

Health Canada: Update on Regulatory Activities & Priorities

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WCBP 2020, Washington, January 28-30

Plen-Shop: Current Regulatory Trends and Hot Topics Around the Globe - Part 1



Presentation Outline

- **Overview of regulatory priorities**
- **Update on recent and ongoing activities**
 - **Regulatory Review of Drugs and Devices (R2D2)**
 - **Clinical trials – regarding “non-investigational” use**
- **Analysing & responding to change**
 - **Introducing a new regulatory paradigm – “The Sandbox”**
- **Updates on biosimilars and cell & gene therapies**
- **Recent guidance documents & “roadmap” for biologics**
- **Implementing ICH-Q12**

Regulatory Priorities

Examining our review system to determine the best approaches to:

- better respond to healthcare system needs, and
- improve timely access to effective products and innovative technologies
 - **Ongoing & Proposed initiatives:**
 - Working with Health Technology Assessment (HTA) bodies to provide joint advice to industry during product development; better align timing & reduce duplication of HTA review to facilitate faster access to important new drugs;
 - Maximizing use of adaptive pathways for drug development and authorization
 - Modernizing IM/IT systems infrastructure
 - Reforming cost recovery regime to ensure long term funding sustainability

Regulatory harmonisation, convergence & work-sharing

- ICH, IPRP WGs, ACSS Consortium, other bilateral & multi-lateral initiatives

Simultaneously ... work is proceeding to develop regulations that will enhance the power of Health Canada as a regulator, including:

- ability to require additional tests & studies for authorized drugs; order a reassessment of a drug's risk/benefit profile; & attach terms and conditions to market authorizations

Continuous improvement efforts – Regulatory Review of Drugs and Devices (R2D2)

Objective: An agile regulatory system that supports better access to therapeutic products based on healthcare system needs



Expanded collaboration with health partners

- Alignment of the Health Technology Assessment (CADTH) Review with Health Canada Review
- Implementing a Mechanism for Early Parallel Scientific Advice
- Use of Foreign Reviews/Decisions
- International Collaboration and Work Sharing in Reviews



More timely access to drugs and devices

- Expansion of Priority Review Pathways
- Improving Access to Biosimilars and Biologics
- Improving Access to Generic Drugs
- Building Better Access to Digital Health Technologies
- Pre-Submission Scientific Advice for Medical Devices
- Special Access Programme (SAP) Renewal



Enhanced use of real world evidence

- Leveraging Data for Assessing Drug Safety and Effectiveness
- Strengthening the use of real world evidence and regulations for medical devices

Modern and flexible operations

Common Submission Intake
Appropriate cost recovery framework
Public Release of Clinical Information

R2D2 updates and next steps

Building international partnerships to increase alignment and bring critical drugs to patients sooner

- ACSS consortium – (as of October, 2019) shared review of 3 new drugs completed, 4 more ongoing, others in planning stages
- Partnerships – participation in ICH, Cluster meetings, IPRP WGs and EMA expert committees to share expertise

Working with domestic health system partners to speed up access to drugs and devices

- Better alignment of reviews by Health Technology Assessment (HTA) bodies (CADTH and INESSS) – (as of October, 2019: 27 completed, 14 ongoing – a formal evaluation of first year of full implementation is ongoing)
- Early parallel scientific advice pilot launched in March, 2019 – supporting drug development plans that will meet regulatory and HTA needs – several meetings scheduled in next few months, processes to be finalized after initial trials

Building significant new review capacity in key scientific areas

- Additional scientific staff hired and trained to ensure ongoing technical capacity

Modernizing review processes to meet healthcare system needs

- Completed consultations on expanded priority review policy
- Completed consultations on draft regulations supporting Special Access Program

Developing ways to better use information from real world use to assess and monitor drug and device safety and effectiveness

- Working with health system partners to optimize the use of information gathered from variety of sources throughout the product life cycle

Project Orbis

- An initiative of the FDA Oncology Center of Excellence (OCE); sponsor must participate in FDA's *Real Time Oncology Review* (RTOR) process and the assessment aid
- A framework for concurrent submission and review of oncology products among international partners that may allow cancer patients to receive earlier access in some countries
- Initially for supplemental oncology approvals; NDA/BLA eligibility will be discussed but more complex due to proprietary information involved
- First action was collaborative review and simultaneous decision (2019-09-17) by FDA, TGA & HC granting accelerated approval to Lenvima (levatinib) in combination with Keytruda (pembrolizumab) for treatment of patients with advanced endometrial cancer
- Initially for supplemental oncology approvals; NDA/BLA possibility will be discussed but more complex due to proprietary information involved
- Participation could be expanded to balance of ACSS membership and other specific regulatory agencies
- Not all drugs are suitable; decision dates can be different; decisions are sovereign

Leaders' Consortium for ATMPs

- FDA is spearheading a “Leaders’ Consortium” consisting of the “heads” (delegated to the relevant level) of FDA, EMA, HC and MHLW/PMDA to discuss regulatory collaboration in the area of ATMPs with an initial focus on gene therapy products
- The increased regulatory interactions could foster true harmonisation - but significant rapid progress towards greater alignment would probably also depend on some level of regulatory convergence
- In addition to achieving greater regulatory alignment amongst “high-income countries” (larger markets), the idea is that the alignment of major regulators would encourage regulatory agencies in “lower-income” countries” to converge on the same requirements and expectations, and thereby, perhaps, reduce delays in the availability of such products in their countries

Clinical Trials

June 2019 - Notice to Stakeholders: Statement on the Investigational Use of Marketed Drugs in Clinical Trials

A marketed drug used off-label in a clinical trial may be considered “non-investigational” by Health Canada if the drug is not the subject of testing in the study (i.e., comparator, imaging, supportive).

The sponsor must provide in their Clinical Trial Application:

- i) a concise summary as to how the proposed use of the drug(s) in the population is in accordance with Canadian “best medical practices” and poses a “low risk” to the population under study; and
- ii) list of supporting references.

If Health Canada accepts the sponsor’s explanation why the use of a marketed drug is not investigational in the clinical trial, the drug will be exempted from Division 5 of the Food and Drug Regulations.

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-statement-investigational-use-marketed-drugs-clinical-trials.html>

Ongoing challenges: Health systems must respond to change



Data

Data-generating and data-reliant systems for all aspects of health



Citizen Agency

Information and resources to manage individual care



Precision & Personalization

Individualization of systems and services



Product Complexity

Innovations that blur product lines and defy standard classification



Production & Distribution

Local, connected, and accountable manufacturing and supply chains



Evidentiary Standards

New technologies, R&D practices, and trial designs challenge review processes

Regulatory Challenges: Advanced Therapeutic Products



Advanced Therapeutic Products

- For some innovative products, the methods with which they are made or distributed, and how data can be collected, has resulted in a shift away from the traditional product development model for which the current regulations are intended
- Some health products are so novel and distinct that it is difficult for them to meet the current regulatory requirements
- Need appropriate regulatory oversight for continuously changing products and innovative business practices

Regulatory Review and Innovation

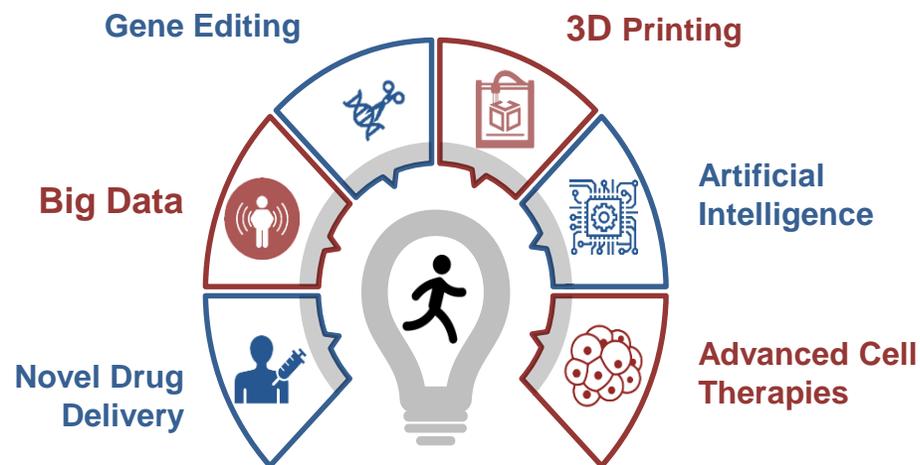
New Pathway for Advanced Therapeutic Products

Issue: Increased product complexity challenges our regulatory world

- Increasingly overlapping product lines causing confusion and regulatory burden.
- New, innovative technology – or advanced therapeutic products (ATPs) – are so novel, complex and distinct, that existing rules are not equipped to handle them

Solution: Creating an agile and responsive approach for regulating complex, novel health products

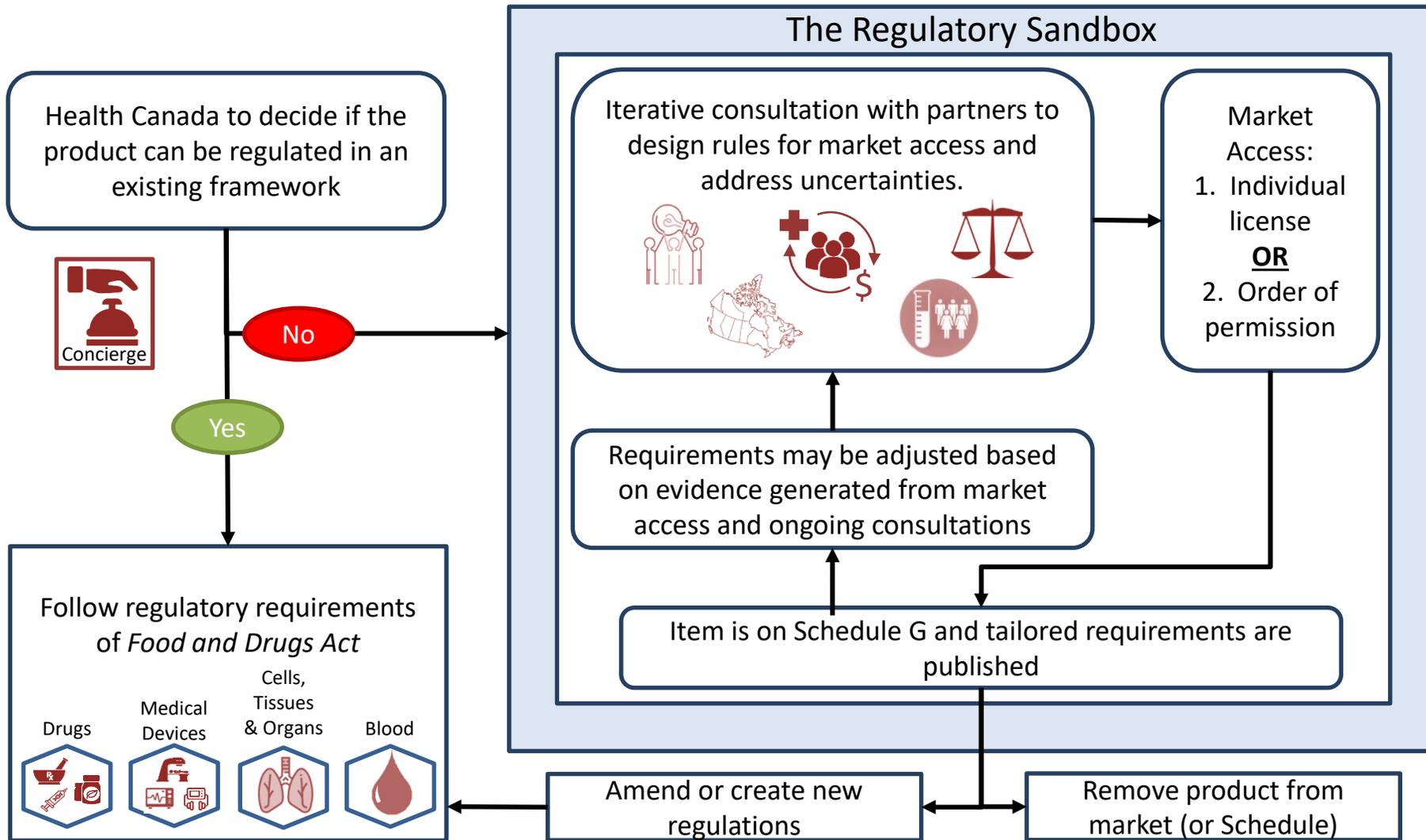
- New classification authority will help resolve regulatory ambiguity (drug, device, combination product, etc.)
- Introducing a new regulatory pathway and concierge service for advanced therapeutic products (i.e., a regulatory ``sandbox``), that would only be used in exceptional circumstances



The Food and Drugs Act - Additions to Schedule G

21.91 (1) For the purpose of preventing injury to health or preventing a person from being deceived or misled, the Minister may, by order, add a description of a therapeutic product or a class of therapeutic products to Schedule G if the Minister believes that **the therapeutic product or products represent an emerging or innovative technological, scientific or medical development.**

Advanced Therapeutic Products and The Regulatory Sandbox



What to Expect with Advanced Therapeutic Products in the Near Future

- Consultation with Stakeholders will continue
 - Meetings with stakeholder groups are anticipated to happen in the new year
- Health Canada is examining options to pilot this exciting new pathway
 - Launch of a website and email address
- Health Canada is developing a Guide to these new innovative authorities
 - Expect a draft for comment in the new year

Biosimilars

- Increasing interest in potential of biosimilars to serve the health care system in Canada (publically funded; provinces & territories bear bulk of drug costs)
 - Ongoing need for informing/educating Canadian stakeholders (Workshop March, 2017)
- Interest remains high for filing of NDSs for biosimilars (18 authorized; others under review; significant pipeline over the next 3 years)
- Updated “*Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (biosimilars)*” released in Dec 2016 to reflect experience gained over the previous 5 years and clarify some positions
 - Guideline: <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/biosimilars-biosimilaires-eng.php>
 - List of key changes: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/annonce-annonce/notice-avis_biosimilars-biosimilaires-eng.php
 - Fact Sheet on Biosimilars (updated August 2019) <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/biosimilars-biosimilaires-qa-qr-eng.php>
- Naming conventions, switching, & interchangeability remain contentious issues

Need for Clarity in Terminology

Interchangeability

- In Canada, the term "interchangeability" often refers to the ability for a patient to be changed from one drug to another equivalent drug, by a pharmacist, without the intervention of the prescriber who wrote the prescription.
- Health Canada's authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug. The authority to declare two products interchangeable rests with each province and territory according to its own rules and regulations.

Switching

- In the context of biosimilar use, Health Canada considers switching between authorized products to refer to a change from routine use of one specific product to routine use of another specific product.
- Biosimilars are authorized by Health Canada for the indications listed in the Product Monograph. Patients and health care providers can have confidence that biosimilars are effective and safe for each of their authorized indications. No differences are expected in efficacy and safety following a change in routine use between a biosimilar and its reference biologic drug in an authorized indication.
- If you have any questions about changing from one biologic drug to another, you should speak to your health care practitioner.

Biosimilars Authorized by Health Canada

2009

- Omnitrope (somatropin)
 - additional indications in 2015

2014

- Inflectra (infliximab)
 - Additional indications in 2016
- Remsima (infliximab)
 - Additional indications in 2016

2015

- Basaglar (insulin glargine)
- Grastofil (filgrastim)

2016

- Brenzys (etanercept)

2017

- Erelzi (etanercept)
- Admelog (insulin lispro)
- Renflexis (infliximab)

2018

- Lapelga (pegfilgrastim)
- Mvasi (bevacizumab)
- Hadlima (adalimumab)
- Fulphila (pegfilgrastim)

2019

- Truxima (rituximab)
- Qgivri (trastuzumab)
- Zirabev (bevacizumab)
- Trazimera (trastuzumab)
- Herzuma (trastuzumab)

Gene and cell therapies at Health Canada at a glance

- 1994 - First clinical trial for a gene therapy is authorized (for intra-tumoral injection of a plasmid).
- 1994 to present – No Objection Letters issued to nearly 200 clinical trials for cell and gene therapies. Increase in activity over the last five years.
- 2012 – Notice of Compliance issued for Prochymal (an allogeneic cell therapy to treat acute graft versus host disease in paediatric patients). Health Canada becomes the first regulator to authorize a cell therapy for general market distribution. The product was authorized through the Notice of Compliance with Conditions accelerated Pathway.
- 2018 (September) – Kymriah (tisagenlecleucel) CAR-T, an autologous cell-based gene therapy, is authorized for general distribution for two indications through the Priority Review accelerated pathway as it meets unmet medical need.
- 2019 (February) – Yescarta (axicabtagene ciloleucel) CAR-T, an autologous cell-based gene therapy, is authorized for general distribution for one indication through the Priority Review accelerated pathway as it meets unmet medical need.

Recent Guidance Documents

Health Canada Policy Position Paper – Autologous Cell Therapy Products

<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/cell-therapy-policy.html>

Guidance Document: Fecal Microbiota Therapy Used in the Treatment of *Clostridium difficile* Infection Not Responsive to Conventional Therapies

<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/regulation-fecal-microbiota-therapy-treatment-difficile-infections.html>

Guidance Document: Radiopharmaceuticals, Kits, and Generators: Submission Information for Schedule C Drugs

<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/drug/radiopharmaceuticals-schedule-c.html>

Regulatory roadmap for biologic drugs in Canada

Roadmap for sponsors:

- wanting to bring a biologic drug to market in Canada,
- wanting to conduct a biologic drug clinical trial in Canada,
- seeking information about post-market requirements and post-approval changes

Gives comprehensive information and internet links covering: regulatory processes, data requirements for clinical (safety and efficacy) and product quality (chemistry and manufacturing), On-site evaluation, Lot Release program, Risk Management Plan, Labelling, etc.

<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/regulatory-roadmap-for-biologic-drugs.html>

ICH-Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- Key Sections
 - Categorization of Post-Approval CMC Changes
 - Established Conditions
 - Post-approval Change Management Protocol
 - Product Lifecycle Management Document
 - Pharmaceutical Quality System and Change Management
 - Relationship Between Regulatory Assessment and Inspection
 - Structured Approaches for Frequent Post-Approval Changes
 - Stability Data Approaches to Support Evaluation of CMC Changes

Categorization of Changes

Health Canada regulatory framework is compatible

- Multiple risk-based communication/reporting categories are available
 - Prior approval submission (two categories) & Notification &/or Annual Report
- Post Notice of Compliance Changes Guidance (PNOCC) document
 - Comprehensive guidance regarding: category, conditions, data expected
- Framework allows for flexibility to move between categories (an enabler)
 - If certain conditions for change are met (captured in PNOCC guidance)
 - When linked to a Post Approval Change Management Protocol
 - To accommodate negotiated Established Conditions and Reporting Categories
 - Provides choices for “best-fit” convergence/harmonisation

Challenges (actually only “tweaking” is needed)

- Introduce a clear delineation between “Immediate Notification” and “Annual Report” (should only require a change in regulatory policy)
 - Reflected with examples in PNOCC guidance document
- Perhaps need an improved “Submission Documentation Form”
 - To inform/orient regulatory affairs staff

Established Conditions

Health Canada regulatory framework is essentially aligned/compatible

- Fully endorse regulatory flexibility deriving from:
 - Fewer ECs and/or “better-focused” ECs;
 - Rationalized/justified lower reporting categories
 - Mixed formats: parameter-based (minimal & enhanced) & performance-based
 - Mixed formats: “proposed/justified” ECs and “default to guidance” ECs

Challenges

- Will benefit from greater experience with proposed/justified ECs
- How to manage regulatory affairs complexity introduced by proposed / justified ECs & associated reporting categories that differ from ECs & associated reporting categories evident from guidance documents?
- Maintaining consistency in reaching decisions and a “level playing field”
- Training of evaluators and regulatory affairs officers
- Perhaps need an improved “Submission Documentation Form”
 - To inform/orient regulatory affairs staff

Post Approval Change Management Protocols

Health Canada not yet aligned

- Concept is well understood
- Multiple communication/reporting categories are available as enablers
- May consider introducing a pilot programme

Challenges

- Change to regulatory policy is needed (no new regulations)
- Perhaps need an improved “Submission Documentation Form”
 - To inform/orient regulatory affairs staff
- Greater scrutiny for “Notifications” as Step 2 of PACMP process
- Adapt to less revenue from supplements?!

Product Lifecycle Management Document

Health Canada is partially aligned (and, probably, more so than others)

- Concept is well understood – we have our CPID (Certified Product Information Document)

Challenges

- What to do with our CPID? Keep as streamlined document separate from submission/dossier or merge with PLCM Document?

Acknowledgements

- Christopher Antonio
- Dr. Nadine Kolas
- Dr. Christopher Storbeck
- Marianne Tang
- Dr. Jian Wang