Review Operation

“Setting Up the Business”

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.
Topics to Discuss

• Context
• Canadian Perspectives on Staffing CT Review Group
• Challenges
• summary

Health Canada: Branches and Agencies

Ministers and Officers
• Minister of Health
• Deputy Minister
• Associate Deputy Minister
• Chief Public Health Officer

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
• Clinical Trials

• Healthy Environments & Consumer Safety Branch
• Legal Services
• Office of the Chief Dental Officer
• Pest Management Regulatory Agency
• Public Affairs, Consultation and Regions Branch
  • Regions

Agencies
• Canadian Institutes of Health Research
• Hazardous Materials Information Review Commission
• Patented Medicines Prices Review Board
• Public Health Agency of Canada
ADVANCED WORKSHOP : REVIEW OF DRUG DEVELOPMENT IN CLINICAL TRIALS

BANGKOK, 2-6 FEB 2009

APEC LSIF PROJECT “Capacity Building For Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 2)”
Health Products and Food Branch (HPFB)

Directorates and Offices

- Biologics and Genetic Therapies Directorate
  - Clinical Trials x 2
- Food Directorate
- Health Products and Food Branch Inspectorate
- Marketed Health Products Directorate
- Natural Health Products Directorate
- Office of Consumer and Public Involvement
- Office of Management and Program Services

- Office of Nutrition Policy and Promotion
- Departmental Biotechnology Office
- Office of the Assistant Deputy Minister
- Policy, Planning and International Affairs Directorate
- Regional Operations
- Therapeutic Products Directorate
  - Clinical Trials
- Veterinary Drugs Directorate

Regulatory Framework

- Business set up should match the Regulations and compliment the review process
- Screening – for completeness
- Assigning to a Review – Manager’s ‘triage’ role
- Initial Review
- Information/clarification = communication with the sponsor
- Timelines for each step
- Final decision
  - No objection
  - Voluntary withdrawal
  - Not satisfactory letter
  - ability to resubmit without prejudice
He who studies medicine without books sails an uncharted sea, but
He who studies medicine without patients does not go to sea at all.

~ Sir William Osler, 1st Baronet

Competencies of staff

- Including manager
- Clinical perspective is imperative
- Mix of expertise – to match the submissions
  - Minimum PhD or MD
- Mix in BGTD
  - Licensed Physicians (part time – tele-workers): Neurologist, Internist, Gastroenterologist, General practitioner
  - Full time staff: Veterinary Toxicologist, Molecular biologist, unlicensed physicians; Romania x 2, China, Guatemala, Armenia and soon (hopefully) an Argentinean Pediatrics Endocrinologist
Clinical perspective is imperative

- Although the majority of CTs come from industry for the purpose of drug registration
- Others that can and should get captured by Competent Authorities’ Regulations include:
  - Academic
  - Clinical Trial Networks, eg.
    - National Cancer Institute (NCI/C)
    - Children’s Oncology Group (COG)
    - National Surgical Adjuvant Breast and Bowel Project (NSABP)
    - Eastern Clinical Oncology Group (ECOG), etc.

Flexibility in the Work Place

Working from Alternate Locations:
- Agreements
- Issues of working off site with deadlines

Fostering a collaborative approach
- Culture of trust
- Respect
  - Safety in numbers
    “none of us is as smart as all of us”
Health Products and Food Branch

Three Clinical Trial Groups in Health Canada

HC’s Clinical Trial set up – iterative process, was one big organization split apart and then has grown organically.

Pharmaceuticals: Therapeutic Products Directorate (TPD)
- chemically synthesized or derived
- small molecules
  - OCT

Biologics: Biologic and Genetic Therapies Directorate (BGTD)
- vaccines, hormones, animal/cell derived molecules, blood products
- complex compounds
  - CBE - CTD
  - CERB - CTD

Post Market (MHPD)
- overlap with safety issues for products still in CT
- (with licensed indications)
BGTD Organization

Regulatory Affairs Directorate (RAD)
part of BGTD’s Centre for Policy and Regulatory Affairs
- BQ-RAD (Biotherapeutics, Quality)
- BTOV-RAD (Blood, Tissue, Organs and Vaccines)

Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics
CERB-CTD
- 9.9 FTEs including a manager

Centre for Biologic Evaluation CBE-CTD
- 2.8 FTEs

Frequent Interaction between CT Review Groups

- smaller biologic molecules can be manufactured synthetically
  - eg hormones, antigens/adjuvants for use in/as vaccines

- target same indications
  - eg. VEGF/EGFR inhibitors, immunosuppressants

- Grouping of products
  - Heparins moving towards being classified as a blood product
  - Oligonucleotides: should they be reclassified as biologics (Gene Therapy) despite being chemically synthesized?

- Harder to define therapeutic approaches
  - eg. Genetically altered Oncolytic Viruses: blend of therapeutic vaccine, gene therapy and viral therapy
Quality (CMC) Review of Clinical Trials

- Different models are in place for Pharmaceutical Drugs and Biologics at Health Canada:
- For Pharmaceuticals, review of the Quality information provided for Clinical Trial drugs is carried out by a dedicated group in the Office of Clinical Trials. This allows for more focussed expectations and interactions between Clinical and Quality reviewers and centralized management of review activity.
- For Biologics, Review of the Quality information is carried out by review staff also responsible for review of New Drug Submissions and post market Changes, organized along Product lines. This allows for more product-specific expertise, and linking expectations and information from clinical development through to licensure.
Background of Quality Reviewers

• Typically Quality reviewers have graduate degrees in a relevant area of science pertinent to the products regulated, and an understanding of the methods of manufacture and analytical testing applied.

• Depending on the product area this could mean various streams of chemistry (analytical, organic, pharmaceutical), biology, biochemistry, molecular biology, immunology, virology, physiology, pharmacology etc.

• Most of our review staff come from either academic or pharmaceutical manufacturing backgrounds

Regulatory Framework

• Business set up should match the Regulations and compliment the review process
  • Requires clear regulatory Mandate and Authority for Decision-making
  • Regulations should be supported by clear Guidances and Policies (your own or adopted) available to all stakeholders that describe:
    • Regulatory expectations (interpretation of regulation)
    • Information requirements (guidance or templates)
    • Decision Making Process
    • Consequences of Decisions
  • Regulations should also be supported by some mechanism for enforcement of compliance and adequate resourcing
Quality System

- Goal: Clear consistent and predictable decision-making
  - Outcomes and timelines
- A set of documentation of internal processes and procedures that describe and define roles, responsibilities and performance expectations around key business activities
  - Screening – for completeness
  - Assigning to a Reviewer – Manager’s ‘triage’ role
  - Initial Review
  - Information/clarification = communication with the sponsor
  - Decision-making and communication of decision
- Supporting these should be job descriptions, a hiring process, systems for information storage and retrieval, and defined managerial responsibility for the processes and their outcomes.

Improvement is an iterative process, and there needs to be a clear means to identify, track and address gaps

Challenges

Resource Issues:

- Small # of reviewers, not organized by Indication or Disease area
  - BGTD clinical reviewers have to cover a broad knowledge base on different disease areas, which has the potential to lead to ill-informed decisions:
    - “Need to know what you don’t know”
- Reviewers have a very short time frame to arrive at a review decision and an increasing workload with a relatively stable # of reviewers and screeners

Increasing Complexity of Trials:

- Increased complexity in science, types of products, and treatment of disease (e.g., gene therapies, product combinations, nanotechnologies)
More Challenges

Lack of clarity over regulations

Interpretation of the regulations = Opportunity for flexibility

- Can be greatest challenge in dealing with staff
- Need consistent strategy in managing differences of opinion with review staff.
- Take the time to listen and effectively communicate
  - Best investment one can make in insuring the ‘business’ runs smoothly!!!

Efficiency in Information and Records Management

- Develop and implement tools to manage documents and information submitted by sponsors
  - Maintain accurate records with a numbering system for sponsor/drug and submissions
  - Clinical trial applications, amendments and notifications
  - ADR database for integration and analysis
  - Submission allocation database
  - Clinical trial inspection database

- System to manage other information such as general enquiries

- Ensure security and maintain confidentiality of records
Measure and Maintain Performance and Transparency

- Measure workload and performance at periodic intervals (e.g., quarterly)

- Use information on workload and performance to develop/revise business plans

- Publish performance measures periodically (e.g., annually)
  - Number of clinical trials, protocol amendments, notifications, ADRs, types of trials, etc.
  - Submission processing and review times

Communicate Effectively

- Provide opportunities for dialogue with sponsors and stakeholders formally and informally (being mindful)
  - Pre-clinical Trial Meetings
  - Telephone Conferencing
  - Informal email enquiries

- Provide an Appeal Process

- Consult with all stakeholders before implementing or adopting new regulations, policies, and guidelines

- Communicate horizontally within organization

- Seek lessons learned through impact analyses
Thank you
Questions?