Modernizing regulations in the context of COVID-19 in Canada

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Objective

• To provide an overview of Health Canada’s regulatory activities in response to the pandemic to support access to COVID-19 biotherapeutic products
  ▪ Interim Order
  ▪ Transition to *Food and Drug Regulations*
  ▪ Submission flexibilities and requirements

• To update the status regulatory initiatives that have been pursued during the pandemic
  ▪ International work sharing initiatives
  ▪ ICH Q12 implementation
Approval and Post-Approval Processes

- New drugs are regulated under the *Food and Drug Regulations*. When market authorization is granted, a **Notice of Compliance (NOC)** is issued.

- Post-NOC quality changes are managed via a science and risk-based approach. Quality Changes are classified within four reporting categories (Level 1 to Level 4):
  - For example, Level 1 category is for major quality changes (e.g. facility addition)
The Minister of Health issued an **Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19** on September 16, 2020 with a one year duration to support expedited access to COVID-19 therapeutics and vaccines.

**Interim Order (IO)** flexibilities included:

- Rolling submissions – data filed as it becomes available; according to a filing plan
- Flexible data requirements
- The use of **Terms and Conditions** on an authorization to manage residual risks

COVID-19 products were issued **authorization under the Interim Order**; not issued an Notice of Compliance (NOC)
Adaptations to transition drugs authorized under the Interim Order

Health Canada introduced amendments to the *Food and Drug Regulations* (FDR) before the Interim Order expired in order to:

- Provide a mechanism for products to gain legal status as soon as possible
  - Enables continued use of an IO-authorised COVID-19 drug while next review is conducted
  - Enables new COVID-19 drugs to seek authorization
  - Issuance of a Notice of Compliance (NOC) to COVID-19 drug

- Maintain agile measures including
  - Rolling submission; according to a filing plan
  - Flexible data requirements
  - Terms and Conditions (T&Cs)
Transition timeline

New filings made under amended FDR pathway only

A COVID-19 FDR submission may be filed for drugs authorized under the IO OR for applications filed under the IO but not yet authorized when the new FDR provisions come into force

New rolling submissions for COVID-19 drugs not filed under the IO can be filed directly under the amended FDR pathway
CMC Flexibility during the Pandemic

- Rolling submissions:
  - Timelines managed through Application Plan
  - Enabled management of workload

- Flexible data requirements:
  - Targeted review approach
  - Leveraging information from platform data or previously authorized products

- Quality Terms and Conditions:
  - Details on failed or aborted lots
  - Filling of additional data as it becomes available
  - Management of amendments including additional facilities

✓ Sufficient evidence to support a conclusion with regard to the uncertainties relating to the benefits and risks to the patient and the necessity to address public need related to Covid-19
✓ Appropriate risk mitigating tools
Other Regulatory Initiatives

• Evolving challenges presented by the pandemic emphasized the need for regulatory efficiency

• International work sharing initiatives
  ▪ Access Consortium
  ▪ Project ORBIS

• Implementation of ICH Q12
International Collaborations for the review of drug submissions (NAS) at Health Canada

- Access Consortium
  - Access - New Active Substance Work Sharing Initiative (NASWI)
  - Multilateral work sharing

- Project Orbis
  - Bilateral work sharing with FDA
  - *Project Orbis, an initiative of the FDA Oncology Center of Excellence (OCE)*, provides a framework for concurrent submission and review of oncology products among international partners.
    
    https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis

Both pathways include sovereign decision and information sharing
Ongoing discussions with regulatory partners to continue building on collaborations
Overview of Access-NAS

• Access-NAS focuses on regulatory work and information sharing initiatives for new active substances (new chemical entities and new biologic entities)

• Access-NAS considers submissions for new substances and new indications (both standard and priority review)

• Access agencies include:
  ▪ Therapeutic Goods Administration (TGA) of Australia
  ▪ Health Products and Food Branch (HPFB) of Health Canada
  ▪ Health Sciences Authority (HSA) of Singapore
  ▪ Swissmedic (SMC), Swiss Agency for Therapeutic Products of Switzerland
  ▪ Medicines and Healthcare products Regulatory Authority (MHRA), of the United Kingdom (U.K.) (joined on October 14, 2020)

• Pathway involves joint review - division of labour among participating regulators (e.g. one regulator to lead review of Mod 3, one Mod 4 and one Mod 5)
Overview of ORBIS

• ORBIS focuses on regulatory work and information sharing initiatives for Oncology products (chemical and biological entities)

• Initiative of the U.S. Food and Drug Administration (FDA) Oncology Center of Excellence

• Bilateral work sharing agreements between FDA and HC

• Goal is to accelerate access to promising cancer treatments

• Review types include
  ▪ Type A: Review sharing, submissions must be within 30 days of each other
  ▪ Type B: Concurrent or overlapping review
  ▪ Type C: Review completed by FDA, completed review documents are shared with HC
Access and Orbis at a glance

<table>
<thead>
<tr>
<th>Access-NAS</th>
<th>Project Orbis</th>
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<tbody>
<tr>
<td>• New drugs and new indications</td>
<td>• New drugs and new indications for oncology products only</td>
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<tr>
<td>• Biologics and pharmaceutics</td>
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<td>• Both standard and priority reviews</td>
<td>• Usually accelerated timelines/priority reviews</td>
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<td>• Joint review - division of labour</td>
<td>• Concurrent review (Type A), information sharing and discussions</td>
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<td>• Aiming for concurrent decisions in all regions</td>
<td>• Aiming for decisions within a similar timeframe</td>
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HC Experience with Access Submissions

• Successes to date:
  ▪ 8 small molecules approved since 2018
  ▪ 6 biologics reviews completed
  ▪ more in review and in the pipeline

• Process used:
  ▪ Initial review of Module 3 conducted by one agency
  ▪ Second review performed by HC if not involved in initial review
  ▪ A common list of questions (LoQ) is typically issued for Module 3
  ▪ The LoQ contains a set of common questions and some region specific questions (ie. Module 1)

• All quality reviews led to the same decisions amongst agencies
HC Experience with Access Submissions

• Challenges:
  ▪ Compressed timelines compared to the regular review process
  ▪ Coordination of reviews
    ▪ (e.g., toxicological consultation for the qualification of impurities is done by a different agency than the one leading the review of Mod. 3)

• Advantages:
  ▪ Better understanding of the decision making process in each agency’s regulatory environment
  ▪ Reduced *de novo* evaluations
  ▪ Allows for a mapping of different approaches to evaluation between jurisdictions
  ▪ Confirmed alignment in the review of the quality information especially on the drug substance side
HC Experience with Orbis Submissions

- Successes to date:
  - 29 submissions complete since 2019
  - More ongoing

- Challenges:
  - Very aggressive timelines

- Advantages:
  - Faster access to medicines for Canadians with an earlier filing in Canada and fast tracked reviews
  - Greater collaboration and technical discussion of issues
  - Allows for a mapping of different approaches to evaluation between jurisdictions
  - Greater alignment in the review of the quality information
  - Both FDA and HC are looking at the MPDs/EBRs
  - Information needed by HC has been filed in response to an IR
Work sharing experiences to date:

**Advantages:**
- Discussion with reviewers from other jurisdictions
  - Sharing of best practices, especially for CMC information
  - Should help increase regulatory convergence/harmonization
- Reduction in workload due to work sharing
- More rapid access to drugs for Canadians

**Challenges:**
- Timelines are difficult to manage in the context of very high workload
- Different approaches to regulation can lead to differences in opinion on how to approach a particular issue. This is both a challenge and an opportunity to increase discussion and collaboration between jurisdictions - ultimately leads to better understanding of the submission and also of differences in approaches between jurisdictions.
HEALTH CANADA
IMPLEMENTATION OF ICH Q12: CMC CHANGES
Background - ICH-Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- This ICH guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. It will provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle.

- As a standing regulatory member of the International Council for Harmonisation (ICH), Health Canada is committed to the adoption and implementation of all ICH guidance.

- Implementation of this new ICH Guideline will promote innovation and continual improvement in the biopharmaceutical sector and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments.
ICH-Q12 – Reached Step 4 in November 2019

The target timeframe for Health Canada implementation of ICH Q12 is set in October/November 2022
ICH-Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

• Key Sections and tools
  ▪ 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
Implementation timelines in Canada

- The Post-NOC Changes guidance document is being updated to incorporate the ICH Q12 tools and concepts (i.e., Established Conditions, Post-Approval Change Management Protocol, product life cycle management document), including the addition of the “Immediate Notification” reporting category

  - **August 2021**: External consultation with stakeholders (120 days)
  - **January 2022**: Finalization of the PNOCC guidance document
  - **January 2022**: Training sessions for the reviewers
  - **March 2022**: Launch of the pilot program (on ECs and PACMPs)
  - **September 2022**: End of the pilot program on ECs and PACMP
  - **October/November 2022**: Implementation of ICH Q12 in Canada (Step 5)
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