Emergence and Advancement of Technologies: Regulatory Challenges and Considerations

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Overview/Objectives

The presentation will elucidate on:

❖ Health Canada organization

❖ Existing Regulatory Frame work of Gene and Cell Therapy Products

❖ Health Canada’s plans to enhance the agility of the health product regulatory framework: making regulations more adaptive to innovation while continuing to maintain our rigorous safety standards
Where does BRDD fit in?

BRDD works to maximize the quality, safety and efficacy of biological and radiopharmaceutical products in Canada.

Mission:
BRDD works to maximize the quality, safety and efficacy of biological and radiopharmaceutical products in Canada.
Where do Cell and Gene Therapies fit within BRDD (for Quality Review)?
Regulatory Framework in Canada

- **Unproven therapies**
  - Autologous (mostly)
  - Allogeneic (except ones under CTO)
  - Non-homologous use
  - More than minimally manipulated
  - Has systemic effect

- **Proven therapies**
  - Allogeneic (except ones under FDR)
  - Homologous use
  - Minimally manipulated
  - No systemic effect

- **Devices containing or formed from human cells or tissues**
  - Devices used in manufacturing of cell therapy products

Regulations permit decision making that is based on:

- **A) Risk-benefit analysis.**
- **B) Sound scientific evidence.**
- **C) Risk management plan post approval.**

Viral vectors, recombinant proteins, antibodies and vaccines are all regulated as biologics (schedule D) under the food and drug regulations.
Gene Therapy:

- Transfer and expression of an exogenous gene compensating for a missing or non-functional endogenous gene including by the following means:
  
  a) Nucleic acid (DNA or RNA) delivered directly or by viral vector resulting in expression of RNA (mRNA, miRNA or siRNA) and in some cases the translation of protein (directly *in vivo* or via *ex vivo* transduction and reintroduction of cells)
  
  b) Modification of genes (expression or repair) without transfer of genetic material
     - Direct treatment of cells in vivo or ex vivo with regulatory RNA or protein that bind DNA is not considered gene therapy but a therapeutic use of nucleic acids and proteins
  
  c) Oncolytic viruses for treatment of cancer
Regulation of Gene and Cell Therapy Products in Canada (cont’d)

- **Cell and Gene Therapeutic Products**
  - Regulated as Biologics, in Schedule D (Biologic Drugs) of the Canadian Food and Drug Regulations
  - Gene therapies are better captured by Schedule D than cell therapies
  - Safety of Human Cells, Tissues, and Organs Regulations for Transplantation Regulations
  - Cell therapies meet the definition of a drug as defined by Food and Drugs Act
    - Food and Drugs regulations are widely applicable to Cell Therapies
    - Assisted Human Reproduction Act: embryonic stem cells
Other Applicable Regulations...

- Canadian Environmental Protection Act
- New Substances Notification Regulations (Organisms/microorganisms)
  - An Environmental Assessment is required for new organisms not already on the “Domestic Substances List”
  - Includes viruses (ie. Gene therapy, oncolytic), but not plasmids
  - Sponsors of New Drug Submission (NDS) or Clinical Trial Applications (CTA) for a viral or bacterial vector should notify Environment Canada
  - Review conducted by Health Canada (HECS)
Although scope excludes CGT’s, many of the principles can and should be applied
  – Eg. Comparability, stability, viral clearance etc.

Relevant ICH Consideration Documents:
  – General Principles to Address Virus and Vector Shedding
  – Oncolytic Viruses
  – General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
Other Guidance Documents Considered

- **FDA Cell and Gene Therapy Guidance Documents**
  - Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) 2020
  - Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up 2020

- **EMA Cell and Gene Therapy Guidance Documents**
  - EMA/CAT/80183/2014- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products
  - EMA/CAT/GTWP/671639/2008 - Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells
  - CHMP/BWP/2458/03 - Guideline On Development And Manufacture Of Lentiviral Vectors
## The Food and Drug Regulations: CGT

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<th>Division in Part C</th>
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<td>Division 1 – General Section</td>
<td>- Drug Identification Number (DIN)</td>
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<td>- Labelling requirements</td>
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<td>- Adverse Drug Reaction Reporting</td>
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<td>Division 1A – Establishment Licensing</td>
<td>- Activity-based (fabricate; package/label; GMP requirements; distribute; import; wholesale)</td>
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<td>- Changes require EL amendment</td>
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<td>- Annual renewal required</td>
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<td>Division 2 – Good Manufacturing Practices</td>
<td>- Control of all manufacturing processes (including premises and cleaning, record keeping and training)</td>
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<td>Division 5 – Clinical Trials (CT)</td>
<td>- CT Application (CTA) to test a drug in humans</td>
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<td>- Verify the clinical efficacy, various pharmacological parameters, safety and look for any adverse events attributable to the drug</td>
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<td>Division 8 – New Drugs</td>
<td>- Sufficient scientific evidence of safety, quality and effectiveness must be provided to Health Canada for market authorisation</td>
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<td>- Preclinical, quality (Chemistry and manufacturing) and clinical, post market plan</td>
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<td>- On site evaluation and lot release for biologics</td>
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Regulatory Challenges: The health context is changing

- Products are becoming increasingly complex and personalized (e.g., AI-enabled devices, advanced cell therapy, 3D-printed bio-products, Big Data, Novel Drug Delivery).

- Growing range of innovative products accompanied by a wider spectrum of risk.

- Canadians demanding faster access to innovative products and greater engagement on decisions about their health.

- The COVID-19 pandemic has reinforced the need for agility and innovation to get high-demand products to Canadians quickly, without compromising safety.
Responding to the need for regulatory agility

Since 2017, Health Canada has initiated a range of regulatory modernization initiatives. Progress has been made through initiatives such as the **Regulatory Review of Drugs and Devices (R2D2)**, the **Self-Care Framework** and the **Medical Devices Action Plan**.

In 2018, the **Health and Bio-Sciences Economic Strategy Table** and **Advisory Council on Economic Growth** highlighted additional opportunities to enhance regulatory agility in support of innovation and economic growth.

Following a **targeted Regulatory Review** of the health and bio-sciences sector, Health Canada consulted a broad range of stakeholders as we developed an ambitious **Roadmap** to achieve greater regulatory agility.

**Budget 2019** announced funding ($120M/5 years) and **Bill C-97** provided the legislative powers to achieve this vision.
Regulating for the future: The 5 pillars of our plan

1. Modernizing clinical trial regulations
   - to encourage clinical trials by creating an environment that supports more innovative trials

2. Enabling Advanced Therapeutic Products
   - to ensure a flexible approach for innovative products that do not fit in the current system

3. Agile licensing for drugs
   - to make sure regulations align with the nature and lifecycle of health products

4. Agile licensing for medical devices
   - to ensure appropriate oversight while better enabling innovation

5. Information to Canadians: A mobile strategy
   - to help empower Canadians to maintain and improve their health
Regulatory innovation objectives

**Modernizing clinical trial regulations**
- Greater flexibility to oversee new trial types and designs
- Proportional oversight of clinical trials based on risk
- Better access to and transparency on information about trials

**Enabling Advanced Therapeutic Products**
- Market access pathway for products that challenge existing regulations
- Use of “regulatory sandboxes” to develop tailored oversight requirements
- Concierge service to support innovators navigate new pathway

**Agile licensing for drugs**
- Allow risk-based approval and oversight of products throughout their lifecycle
- Provide more agile regulatory tools to optimize oversight, e.g., Terms and Conditions (T&Cs)
- Support the use of decisions from trusted foreign regulators in specific situations

**Agile licensing for medical devices**
- Use of foreign regulatory decisions
- Use of T&Cs
- Better classification for lower-risk devices

**Information for Canadians: A mobile strategy**
- Develop a mobile platform that delivers credible and unbiased health product information
- Information and services tailored to consumers’ needs and expectations
- Serves as authoritative source of choice for health product information
In 2020, COVID-19 required an unprecedented regulatory response to ensure Canadians had access to needed health products

Our approach:

**Proactive engagement and collaboration**
with stakeholders and health system partners to provide timely advice and guidance, as well as heightened collaboration with international regulators to ensure alignment.

**Emergency regulatory pathways and measures**
to prioritize and expedite the review and licensing processes, including use of agile regulatory tools and approaches (e.g., T&Cs, rolling reviews).

**Enhanced post-market surveillance**
of safety and effectiveness, including life-cycle oversight of approved products, adjusting T&Cs based on emerging information, real-time response to and information sharing of safety signals.

**Increased communications and transparency**
including release of clinical data, to support high demand for information and data from broad range of stakeholders on regulatory requirements and decisions.

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5 vaccines  
2 treatments  
600+ medical devices  
4500+ sanitizers & disinfectants
COVID-19 an opportunity to “test” agile ways of regulating...

...enhancing Health Canada’s pandemic response while informing our longer-term regulatory innovation plans.

• COVID-19 reinforced importance of regulatory agility to enable timely access to needed health products.

• Regulatory response to pandemic provided an opportunity to “test” certain agile measures planned as part of the Regulatory Innovation Agenda (e.g., T&Cs).

• We’re currently implementing a transition approach for COVID-19-related products approved under these temporary measures, so that:
  – Canadians have uninterrupted access
  – Industry continues to benefit from similar flexibilities

• Early insights learned from the temporary measures are helping us continue to enhance the agility of Canada’s health product regulations, and will inform the Regulatory Innovation Agenda moving forward.
By 2024, our efforts will have contributed to tangible results

- Encouraging clinical trials in Canada by creating an environment that supports more innovative trials.

- Enhancing patient access to new and innovative health products that do not fit in today’s regulatory system.

- Advancing timely access to drugs and devices while more effectively overseeing their safety and effectiveness by:
  
  - Leveraging agile regulatory tools such as T&Cs;
  - Allowing the use of foreign decisions to help address unmet health needs; and,
  - Providing more transparency about the risks, benefits and uncertainties of drugs.

- Supporting innovation and economic growth by:
  
  - Creating a more modern regulatory system that removes outdated requirements and irritants;
  - Increasing harmonization and alignment with international regulators; and,
  - Enabling a low-cost market authorization pathway for low-risk drugs.
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