Vaccine Regulatory Process in Canada

Introduction

- With the introduction of COVID-19 vaccines, vaccine safety is paramount in ensuring vaccine confidence for public health, health system stakeholders and the public in Ontario.

- Vaccine safety monitoring is a continuous process starting at the time of clinical trials and continuing once vaccines have been authorized for use and incorporated into immunization programs. The ongoing monitoring of vaccine safety involves many groups, including federal and provincial governments and health agencies, public health units, health care providers, and the public.

- Post-marketing surveillance assesses the effectiveness and safety of vaccines and begins after vaccines are approved for use, and includes the monitoring of adverse events following immunization (AEFIs).

- In Ontario, Public Health Ontario (PHO) is responsible for provincial surveillance of AEFIs in collaboration with local public health units and health care providers and contributes this information to Canada’s post-marketing surveillance system.

- This document describes how vaccines are approved for use in Canada and how vaccine safety continues to be monitored after approval in Canada and Ontario.

Who is responsible for approving a vaccine in Canada?

- Health Canada is the federal authority responsible for the regulation of vaccines for human use under the Food and Drugs Act, and Food and Drugs Regulations.

- Health Canada reviews clinical and manufacturing information of vaccine submissions, and authorizes the sale of vaccines in Canada.

What is the regulatory process?

- Manufacturers must provide scientific evidence from human clinical trials on the safety, efficacy and quality of a vaccine by filing a New Drug Submission to Health Canada.
• Submissions contain extensive data about the vaccine’s safety, efficacy and quality; results of pre-clinical and clinical studies (up to Phase 3); details about production; and information on side effects and adverse reactions that occur following immunization.\textsuperscript{4,5}

• The \textit{scientific information} is reviewed by Health Canada.\textsuperscript{6}

• Vaccines are approved for use and authorized for sale in Canada by Health Canada only if they are shown to be safe, effective, and of high quality, and with benefits outweighing their risks.\textsuperscript{4}

• All approved vaccines in Canada are continuously monitored to ensure that their safety, effectiveness and quality are maintained once marketed.\textsuperscript{4}

• Health Canada issues both a Notice of Compliance (NOC) and a Drug Identification Number (DIN), which is necessary for the sale of a vaccine in Canada.\textsuperscript{4}

• If the manufacturer wants to modify the product monograph to include additional uses after the initial authorization by Health Canada, they must re-submit the safety and efficacy data to Health Canada for scientific review, approval, and authorization based on updated evidence.\textsuperscript{4}

\section*{How long does the regulatory process take?}

• Health Canada’s review of a vaccine can often take several years.\textsuperscript{4}

• Given the urgency of the COVID-19 pandemic, the Government of Canada, including Health Canada, made revisions to expedite the regulatory approval process without compromising safety, efficacy and quality standards.

\section*{How is a vaccine’s safety and efficacy monitored?}

• Before a vaccine is authorized for use, Health Canada confirms there are no significant safety concerns based on phases 1-3 of human clinical trials.\textsuperscript{4}

\section*{Four phases of human clinical trials}

• Phase 1 studies a vaccine on a small group of people (usually fewer than 100) for the first time, examining its safety including dosage range and side effects.\textsuperscript{7}

• Phase 2 studies a vaccine on a larger group of people (usually several hundred or more), to see how effective the vaccine is in preventing a disease, confirming its safety and its optimum dosage.\textsuperscript{7}

• Phase 3 studies a vaccine on a larger group of people (usually many thousands) to confirm that it is both effective and safe by monitoring its side effects and any adverse reactions.\textsuperscript{7}

• Phase 4 occurs after the vaccine has been approved for use and is incorporated into immunization surveillance programs. This is also known as post-marketing surveillance. This includes ongoing safety monitoring, assessing vaccine effectiveness in specific population groups, and determining the duration of immunity to inform future decisions on the need for booster doses.\textsuperscript{7}
• Phases 2 and 3 are often combined during clinical trials since this provides more information on a larger group of people in a shorter time about the vaccine’s safety and effectiveness, in order to expedite the approval process.

Post-marketing surveillance
• Post-marketing surveillance is a shared responsibility between Health Canada, vaccine manufacturers, the Public Health Agency of Canada (PHAC), provinces and territories, as well as local public health authorities. 
  • Health Canada provides regulatory oversight for safety, quality and effectiveness.
  • PHAC collaborates with provincial and territorial public health stakeholders in monitoring and reporting of AEFIs.
  • All serious adverse events associated with vaccines approved in Canada (whether they occur in Canada or outside of Canada) must be reported by the vaccine manufacturer to Health Canada within 15 days of having received this information.

How is a vaccine’s quality monitored?
• An important component of vaccine safety is the quality of the vaccine product. Health Canada assesses the quality of the manufacturing process to ensure that there are necessary quality controls for production of the vaccine in place.
• Once a vaccine is approved, the manufacturer must provide samples from three to five consecutive lots for testing in Health Canada's laboratories, to confirm that the manufacturer is consistently producing high-quality lots of the vaccine.

How has the regulatory process in Canada changed with COVID-19?
• To facilitate earlier access to COVID-19 drugs or vaccines, Health Canada prioritized the review of these products while ensuring there is adequate evidence of their safety, efficacy and quality. Additional scientific resources were put in place to complete these reviews so that they could be done quickly while ensuring the integrity of the comprehensive review process.
• In March 2020, Health Canada put in place Interim Orders (IO) to respond to the urgent need for access to health products as a result of the COVID-19 pandemic, including clinical trials for medical devices, drugs and vaccines.

What was the timeline and process for approving COVID-19 vaccines in Canada?
• An Interim Order was made under subsection 30.1(1) of the Food and Drugs Act (the Act), to allow the Federal Minister of Health “...to make temporary interim orders if the Minister
believes that immediate action is required to deal with a significant risk, direct or indirect, to health, safety or the environment.”

- On September 16, 2020, the Federal Minister of Health signed an Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 (ISAD IO) to expedite the approval process of potential COVID-19 vaccines by allowing Health Canada to accept COVID-19 drug and vaccine submissions that are already in clinical trials with initial evidence of safety and efficacy, directly from manufacturers.

- This meant that manufacturers could present their vaccine submission to Health Canada as a rolling submission (i.e., data is presented as it is collected at different times during the phases of the clinical trials). This assists Health Canada in reviewing information as it is submitted, taking into consideration urgent public health needs, and is distinct from a more typical process that requires all studies to be completed and data to be submitted at the same time.

- In October 2020, Health Canada began receiving submissions including potential COVID-19 vaccines for approval under the ISAD IO for COVID-19.

- Health Canada authorized the first COVID-19 vaccine for administration in Canada under the ISAD IO on December 9, 2020 after it met safety, efficacy and quality requirements.

- COVID-19 vaccines authorized under the ISAD IO are able to transition to a new drug submission under the Food and Drug Regulations. On September 16, 2021, the ISAD IO expired.

- On September 16, 2021, Health Canada granted full authorization to the Pfizer-BioNTech Comirnaty® and Moderna Spikevax® COVID-19 vaccines under the Food and Drug Regulations. The AstraZeneca Vaxzevria™ and Janssen (Johnson & Johnson) COVID-19 vaccines are still authorized for use in Canada under ISAD IO, and will continue to be authorized after September 16, 2021 while these submissions are under review for transition to the Food and Drug Regulations. COVISHIELD vaccine previously provided a temporary supply of vaccine to Canada, but was not transitioned to the Food and Drug Regulations when the ISAD IO expired on September 16, 2021.

What is the regulatory process for COVID-19 vaccines: additional doses and expanded age groups?

- For indications of vaccine and age groups that were not included in the original clinical trials, Health Canada continues to review submissions from manufacturers which include immunogenicity and safety data.

- However, these submissions undergo the same high quality review process by Health Canada with authorization only after vaccines demonstrate that they are safe, efficacious and high quality.

- In general, provinces and territories in Canada may choose to allow off-label use of COVID-19 vaccines for indications that have not been authorized by Health Canada.

- At present, NACI has made recommendations for the off-label use in the following groups:
Third doses to complete a primary series for moderately to severely immunocompromised individuals\textsuperscript{22} and booster doses for long-term care residents and seniors living in other congregate settings.\textsuperscript{23}

What is the regulatory process for modified COVID-19 vaccine that respond to Variants of Concern?

- Health Canada has updated guidance,\textsuperscript{24} outlining how currently authorized COVID-19 vaccines that are modified in response to new variants of the virus will be reviewed and authorized in Canada.\textsuperscript{25}
- This process is similar to the established regulatory approach used for seasonal influenza vaccines, where annual updates are needed to match the strains circulating each year.\textsuperscript{24}
- Vaccine manufacturers will need to provide evidence that the modified vaccine produces an immune response in a sufficient number of people. New clinical studies will not be needed since they do not add to the regulatory understanding of a vaccine’s safety, efficacy or quality.
- They will also need to provide evidence of the modified vaccine’s safety and quality, which may include using data from the original clinical trials and ongoing real-world studies.\textsuperscript{24}
- Overall, this process will reduce the length of time needed for a modified vaccine to be ready for use.\textsuperscript{24}

How will vaccine safety be monitored in Ontario?

- Ontario will work with federal/provincial/territorial partners to conduct post-marketing surveillance to monitor the safety of COVID-19 vaccines.
- This process will rely in part on reporting of AEFIs by health care providers, vaccine recipients or their caregivers to their local public health unit (PHU). The Ontario AEFI reporting form\textsuperscript{26} is used by health care providers to submit AEFI reports to their local PHU.
- Additional information on COVID-19 vaccine safety surveillance in Ontario can be found on PHO’s website\textsuperscript{27}.

Conclusion

- With the authorization of COVID-19 vaccines in Canada, post-marketing surveillance will be essential in ensuring the ongoing monitoring of the safety and effectiveness of these vaccines.
- Vaccine safety monitoring is a continuous process spanning all phases of the vaccine product life cycle, starting at the time of clinical trials and continuing to post-marketing surveillance activities, including provincial AEFI surveillance coordinated by PHO. The ongoing monitoring of vaccine safety is a collaborative effort involving many groups, and is an important component of public confidence in vaccines.
References


20. National Institutes of Health. A study to evaluate safety and effectiveness of mRNA-1273 COVID-19 vaccine in healthy children between 6 months of age and less than 12 years of age [Internet].


Summary of Revisions

First published: December 16th, 2020

This document is current to October 8th, 2021. New material in this revision is highlighted in the table below.

<table>
<thead>
<tr>
<th>Section</th>
<th>Revision</th>
<th>Implementation Date</th>
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<tbody>
<tr>
<td>What is an interim order?</td>
<td>Updated section to include information on transition of COVID-19 vaccines authorized under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 (ISAD IO) to new drugs authorized under the Food and Drug Regulations. Added information on vaccine trade names.</td>
<td>08/10/2021</td>
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<tr>
<td>What is the regulatory process for COVID-19 vaccines: additional doses and expanded age groups?</td>
<td>Updated section includes information on the authorization process for additional doses to complete a primary series in certain populations (i.e., moderately to severely immunocompromised individuals, long-term care residents and seniors living in other congregate settings) and for pediatric population.</td>
<td>08/10/2021</td>
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Citation

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