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Canada

Modernizing regulations in the context of COVID-19 in Canada

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YOUR HEALTH AND SAFETY... OUR PRIORITY.

Objective

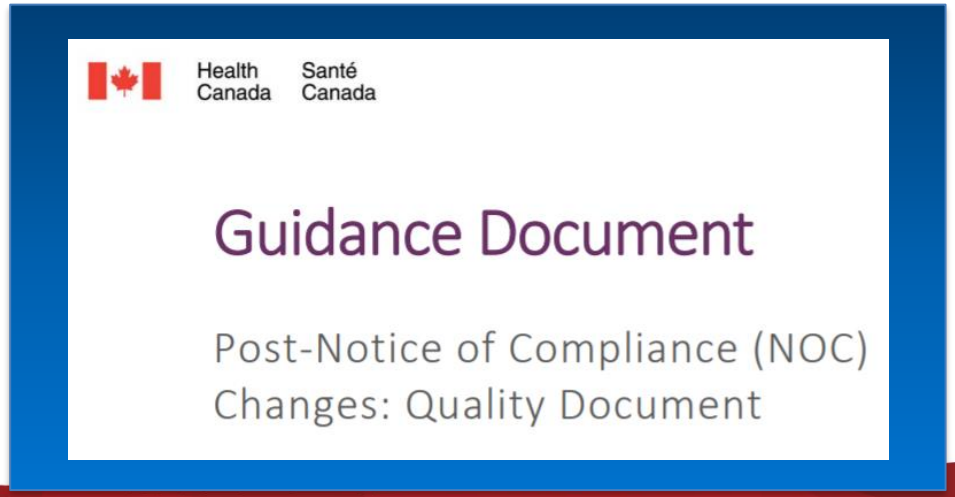
- To provide an overview of Health Canada's regulatory activities in response to the pandemic to support access to COVID-19 biotherapeutic products
  - Interim Order
  - Transition to *Food and Drug Regulations*
  - Submission flexibilities and requirements

- 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)



Adaptations for approval process to respond to COVID-19

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)

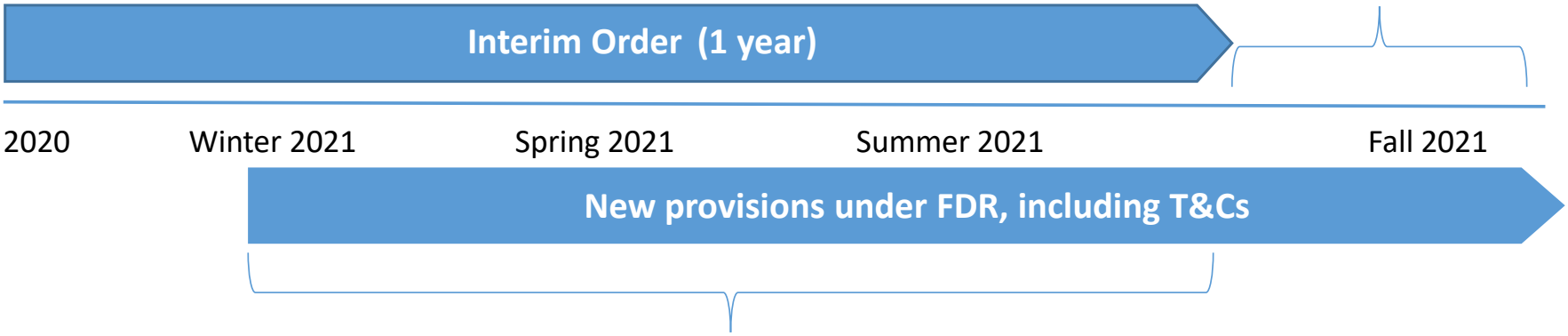
Adaptations to transition drugs authorized under the Interim Order

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-authorized 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

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

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.

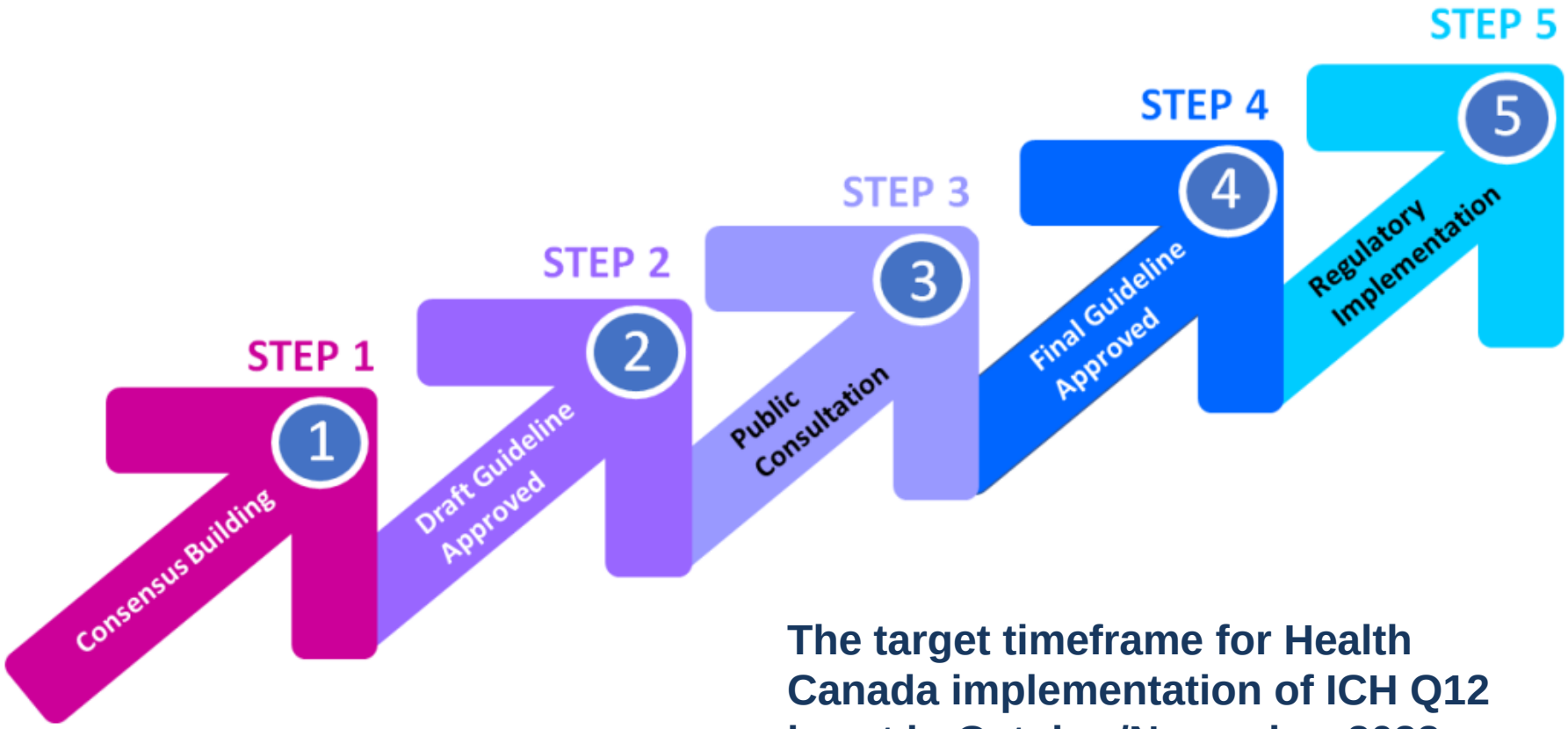
HEALTH CANADA IMPLEMENTATION OF ICH Q12: CMC CHANGES

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

5 Step Process



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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Questions and comments