1.2 - Overview of Regulation of Clinical Trials in Canada

Presentation to APEC Preliminary Workshop on Review of Drug Development in Clinical Trials

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Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Objectives

Regulations & guidelines
Number of Clinical Trial Applications
Current initiatives
Clinical Trial Regulations for Drugs

• Regulations prior to September 1st, 2001, were:
  – the IND regulations implemented in the early 60’s
  – under Division 8 of Part C of the Food and Drug Regulations

• Current regulations under Division 5 have been in effect since September 1st, 2001, and were implemented with two overarching objectives:
  – strengthen protections for human research subjects
  – increase R & D investment in clinical trials in Canada
A regulatory framework that...

• Incorporates essential elements of Good Clinical Practices
  – Sound research protocol
  – Informed consent of research subjects
  – Obtain REB approval and continuing oversight
  – Appropriate qualifications of investigator and staff
  – Monitor and report serious, unexpected, adverse drug reactions
  – Maintain accurate records

• Gives the Minister clear authority to reject, suspend or cancel the authorization of a clinical trial
Guidelines adopted by Health Canada

• ICH

  – Quality: Q1A(R2), Q1B, Q1C, Q1D, Q1E, Q1F, Q2A, Q2B, Q3A(R), Q3B(R), Q3C, Q5A, Q5B, Q5C, Q5D, Q6B, Q7A

  – Multidisciplinary: M3, M4

  – Safety: S1A, S1B, S1C, S1C(R), S2A, S2B, S3A, S3B, S4A, S5A, S6, S7A, S7B, Health Canada Q & A document for S7B and E14

  – Efficacy: E1, E2A, E3, E4, E5, E6, E7, E8, E9, E11, Health Canada Addendum to E11, E14
Guidance documents developed by Health Canada

- Standards for clinical trials in type 2 diabetes in Canada
- Clinical Trial Applications
- Clinical Trial Applications for comparative bioavailability studies for pharmaceuticals
- Quality (chemistry and manufacturing) guidance for pharmaceuticals, biologics, and radiopharmaceuticals
- Inclusion of women in clinical trials
- Requirements for tuberculosis screening
- Submission of pharmacogenomic information
Clinical Trials Regulated (1)

- Trials subject to a clinical trial application (CTA):
  - Phase I, II, and III trials
  - Includes trials investigating off-label uses
  - Independent of type of sponsor
Clinical Trials Regulated (2)

- Phase IV trials (investigations on-label):
  - exempted from CTA filing
  - REB approval required
  - GCPs must be observed
  - record-keeping required
Regulatory Requirements

• Legal accountability lies with the sponsor

• Clinical Trial Application (CTA) and CTA-amendment

• 30 calendar day review period with 2-day turnaround for requests for additional information
  – No-Objection-Letter (NOL)
  – Not-Satisfactory Notice (NSN)

• Post authorization requirements, including reporting of serious, unexpected adverse drug reactions

• Clinical trial site inspection program
Overview of CTA Process

Requirements after NOL

NOL

SPONSOR

Dialogue

NSN

Withdrawal

Study/Trial

CTA

Pre-CTA Meeting

Withdrawal requirements after NOL.
Format of a CTA

- Module 1
  - Administrative information
  - Clinical
- Module 2
  - Chemistry and manufacturing templates
- Module 3
  - Supporting chemistry and manufacturing information
Content of a CTA

- Covering letter
- HC/SC form 3011
  - Attestation
- Protocol and Informed Consent Form
- Investigator’s Brochure or Product Monograph
- PSEAT
- Clinical trial site information form (CTSI)
- REB refusals
- Letter of authorization to cross-reference information filed by a different sponsor
- Module 2 and 3 with chemistry & manufacturing
CTA Review by Health Canada

• The reviewers assess all the information provided by the sponsor, including:
  – Scientific merit: rationale, study design, patient population, dosage regimen, safety and efficacy variables
  – Sufficient information to support the safety of the drug for the purposes of the clinical trial
  – Adequate communication of potential risks and anticipated benefits to clinical trial subjects
  – Acceptable chemistry and manufacturing information

• Other sources of information:
  – ICH guidelines
  – Current clinical practice guidelines
  – Published literature & information
  – Expert opinion (e.g., consultation with other HC bureaus, scientific advisory committees)
Requirements after NOL

- Clinical Trial Site Information form and REB approval
- Serious, Unexpected, Adverse Drug Reaction Reporting
- Changes to the protocol or quality information (amendments and notifications)
- Premature discontinuation of a trial
- Research Ethics Board refusals
- Lot release information provided through fax-back form (for Biologics)
- Records retention
CTA-Amendments

• A *CTA-amendment* is required for changes to the protocol that:
  – affect the selection, monitoring or dismissal of a clinical trial subject
  – affect the evaluation of the clinical efficacy of the drug
  – alter the risk to the health of a clinical trial subject
  – affect the safety evaluation of the drug
  – extend the duration of the clinical trial

• Changes to the chemistry and manufacturing that may affect the safety or quality of the drug

• If clinical trial endangers the health of a clinical trial subject or other person, may implement an amendment immediately and file the *CTA-amendment* within 15 days
Biologics and Radiopharmaceuticals

Number of CTAs

Year

Phase 1 HH
Phase 1 Patients
Phase 1/2
Phase 2
Phase 2/3
Phase 3
Phase unassigned
Ongoing Initiatives

– Review of the regulatory framework supported by Division 5

– Implementation of Canada Vigilance System for the management of ADRs

– Research Ethics: development of voluntary standards for REBs

– Clinical Trials Registration and Disclosure
Summary

• Clinical trials regulated under a legal framework incorporating GCPs
• CTA required for Phase I, II, III
• 30 calendar day review period with 2 day turnaround for requests for additional information
• Ongoing requirements after authorization
• Clinical trial inspection program
• ICH guidelines and HC guidance documents
• Number of CTAs have increased since 2001, but stable since 2004
• Ongoing HC initiatives impacting on clinical trials
## References

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