Health Canada Santé Canada

Therapeutic Products Directorate

Direction des produits thérapeutiques

Health Products and Food Branch

Direction générale des produits de santé et des aliments

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

Regulatory Framework

Food and Drugs Act
Definition of Drug and types of drugs
Inspection authority

Food and Drug Regulations
Part C: Drugs

Other Regulations…

Division 5:
Drugs for Clinical Trials Involving Human Subjects

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

Study/Trial

NOL

CTA

SPONSOR

Dialogue

NSN

Withdrawal

Pre-CTA Meeting

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

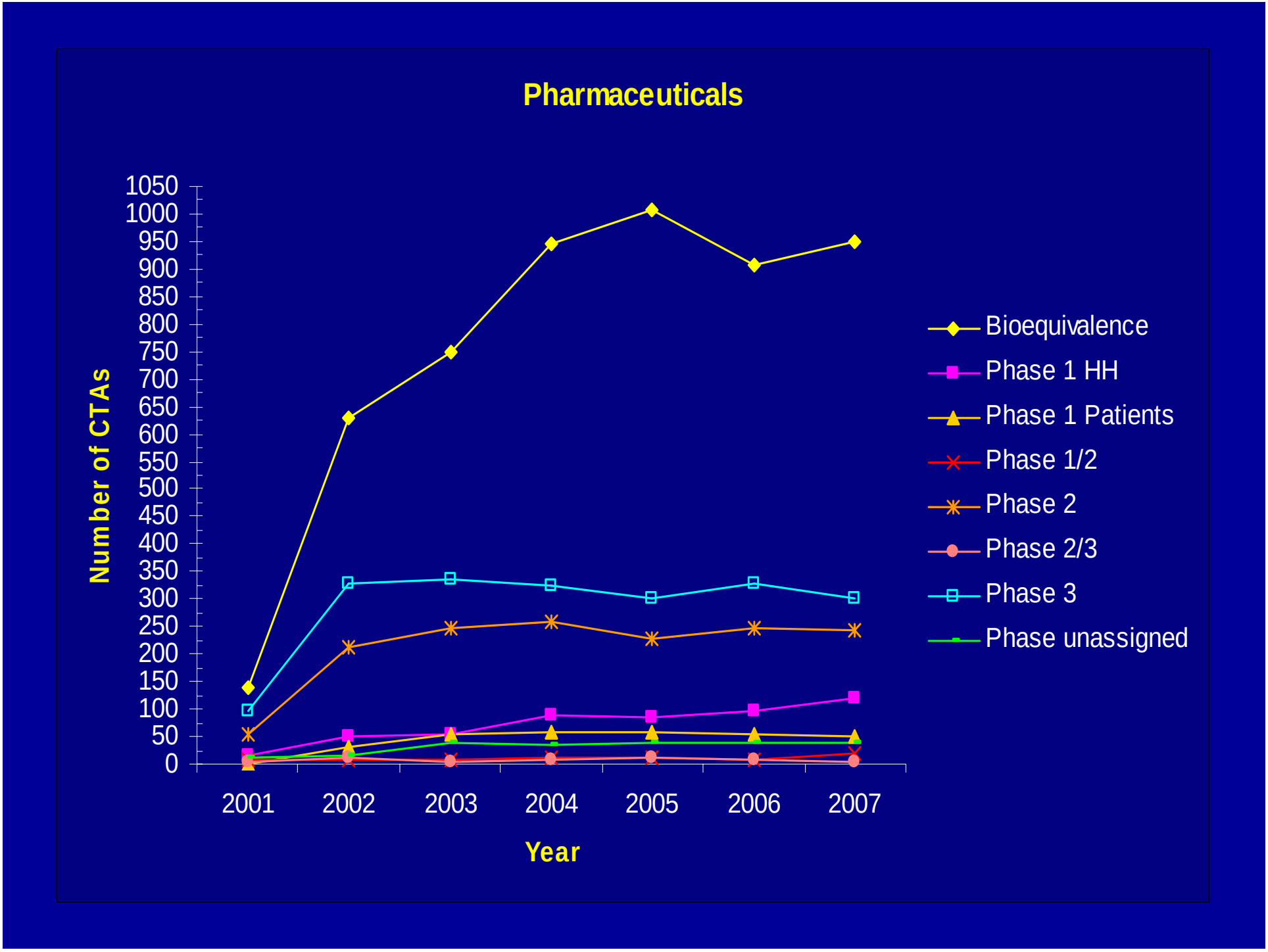
- The reviewers assess all the information provided by the sponsor, including:
  - Scientific merit: rationale, study design, patient population, dosage regimen, safety and efficacy variables
  - Sufficient information to support the safety of the drug for the purposes of the clinical trial
  - Adequate 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)

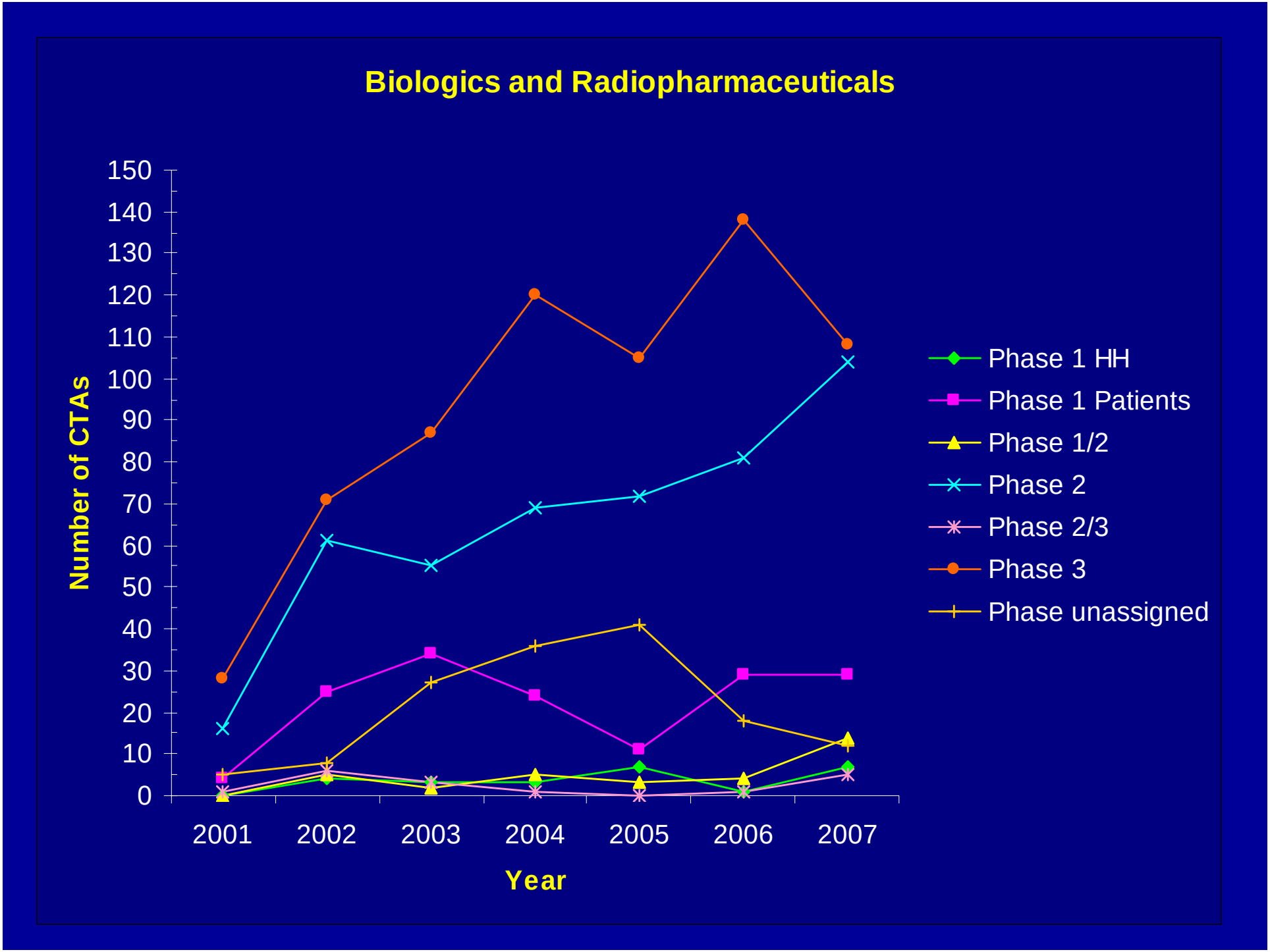
Requirements after NOL

- 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


Pharmaceuticals
Number of CTAs
1050
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
2001
2002
2003
2004
2005
2006
2007
Year
Bioequivalence
Phase 1 HH
Phase 1 Patients
Phase 1/2
Phase 2
Phase 2/3
Phase 3
Phase unassigned


Biologics and Radiopharmaceuticals
Number of CTAs
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
2001
2002
2003
2004
2005
2006
2007
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

Division 5 Regulations	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/1024_e.pdf
Clinical Trials e-Manual	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_intro_e.html
Review of the Regulatory Framework for Clinical Trials	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/index_e.html
Registration and Disclosure of Clinical Trial Information	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/enreg-clini-info/index_e.html
Other/Relevant Information related to Clinical Trials	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/index_e.html http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/qtqtc/index_e.html