Health Canada Santé Canada

Your health and safety...our priority *Votre santé et votre sécurité... notre priorité*

Helping the people of Canada maintain and improve their health

Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

NEW INVESTIGATOR CLINICAL TRIALS COURSE

NCIC CTG Collaborations and Interactions:

Academic, **Regulatory** and Industry

Dr. Norman Viner
Chief, Clinical Trials Division
Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada

Canada

Outline

1. **Brief Overview (Health Canada 101)**
   - Regulations and Review
   - Organizational Structure

2. **What we do and how we do it**
   - How do we interact with Industry and what are the benefits?
   - Progressive Licensing Model: Regulating the lifecycle of therapeutics
   - Clinical Trials Design: A regulatory view
   - Endpoints and Disease Activity
   - Protean Diseases provide best examples
   - Challenges in measuring endpoints
   - Benefit/Risk assessment

3. **Last thoughts and challenges**

LEGISLATIVE FRAMEWORK

FOOD AND DRUGS ACT

Food and Drug Regulations

PART C: DRUGS
Division 1
Division 1A: Establishment Licenses
Division 2: Good Manufacturing Practices
Division 3
Division 4
Division 5: Clinical Trials Involving Human Subjects
Division 6
Division 7
Division 8
Division 9

Joint Reviews

CONTROLLED DRUGS AND SUBSTANCES ACT

Medical Devices Regulations

Natural Health Products Regulations

FOOD & DRUG REGULATIONS: PART C, DIV 5

- **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

FOOD & DRUG REGULATIONS: PART C, DIV 5

- Canadian clinical trial regulations for biologics, radiopharmaceuticals, and pharmaceuticals.
- In effect since September 1st, 2001.
- Applies to the “sale” of a drug for the purposes of clinical testing in or on humans, independent of who is sponsoring or funding the trial.
- Includes several definitions and requirements [pre & post authorization].
- Gives the Minister clear authority to reject, suspend or cancel the authorization of a clinical trial [e.g., Phase I, II or III, bioequivalence and comparative bioavailability trials, TQT/QTc study, etc.].
- Two overarching objectives:
  - **Strengthen protections for human research subjects; and**
  - **Increase research and development investment in clinical trials in Canada.**

ORGANIZATIONAL STRUCTURE

Health Canada: Branches and Agencies

Ministers and Officers

- Minister of Health
- Deputy Minister
- Associate Deputy Minister
- Chief Public Health Officer

Agencies

- Canadian Institutes of Health Research
- Hazardous Materials Information Review Commission
- Patented Medicines Prices Review Board
- Public Health Agency of Canada

Branches, Offices and Bureaus

- Audit and Accountability Bureau
- Chief Financial Officer Branch
- Corporate Services Branch
- Departmental Secretariat
- First Nations & Inuit Health Branch
- Health Policy Branch
- **Health Products & Food Branch**
- Healthy Environments & Consumer Safety Branch
- Legal Services
- Office of the Chief Dental Officer
- Pest Management Regulatory Agency
- Public Affairs, Consultation and Regions Branch
  - Regions

ORGANIZATIONAL STRUCTURE

- Health Products and Food Branch
  - Biologics & Genetic Therapies Directorate
    Biologics & Radiopharmaceuticals
    - Centre for Policy & Regulatory Affairs
      - Regulatory Affairs Divisions
  - Therapeutic Products Directorate
    Pharmaceuticals
    - Office of Clinical Trials
      - Submission Management/ Review/Adverse Drug Reaction

BGTD

Centre for Vaccines and Evaluation
Alan Mortimer, Ph.D.
Director

Office of Regulatory Affairs
Georgette Roy, M.BA.
Director

Centre for Blood and Tissues Evaluation
Peter Ganz, Ph.D.
Director

Centre for evaluation of radiopharmaceuticals and biotherapeutics
Agnes Klein, M.D.
Director

Regulatory Affairs BTO & Vaccines
Meera Makim
Manager

Regulatory Affairs Biothera-peutics & Radiopharm-aceuticals
Georgette Roy
Manager

Submission Screening Units

Submission Screening Units

CTAS

Vaccine Evaluation
Gina Coleman, M.D.
Chief

Clinical Evaluation Division
Farid Hindieh, M.D.
Chief

Hemostatic Agents & Blood Substitutes
Will Stevens, PhD.
A/Chief

Plasma Derivatives
Will Stevens, PhD.
Chief

Bacterial & Comb Vaccines
Maria Baca-Estrada, PhD.
Chief

BTOX
Francisca Agbanyo, PhD.

Viral Vaccines
Aline Rinfret, PhD.
Chief

Clinical Trials Division
Norman Viner, M.D.
Chief

Pre-Market Clinical Review Division I
Jian Wang, M.D., Ph.D.

Pre-Market Clinical Review Division II
Kader Kourad, M.D., Ph.D.

Monoclonal Antibodies
Chantal Cazeault, B.Sc.
Chief

Hormones & Enzymes
Nancy Green, Ph.D.
Chief

Cytokines
Dexi Dai, Ph.D.
Chief

Radiopharmaceuticals
Anthony Ridgway, Ph.D., Chief

TPD: OFFICE OF CLINICAL TRIALS

A/Director
Dr. John Patrick Stewart

SAP
Ian MacKay, MSc
Manager

Associate Director
Joanna O'Reilly

ADR
Hoda Eid, Ph.D
Manager

SMD
Burt James
Manager

Clinical I
Celia Lourenco, Ph.D.
Manager

Clinical II
Yadvinder Bhuller, M.Sc.
Manager

Quality
Paul Smeaton
Manager

Health Canada ROLES and RESPONSIBILITIES (CTs)

To minimize the probability of risk that participants may be exposed to:

- Assess the protocol, informed consent and the information provided in the IB
- Assess the quality related information (e.g. purity, stability etc.)
- ADRs – Safety Database in place to collect such information

Sponsor's ROLES and RESPONSIBILITIES

- **Notification**
  - Notify within 15 days
  - C&M change that does not affect quality or safety of drug*
  - Protocol change that does not alter the risk to subject*
  - Updated IB (annually or as needed)
- **Amendment**
  - Subject to 30-day default review
  - Safety concerns – sponsor may make one or more of the amendments immediately - Provide CTA-A within 15 days
  - Otherwise, Changes can only be implement after NOL for CTA-A is received
- **GCPs**
  - **Labeling**
  - **Records**
    - **QIU form**
    - **Maintain records for 25 years**

Sponsor's ROLES and RESPONSIBILITIES

- Serious Unexpected ADRs
  - Expedited Reporting: Serious and Unexpected
  - Inside or outside Canada
  - Neither Fatal nor life-threatening = 15 days
  - Fatal or life-threatening = within 7 days and within 8 days complete follow-up report
- Discontinuation of a CT
  - No later than 15 days
  - Detailed rationale
  - Impact on proposed/ongoing trials
  - Confirm that distribution stopped, unused drug returned and investigators notified

CLINICAL TRIAL APPLICATIONs (CTAs):

Approximate number of Applications received by TPD and BGTD combined (not including bioequivalence trials)

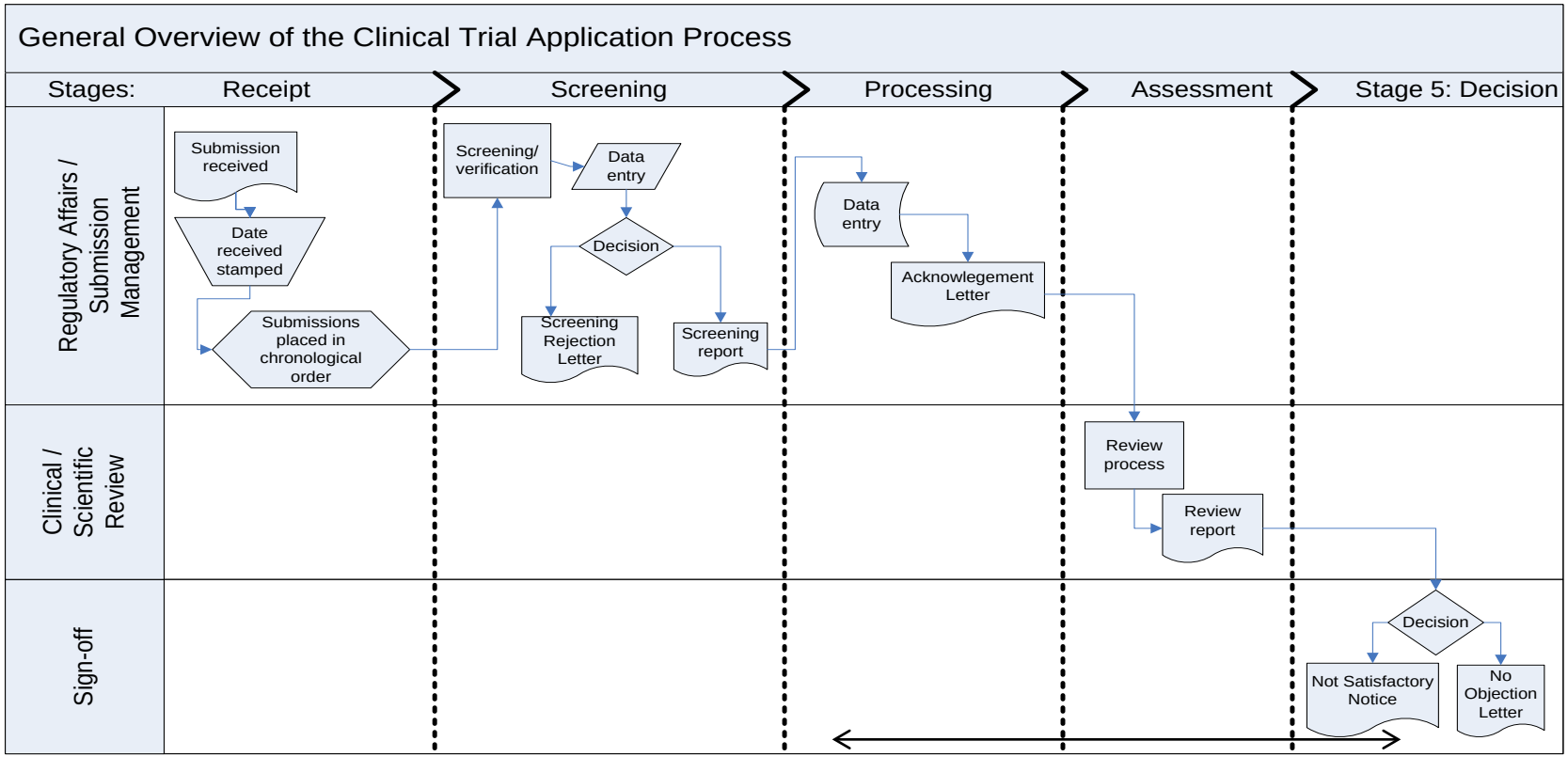
- CTAs ~ 1,000 per year
- CTA-AMs ~ 1,300 per year

REVIEW PROCESS

- The review looks at 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)

CLINICAL TRIAL APPLICATION: PROCESS

Note: there is not very much time for the assessment!



30 day default [7-day target: does not apply to biologics]

How do we interact with Industry?

- Interactions with Industry can be formal or informal
- The purpose and scope differ depending upon the degree of formality and the overall purpose of each meeting
- Interactions with Industry are increasingly viewed as a “best practices” approach to carry out regulatory mandates
- Interactions with Industry can also occur at multiple levels of both Government and Industry

Mechanistic Interactions during drug development

- What are we consulted on?
  - How to approach the filing of a clinical trial application?
  - Is the product a drug?, a biological?, a device?, a combination product?
  - Who/which part of the organisation will conduct the evaluation of the clinical trial and the subsequent submission for marketing?
  - Is there a possibility that other sections of the regulations apply than the obvious ones?

Types of Interactions during drug development

- Meetings may be conducted by teleconference or in person (e.g. pre-CTA meetings)
- Ongoing informal consultation during drug development often happens as the sponsor works on their plans and changes them as development progresses or not
- Best examples of these interactions are when academic centres or research network approach the regulator to obtain guidance on their plans, strategy and logistics, an ongoing process

Timing of Interactions during development

- Types of meetings:
  - Early: Pre Phase I; Pre Phase II
  - End of Phase II
  - Other consultation meetings
  - Later:
    - Often held for information only on a submission just prior to filing of a marketing submission
    - Other, various situations usually for clarification from the sponsor for benefit of the regulator or their own benefit (clarifications on questions)

Interactions during drug development

- Pre-submission meetings with multiple objectives:
  - Seek concurrence to development strategies and plans on a product basis
  - Provide a view of current status of knowledge on the product/drug
  - Seek advice on how the agency views the science: this is not scientific advice in the way it is viewed by the EMA, but allows the agency to make its views known

Benefits to the Regulator

- Understand the sponsor's development plans and strategies
- Have an opportunity to ascertain the status of the drug product under development
- Helps to evaluate the file and minimises questions posed during the CT and premarket evaluation periods
- Allows for the timely completion of the evaluation
- Allows to improve the safety of the study and avoid pitfalls

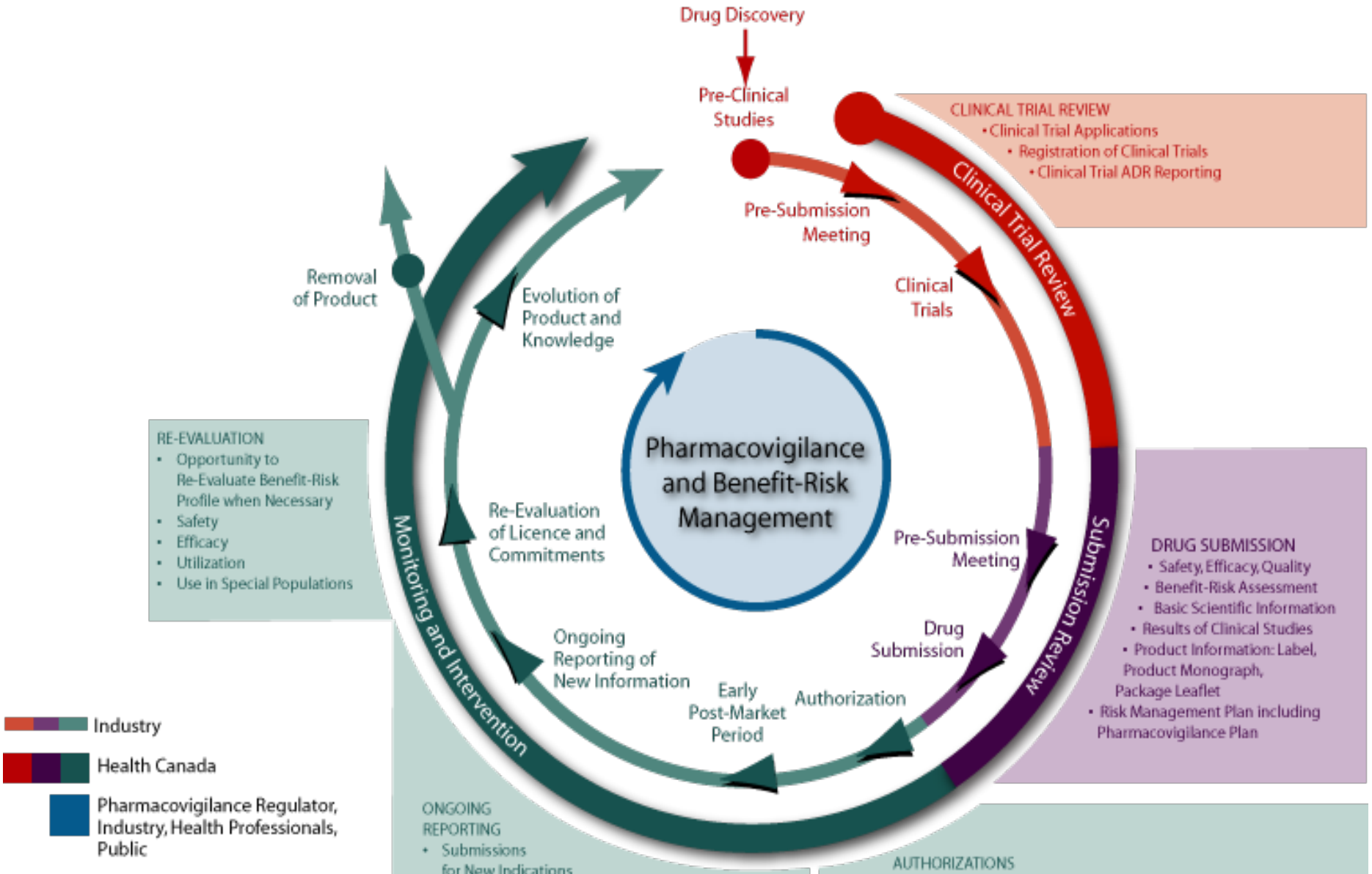
Benefits to Industry and other sponsors

- Understanding of the thinking of the regulator on the specific product and subject matter
- Opportunity to pose targeted questions and be provided specific answers
- Opportunity to start thinking, early, about their marketing submission
  - Most pertinent for: overseas sponsors, small biotech companies, academic institutions and research networks
- Opportunity to ensure consistency on the part of the regulator

Interactions during the evaluation of a CT

- Interactions occur frequently with written clarifications requested on areas of weakness or on inconsistencies
- These interactions can be at the request of the regulator to ensure clear understanding of a question prior to its being forwarded
- They can also be at the request of a sponsor to explain the rationale of a question posed and discuss a path to resolution. May result in application withdrawal and resubmission

Progressive Licensing Model



Clinical trials design: A regulatory view:
How do sponsor's arrive at their final designs

- Consultation with major regulatory agencies (EMA and FDA)
- Less consultation with smaller agencies (e.g. Canada)
- Consultations with investigators and/or other experts and biostatisticians
- Consideration may be given or not, to practice guidelines and/or standards of care.
- The result is a hybrid design that may satisfy all regulators, some or none

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Do endpoints actually measure disease activity?

- Some of the best examples are drawn from Oncology,
  - Patient Reported Outcomes (PROs)
  - Several antineoplastics or drugs used in patients with cancer authorized for market based on PROs:
  - Surrogate endpoints vs measures of clinical benefit **(at the heart of the matter)**
    - Examples: Mitoxanthrone in Prostate Cancer; Gemcitabine in Pancreatic Cancer; Topotecan in SCLC; Palifermin in chemotherapy-induced mucositis; Eculizumab in Paroxysmal Nocturnal Haemoglobinuria;
- The above have commonalities in outcome ascertainment
- The longer-term clinical benefit is uncertain

Challenges in measuring endpoints

- Incidence and prevalence of disease
- Size of clinical trials - Does size matter?
- Do CT results measures as disease activity translate into clinical benefit (of interest to regulators and Provincial Health Care Systems)
- Do the endpoints qualify to “measure disease status” and “improvements”
- Influence of Personalised Medicine on the design, conduct and outcome of trials
- Effects on the applicability and practicability of outcomes

Regardless of the endpoints and how established, there are multiple challenges in establishing scientifically and clinical valid endpoints that the regulator can analyse to everyone’s satisfaction

Some Thoughts

- The regulatory system as well as the healthcare delivery-related technology assessment like solid evidence and a level of certainty: this presents challenges to everyone, not always easy to resolve
- That is why regulators may be at times hesitant to recommend novel designs and novel outcomes without adequate validation
- If the process is unsuccessful, a product that is potentially useful may never be marketed
- However, despite the ‘conservative nature’ of the Regulatory process we remain open to innovation as the current trial designs do not provide certainty

Some of the Regulator's challenges

- Resource Issues : Maintaining corporate and scientific knowledge
- 30-day default period/7-day administrative targets
  - Reviewers have a very short time frame to arrive at a review decision.
- No control on what comes in: Fluctuations in workload with a relatively stable # of reviewers and screeners => catalyst for stress.
- Increasing Complexity of Trials:
  - Increased complexity in science, types of products, and treatment of disease [e.g., gene therapies, product combinations, nanotechnologies, etc.].
  - The sponsor is the expert not the Regulator
- Lack of clarity over regulations:
  - Interpretation = > Opportunity for flexibility?

Thank you!

- to the audience, for your attention
- Dr. Agnes Klein, Director of CERB (a wonderful mentor) and,
- my staff and colleagues, for the ongoing opportunity to consider many points of view.

Any questions?

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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
Information on the Inspection Program	http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/index_e.html
ADR for Clinical Trials: Expedited Reporting Summary Form	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctadr_dceim_e.pdf
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
Government Electronic Directory Services	http://direct.srv.gc.ca/cgi-bin/direct500/TE?FN=index.htm

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ICH E8 – General Considerations for Clinical Trials	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e8-eng.php
Management of Drug Submissions	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php
Clinical Trial Site Information Form	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctsif_dldcf_e.pdf
HC/SC 3011 Form	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/hc3011_sc3011-eng.php
Electronic Specifications for Clinical Trial Applications	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/notice_cta_avis_dec-eng.php
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