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AT A GLANCE

Vaccine Regulatory Process in Canada

2nd edition: April 2022

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).[1]
- 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.[2]
- 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*.[3,4]
- Health Canada conducts an independent review of clinical and manufacturing information of vaccine submissions, and authorizes the sale of vaccines in Canada.[5]

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.[5,6]
- 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.[5,6]
- The scientific information is reviewed by Health Canada.[7]
- Vaccines are approved for use and authorized for sale in Canada by Health Canada only if they are shown to be safe, effective, of high quality, and with benefits outweighing their risks.[5]
- Health Canada issues both a Notice of Compliance (NOC) and a Drug Identification Number (DIN), which are ~~is~~ necessary for the sale of a vaccine in Canada.[5]
- All approved vaccines in Canada are continuously monitored to ensure that their safety, effectiveness and quality are maintained once marketed.[5]
- 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.[5]

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.[5]

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.[8]
- 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.[8]
- 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.[8]
- 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 data collection of vaccine effectiveness and program impact as well as reporting and surveillance of adverse events following immunization (AEFIs).[5]
- Phase 4 occurs after the vaccine has been approved for use and is incorporated into immunization programs. This phase 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.[8]

- 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.[5]

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.[5]

- 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.[5]

What was the timeline and process for approving COVID-19 vaccines in Canada?

- 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.[9-13] 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.

- Health Canada put in place Interim Orders (IO) under *subsection 30.1(1) of the Food and Drugs Act* 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.[3,14-17]

- In May 2020, Health Canada issued IO No.2 Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19 which introduced an alternate pathway to facilitate the authorization and implementation of COVID-19 related clinical trials for COVID-19 related drugs and medical devices.[15] This was eventually replaced with Health Canada's Clinical Trials for Medical Devices and Drugs Relating to COVID-19 Regulation which came into effect in February 2022.[17]

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

- The ISAD IO allows manufacturers to 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).[16] 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.[16,18]

- 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.[16,19]

- COVID-19 vaccines authorized under the ISAD IO are able to transition to a new drug submission under the *Food and Drug Regulations*.[16,4]

- 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*.[20,21,4] The AstraZeneca Vaxzevria and Janssen (Johnson & Johnson) COVID-19 vaccines were also granted full authorization for use in Canada under the *Food and Drug Regulations* on November 19, 2021 and November 23, 2021, respectively.[22,23,4] The 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.[4,16,18,21] Novavax Nuvaxovid and Medicago Covifenz COVID-19 vaccines received full authorization from Health Canada on February 17, 2022 and February 24, 2022, respectively.[24,25]

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.[26,27]

- 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[a] of COVID-19 vaccines for indications that have not been authorized by Health Canada.

- Under the *Food and Drug Regulations*, Pfizer-BioNTech Comirnaty is authorized in Canada as a primary series for individuals five to 11 years (10 mcg dose) and 12 years of age and older (30 mcg dose), with a booster dose of Pfizer-BioNTech Comirnaty (30 mcg dose) authorized for individuals 18 years of age and older at least six months after completing their primary vaccine series.[4,28] Moderna Spikevax is authorized in Canada as a primary series for individuals six to 11 years (50 mcg dose) and 12 years and older (100 mcg dose), with a booster dose of Moderna Spikevax (50 mcg dose) authorized for individuals 18 years of age and older at least six months after completing their primary vaccine series.[29] Under the *Food and Drugs Regulation*, Novavax Nuvaxovid is authorized for use as a primary COVID-19 vaccine series in adults 18 years of age and older and Medicago Covifenz in adults 18-64 years of age as a primary vaccine series.[4,25,30,31]

[a] The term “off-label”refers to any use of a drug beyond what Health Canada has reviewed and authorized to be marketed in Canada and as indicated on the product label.

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

- Health Canada has updated guidance 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.[32]
- 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.[32]
- 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.[33]
- 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.[33]
- Overall, this process will reduce the length of time needed for a modified vaccine to be ready for use to repond to new variants of concern.[33]

How will vaccine safety be monitored in Ontario?

- Ontario continues to work with federal/provincial/territorial partners to conduct ongoing post-marketing surveillance to monitor the safety of COVID-19 vaccines.
- This process includes reporting of AEFIs by health care providers, vaccine recipients or their caregivers to their local public health unit (PHU). The Ontario AEFI reporting form is used by health care providers to submit AEFI reports to their local PHU.[34]
- For additional information on COVID-19 vaccine safety surveillance in Ontario and Canada, visit:
    - COVID-19 Vaccine Safety Surveillance in Ontario[35]
    - How vaccine safety is monitored in Canada[36]

Conclusion

- Health Canada's regulatory approval process has been adapted in order to be responsive to the urgent need for access to health products as a result of the COVID-19 pandemic without compromising efficacy, safety, manufacturing standards, and risk assesment.
- With the authorization of COVID-19 vaccines in Canada, post-marketing surveillance is 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 clincal trials and continuing to post-marketing surveillance activities, including provinical AEFI surveillance coordinated by PHO.[37] The ongoing monitoring of vaccine safety is a collaborative effort involving many groups, and is an important component of public confidence in vaccines.

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Publication History

1st Edition: 2020

2nd Edition: April 2022

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Vaccine regulatory process in Canada. 2nd ed. Toronto, ON: Queen's Printer for Ontario; 2022.

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