mitigation/management, including revisions to the Investigator’s Brochure, Protocol, Informed Consent Form, etc.
- Prepare a Final Safety Report document
- Communicate the safety signal to:
  - The Clinical Trials Group
  - If a New Drug Submission is under review, share the safety signal with the respective Clinical Review Bureau
  - If the drug is marketed and in clinical trials, share the signal with the Clinical Review Bureau and with MHPD
Limiting Factors to Safety Signal Generation
Quality of the ADR Reports received

• **Clinical trials reports:**
  - Detailed information about the patient, including accurate estimates of exposure to a drug
  - Most often causality is provided by either the investigator and/or the sponsor
  - Follow-up information on patient/event is provided throughout the trial
  - The controlled setting of a clinical trial allows for confounding factors to be taken into account

• **Post-Market Reports**
  - Missing key information from most post-market spontaneous cases received: usually do not contain accurate accounts of dose exposure and do not include patient history, making their assessment very difficult

• **CT-ADR:** High quality reports that allow the identification and efficient assessment of safety signals
Limited Guidance in Reporting and Interpreting Safety Data

• Underreporting of ADRs: when drug is being developed simultaneously in different countries and where Guidance Documents, such as the ICH E2A and ICH E6, have not yet been adopted by some of these countries

• Inaccurate coding of the safety event: Loss of the safety information between the verbatim term and the preferred term

• Interpretation of the safety data received
Harmonization of ADR Reporting Requirements
(I) Adherence/adoption to the ICH E2A Requirements for Reporting ADRs

- Guidance to sponsors and investigators
- Standards for expedited reporting
- Larger number of ADR reported increase the probability for the identification of safety signals
- Subsequent under-reporting of adverse events reduces the ability to quantify risk accurately
- A more accurate numerator when taking into account patients’ exposure
(II) Standards for Expedited Reporting: key definitions and concepts

- Distinction between serious and severe reaction
- When an event is expected vs unexpected
- When an expected event becomes unexpected and needs to be reported?
- How causality assessment is done
- How to manage/report blinded therapy cases?
- What information is required in the expedited reports of ADRs
(III) Codification and Standard Global Practices

- Internationally agreed medical coding terminology-dictionary MedDRA (Medical Dictionary for Drug Regulatory Activities) that sponsors should use for events codification. Inconsistencies in clinical event classification and/or codification are common not only among investigators within the same study but also among sponsors using different adverse event coding terminologies/dictionaries (CIOMS VI)

- Consistency between different countries’ regulations to allow for standard global practices by Industry in reporting of safety data
Future Considerations
HPFB’s Canada Vigilance Project as a repository for pre- and post-market safety information

- Replacement of multiple systems (across the Branch) with a single database for both pre- and post-market product safety information
- Direct access to product safety information across its lifecycle
- Adoption of international standard terminology
- Significant increase in data quality through standards, common look-ups, and validations for a fast and full retrieval of safety information on a drug when needed
- Capacity for signal generation and statistical analysis
- Provide the ADR Division with a superior advantage for a timely signal generation and drug safety assessment
References:

Clinical Trial Manual:

Health Canada / ICH Guidance Document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting:

ICH Guidance E6: Good Clinical Practice: Consolidated guideline:

Division 5 of the Food and Drug Regulation: Guidance for Clinical Trial Sponsors: Clinical Trial Applications:

Thank You