Canadian Perspective on Biologics Regulation; and Review of Gene Therapy Activity

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Presentation Outline

- Regulation of Biologics
  - Regulatory Challenges and Responses
  - Legislative Renewal & Progressive Licensing
  - Review of Gene Therapy Activities
Regulatory Framework

- **Statutes (Acts):** provides scope, and legal authority to make regulations
- **Regulations:** interpret the Act, provide general details on what must be done
- **Guidelines:** interpret and provide details of how to meet the regulations, allow flexibility and adaptation to change, faster and simpler to introduce (not legally binding)
- **Policies:** expand or modify interpretation of the regulations, provide a “quick fix” pending re-drafting of regulations (can be legally challenged); usually relax or simplify
Canadian Food and Drugs Act

Definition of a Drug

...any substance or mixture...blah..blah..blah manufactured, sold or represented for use in:

a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof...blah..blah..blah;

b) restoring, correcting, or modifying organ functions...blah..blah;

c) disinfection...blah..blah..food is manufactured...blah..blah.
What are Biologics?

• No current written definition in Canada

• Listed on Schedule D to the Food and Drugs Act (specifically or within a class)

• Generally derived from or through the metabolic activity of living organisms, natural or genetically modified

• Examples include: vaccines, blood and blood products, gene therapies, and protein therapeutics such as cytokines, hormones and MAbs
Schedule D Drugs

- Allergenic Substances
- Aprotinin
- Cholecystokinin
- Drugs from microorganisms (other than antibiotics)
- Gonadotropins
- Immunizing Agents
- Interferon
- Secretin

- Drugs by r-DNA procedures
- Glucagon
- Human Plasma by plasmapharesis
- Insulin
- Monoclonal Antibodies
- Urokinase
- Snake venom
- Anterior pituitary extracts
- Blood and Blood Derivatives
Distinction between Natural Health Products and Biologics

• In general, not a NHP if listed on Schedule D
  ➢ Not a NHP if product is specifically listed by name
  ➢ Some products captured under certain group listings might be NHPs, e.g. some products of microorganisms

• NHPs must be suitable for self-administration (if intervention of a physician is advisable then it is not a NHP)

• If administered via puncturing the dermis it cannot be a NHP
Differences between Biologics and Chemical Drugs

• Starting material and some raw materials used for biologics are variable in nature (serum derivatives, enzymes, cell substrates).

• Manufacturing processes are biological in nature and variable
  ➢ procaryotic or eucaryotic cell systems
  ➢ stages of manufacture are often carried out under conditions that cannot meet the same manufacturing standards as conventional pharmaceuticals
  ➢ system of in-process controls required
  ➢ aseptic processing
  ➢ no terminal sterilization in container

• Complex structure of final product
  ➢ molecular weight and structure may be undefined
  ➢ composition may be undefined (vaccines)
Differences between Biologics and Chemical Drugs

• Test methods needed to characterize batches of the product are variable in nature
  ➢ potency, purity and safety of most biologics cannot be adequately tested by chemical or physical means alone
  ➢ bioassays have a high degree of variability / invalidity

• Quality cannot be established entirely by tests on the material in the final container
Submission Review Team

Screened Submission

Regulatory Support

OSE

LAB Analysis

Clinical Review

C&M Review

Admin Support

Team

Medical Devices Bureau

Issuance of NOC

Centre for Biologics Research

HPFB Inspectorate
Laboratory Testing

• Addressed early in the review process
• Choose a subset of the release tests

Release tests are chosen based upon

• Probative/investigational value
  – Bioactivity, stability indicating HPLC analyses

• Available resources
  – Equipment
  – Personnel
On-Site Evaluation

- Pre-approval inspection of the manufacturing facility.
- Product and process specific inspection rather than facility specific.
- Some obvious overlap with cGMP but this is not the primary focus.
- Both Drug Substance and Drug Product manufacturing facilities are subject to an OSE.
On-Site Evaluation

- Decision to conduct is based upon
  - Experience with the manufacturer
  - Experience with the manufacturing process
  - Facility issues identified in the review
  - Laboratory testing problems
  - Known compliance problems at the facility
  - Not in production
Lot Release Program

On-going Assessment of Biological Drugs to ensure Safety and Efficacy

Four assessment categories from full and complete testing through protocol review down to notification and tracking
Lot Release

- a system of approval given for the release onto the Canadian market of a specific lot of biological product based upon certification that the lot meets appropriate in process controls and control tests on final products.

- such controls to be applied to the release of batches of the product have been decided at the time of licensing of the biological product (but may change).

- Lot release is necessary because of the complex nature of biological drugs.

- The Lot Release program has been rationalized based on a risk assessment model.
Lot Release

• **Factors influencing the degree of assessment:**
  • **Product Indication**
    – Age/health status/size of target population
    – Disease state & duration of treatment
  • **Nature of the product**
    – Source and level of control of the raw materials
    – Complexity, robustness and control of the process
    – Chemical/biological complexity of the DS and DP
    – Reliability/complexity of the methods used to evaluate identity, purity, and potency
Lot Release

• **Factors considered in determining the degree of assessment:**
  - Production history
    - Consistency of manufacturing
    - Changes in the incidence of reprocessing lots
    - Incidence and seriousness of lot failures
  - Inspection history
    - Major quality and safety issues at OSE or cGMP inspection
  - Testing history (manufacturer and BGTD)
  - Post-market experience
    - Adverse drug reactions (ADRs), product recalls/withdrawals
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Challenges – workload vs resources

- 300-400 new biologics under development
- New types of products, and technologies
- Each approved NDS → 10 supplements and 30 NCs
- Financial resources will continue to be limited
- Competition for available expertise
- Different regulatory approaches will be required

Opportunities

- Availability of better medications; and treatments for currently unmet needs
- For regulators to show leadership/innovation; and to enhance trust/respect shown by the public & health sector
Challenges – public expectations

• Faster access to new medicines AND safer products with fewer adverse drug reactions (ADRs)

• Transparency r.e. regulatory decisions

• Access to more and clearer information along with greater responsibility for treatment decisions

Opportunities

• To better explain what we do and how we do it

• To win support for risk-based approaches

• For sharing of risks with end-users and practitioners
Challenges – ICH Q8, Q9, Q10

• Increased interaction/guidance during product development
• New approaches to evaluation of manufacturing process and facilities
• Risk managing the relaxation (?) of oversight

Opportunities

• Regulatory relief to industry, increased efficiencies
• Workload relief to regulators (on balance due to fewer submissions for manufacturing changes)
• Greater international harmonization
Challenges – Biosimilars

- Developing/rationalizing regulatory pathways
- Appropriate level of regulatory oversight
- How similar? How much new clinical data?
  (Few in total but with public and political interest)

Opportunities

- Greater choice, cheaper products
- Incentive for new developments by innovators
Meeting the Challenges - Workload

• Harmonizing at ICH

• Taking steps to share/leverage effort and expertise
  – Developing MOU; Mutual Recognition Agreements
  – Parallel review project with TGA, Australia
  – “work-sharing” initiative

• “Rationalized” review
Meeting the Challenges - Regulatory

- **Revising guidance on post-approval changes**
  - More examples; more clarity; details on data to provide
  - Risk-rationalized lowering of level of submission
    - e.g.: S/NDS → NC; or NC → Notification/Annual Report
- **Developing clear pathway for biosimilars**
  - external consultation in February, 2008
- **Planning/working to implement Q8, Q9, Q10**
  - Educating/training reviewers
  - Needs coordinated approach at ICH
- **Legislative renewal (all Health Canada activities)**
- **Progressive Licensing Framework (medicinal products)**
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Legislation Renewal: Objectives and Scope

Objectives:
– Modernize, strengthen and integrate existing federal health protection legislation
– Provide overall policy direction for coherence and address gaps

Scope:
• A new legislative framework to replace and integrate:
  – *Food and Drugs Act* (1953)
  – *Quarantine Act* (1970)
The Motivating Policy Issues

• No expressly stated guiding principles, philosophy or values.
  – What are the principles that should be applied consistently across products?
  – No clear mandate for health surveillance and research

• No policy direction in risk-decision making grounded in legislation
  – What is our philosophy when addressing health risks, on issues such as consumer choice or the concept of precaution?

• Archaic enforcement powers
  – Current $5,000 maximum fine against drug manufacturer; no power to order manufacturer to take corrective action; way behind what exists in other federal legislation and internationally
The Motivating Policy Issues (cont’d)

• Gaps in What is covered:
  – No clear authority to deal with new and emerging technologies and certain health and safety related activities
  – Limited authority to conduct post market surveillance (e.g. follow through to health outcomes)
  – Rules regarding Privacy not well suited to the public health context (e.g. sharing of information with agencies across levels of government)
  – No effective mechanism to categorize products between Acts (e.g. FDA-HPA-PCPA), or within same Act (e.g. FDA: food-drug-device?)

• Legal barriers to improving the efficiency and transparency of review processes
  – E.g. unclear rules in legislation regarding the confidentiality of commercial information
New Authorities To Be Sought: To Collect and Use Confidential Information

• In reviews of new drugs, medical devices, food and other products

• When seeking external advice

• To verify compliance with the legislation and regulations

• For reasons of public health and safety (i.e. significant risk to health)

• To collaborate with foreign jurisdictions for health and safety

• To endorse a standard or code of manufacturing or laboratory practice
New Authorities To Be Sought:
To Disclose Confidential information

With respect to:

• public health and safety (significant risk to health);
• details regarding products that would enable the public to make informed choices;
• existence of Clinical Trial Applications and ongoing clinical trials (drugs), Experimental Studies Certificates (devices), and Investigational New Drugs (veterinary);
• existence of submission filed and stage of review process
• regulatory decisions;
• changes made to products that would be relevant to the public and help them make informed choices;
• letters of authorization for sale of an approved drug for human or veterinary use in emergency treatment (SAP/EDRP);
• Health Canada’s recognition of, or action against, a registrar.
Guiding Objectives of the Progressive Licensing Framework

– PLF is guided by two continuing goals:
  • **protect the public from the marketing of unsafe drugs; and**
  • **support the safest use of drugs.**

– Three further supporting objectives have guided the design of PLF:
  • Align PLF with the system of health care in Canada to achieve positive health outcomes

  • Ensure that PLF enables Health Canada to implement best international regulatory practices and maintain appropriate oversight without unduly increasing regulatory burden; and,

  • Encourage and make best use of evolutions in the science of drug development and regulation.
Life-Cycle

• The central concept of PLF is that over time there is a progression in knowledge about a drug;

• The emphasis of PLF is to identify opportunities within this progression over the life-cycle of a drug, rather than placing the regulatory focus only upon pre-market assessment;

• This represents a fundamental shift from the idea that the pre-market testing of a drug assures its safety and efficacy;

• PLF proposes that a drug should be evaluated throughout its life-cycle for its benefit-risk profile. There will be a requirement to file a life-cycle management plan.
Current Point-in-Time Process
Approach

• PLF is being developed as a strategy for the modernization of the existing framework for the regulation of drugs (pharmaceuticals and biologics), under the *Food and Drugs Act and Regulations (FDA and FDR)*

• Changes to the *FDA* are required for the purposes of:
  – Eliminating provisions that have become outdated or that are not actively used by Health Canada
  – Providing explicit authority for the way in which certain products are currently regulated (such as medical devices) and for certain activities that Health Canada currently carries out.
Definitions

**Therapeutic product:**

- Introduce a definition for “therapeutic product” which should include any drug or device (‘drug’ and ‘device’ being themselves defined in the *Act*).

- This will provide the ability to regulate, through a life-cycle approach, a range of products broader than those falling within the existing definition of “drug”, including drug/device combination products.
Authorizations

- Increased authority to create ongoing obligations on the market authorization holder; and that could be amended, suspended or cancelled.

- Regulation-making powers respecting the issuance, amendment, suspension and cancellation of market authorizations, including the imposition of obligations relating to:
  - Pre-submission meetings
  - Registration and disclosure of clinical trial information
  - Post-market studies
  - Pharmacovigilance activities
  - Reassessments
  - Changes to product labels
  - Risk Communications
Authorizations

• Regulation-making power respecting the risk-based classification of different types of therapeutic products

• This will allow us to set submission requirements and impose obligations on market authorization holders based on the level of risk associated with the type of therapeutic product
Miscellaneous

- Employee immunity clause to protect employees of Health Canada against liability arising from decisions made as part of the product review process.

- Reporting from institutions: Integrate into the Act a mechanism for increasing reporting of serious adverse drug reactions by institutions.

- Compliance and Enforcement: increase penalties, authority to recall

- Openness and Transparency: enhance information sharing capacities
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Regulatory Process for Clinical Trials

Pre-CTA Advisory Meeting with Sponsor (optional)

IREB Approval

Clinical Trial Application (CTA)

30 Day Default*

No "clinical hold" in Canada

Each lot of clinical material meets specifications (Fax-Back form)

Trial Proceeds

Review Team
Clinical CMC Lab
## Gene Therapy Trials in Canada II

<table>
<thead>
<tr>
<th>Indications</th>
<th>number and type of vectors used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Retrovirus</td>
</tr>
<tr>
<td>16 adenovirus</td>
<td>3 retrovirus</td>
</tr>
<tr>
<td>Carcinomas: breast, liver, prostate, ovary, bladder</td>
<td>NSCLC, SCCHN</td>
</tr>
<tr>
<td>Carcinoma of breast</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>BMT (mdr)</td>
</tr>
<tr>
<td>Malignant myeloma</td>
<td>AML, CAD, Prophylactic HIV vaccine</td>
</tr>
</tbody>
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**Vectors Used:**
- HSV-2
- AAV
- HSV
- Vaccinia
- Adenovirus
- Retrovirus
- DNA
- wt viruses
- RNA
- AAV
- HSV
- Vaccinia
Gene Therapy

Regulatory Comments I

- Canada is consistent with the international community in the regulation of gene therapy.
- Canada has experienced significant growth in gene therapy clinical trials.
- Regulatory and ethical challenges have been few due to the serious and often terminal nature of the diseases treated.
Gene Therapy

Regulatory Comments II

- Careful attention is paid to minimizing the chance of third party exposure to vector
- Germ-line gene transfer is prohibited by law in Canada
- There are no gaps in regulation