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Guidance for market authorization requirements for COVID-19 vaccines



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Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

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Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy, or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable Guidance documents.

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Overview

Background

COVID-19 is the infectious disease caused by the most recently discovered coronavirus, SARS-CoV-2. This new virus and disease were unknown before the outbreak began in December 2019 and have since spread around the world.

COVID-19 has been known to cause respiratory symptoms, fever, cough, shortness of breath and breathing difficulties. In more severe cases, COVID-19 infection can cause pneumonia, severe acute respiratory distress, kidney failure and death. Older people and those with underlying medical problems, such as high blood pressure, obesity, heart problems or diabetes, are more likely to develop serious illness.

The availability of safe, effective and high-quality vaccines will offer a potential means to reduce the spread and severity of disease and address its social and economic consequences.

About this guidance document

This document provides guidance to vaccine manufacturers seeking authorization for their vaccine that targets the SARS-CoV-2 virus. This guidance applies to applications under the [interim order respecting the importation, sale and advertising of drugs for use in relation to COVID-19](#) as per subsection 30.1(1) of the *Food and Drugs Act*. This should be read along with the guidance document concerning [information and application requirements for drugs authorized under the IO](#).

Guidance includes information on developing the evidence and documentation needed to obtain an authorization for importing or selling a COVID-19 vaccine under the IO.

About the IO and market authorizations for a COVID-19 vaccine

Health Canada is committed to helping Canadians protect and improve their health by facilitating access to COVID-19 vaccines that are safe, effective and of high quality. The IO introduces new regulatory mechanisms to expedite the authorization of COVID-19 drugs, including vaccines, while protecting the health and safety of Canadians.

Vaccine manufacturers seeking to obtain market authorization through the IO should consult with us early on and throughout the development process. While the IO doesn't specify any timelines, we are committed to prioritizing the review of any application seeking authorization of a COVID-19 vaccine.

Health Canada will grant authorizations only if we determine that the benefits of the vaccine outweigh its potential risks. We will base our decision on the evidence provided on the vaccine's safety, quality and efficacy. Risk-benefit analysis weighs the uncertainties about a potential vaccine against the urgent public health need for a vaccine at the time of the decision.

The IO makes it possible for initial authorization, based on early data, while the manufacturer continues working on developing a vaccine. After receiving additional data and information on the drug's quality, safety and efficacy, we can move toward market authorization (under the [Food and Drug Regulations](#)).

The requirements described in this guidance are a minimum acceptable standard under the IO. Health Canada will consider alternate proposals for evidence standards and a rationale for using these standards. As we learn more about the virus and the effectiveness of new vaccines and treatments, we will adjust the evidence requirements as required.

As with all drugs, Health Canada will assess and monitor the safety and effectiveness of all vaccines authorized under the IO. We will impose terms and conditions when necessary and take immediate action, if required, to protect the health and safety of Canadians. This action may include suspending or cancelling authorizations or establishment licences.

Guidance for implementation

Industry sponsors have been seeking guidance from regulatory authorities on the requirements for developing a COVID-19 vaccine. Guidance has been discussed in pre-submission meetings with Health Canada and other regulators, and through publications following workshops under the International Coalition of Medicines Regulatory Authorities (ICMRA). Guidance documents have also been published by the US Food and Drug Administration (US FDA), World Health Organization (WHO) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA).

Health Canada's guidance is aligned with these international regulators.

Rolling submissions and non-clinical requirements

Standard for accepting a rolling submission

The IO allows for the filing of rolling submissions. The ability to review data from early development while later-stage clinical trials are taking place helps to expedite the regulatory review process.

Before filing an application for a rolling review, sponsors of clinical trials are expected to have gathered a certain level of evidence on the safety, quality and efficacy of their vaccine. We advise sponsors to consult with us before filing an application.

To file an application for a rolling review, sponsors should have, at a minimum:

- non-clinical and clinical phase 2 data that demonstrate promising evidence of safety and efficacy
- confirmation that phase 3 trials have started and there are enough people enrolled to provide evidence of safety and efficacy within a reasonable amount of time (expected to be within 6 months from initial filing)
- evidence that manufacturing is in compliance with good manufacturing practices (GMP) and that product quality and consistency are well controlled

Sponsors must also file a submission plan giving the anticipated timelines for submitting the various components of the application. A preliminary submission plan should be included in the initial filing.

For details on submission plan requirements, see our guidance document on [information and application requirements for drugs authorized under the IO](#).

Non-clinical requirements for authorization

Some non-clinical data requirements and the methods used for non-clinical testing may be specific to the type of vaccine being developed. However, certain non-clinical data will be required for all vaccines.

For the development of a COVID-19 vaccine, the non-clinical data package must include:

- studies that assess the toxicology of the vaccine
- proof of concept, including antibody and cell mediated immune responses and protection
- assessment of the theoretical risk of vaccine-associated enhanced respiratory disease (VAERD)

Assessment of toxicity

The development and authorization of COVID-19 vaccines must be supported by toxicology studies in relevant animal models. Key animal studies need to be conducted in compliance with the international standards of good laboratory practices. These studies look at the general toxicity, local tolerance and other relevant toxicity endpoints.

If the vaccine is to be used in pregnant women, developmental and reproductive toxicity studies must be conducted to better understand the risks.

Proof of concept assessment

We require non-clinical tests or studies that characterize the ability of the vaccine to elicit a neutralizing immune response against the SARS-CoV-2 virus. These studies should be performed before proceeding to first-in-human clinical trials. In vivo studies in relevant animal models should evaluate the vaccine's ability to elicit neutralizing immune responses using the same dosing regimen and formulation intended for humans (for instance, single-dose or repeat-dose, adjuvanted).

When demonstrating immune responsiveness, consideration should be given to the humoral and cellular immune responses. Non-clinical data should also demonstrate the capacity of the vaccine to protect from SARS-CoV-2 using an appropriate animal challenge model.

Vaccine-associated enhanced respiratory disease (VAERD)

Vaccines developed against some respiratory viruses, including other corona viruses, have been associated with VAERD. This occurs when people who are vaccinated and then exposed to the virus develop a worse form of the disease.

At the time of this guidance, the potential for vaccines against SARS-CoV-2 to induce VAERD is theoretical. However, it will be important for the non-clinical vaccine development program to address this theoretical risk. Viral challenge studies intended to demonstrate the capacity of the vaccine to protect against SARS-CoV-2 can provide a suitable model for assessing VAERD. This is the case if studies also include assessments that address enhanced disease such as T-helper cell type 1 and T-helper cell type 2 responsiveness, lung histopathology and immune cell infiltrates.

Clinical testing requirements for authorization

Assessing safety

To assess the safety of a vaccine, Health Canada requires:

- an adequate number of vaccine recipients
- monitoring for a sufficiently long time

This requirement is needed to detect common and expected adverse reactions, as well as events that are less common but potentially more severe.

In line with the pre-authorization safety database requirements for preventive vaccines for infectious diseases, the safety database for a COVID-19 vaccine should have at least 3,000 study participants. They should be vaccinated with the dosing regimen intended for authorization.

The data should come from phase 3 randomized placebo-controlled trials that allow for the collection of adverse events in the vaccinated (>3,000 participants) vs. the placebo (>3,000 participants) group. This enables the detection of more common adverse events, which are in the range of at least 1 in 1,000 doses given.

Common adverse reactions include:

- redness and pain at the injection site
- sore arm
- fever
- headaches
- malaise

These should be monitored closely for at least 7 days to adequately characterize the frequency of those events.

Uncommon, rare or adverse events that may take longer to manifest should also be monitored closely. The median duration of safety follow-up to support authorization should be at least 2 to 3 months after all doses in the schedule have been given. Most adverse events are expected to occur within 2 months of vaccination.

Given the previous history with vaccines for other respiratory viruses, which have resulted in enhanced disease in people who were vaccinated and subsequently exposed to the virus (VAERD), this risk should be closely monitored for SARS-CoV-2 vaccines. The stability of the immune response following vaccination should be monitored. A period of 6 months may be required to assess for the potential for VAERD, if data from earlier phase clinical trials suggest that longer-term follow up is needed prior to authorization.

Following authorization, clinical trial participants should be monitored for as long as feasible. The ideal time is at least 1 to 2 years. This length of time is needed to assess the duration of protection and the potential for enhanced disease.

Health Canada may issue terms and conditions requiring the sponsor to provide longer-term clinical follow-up and post-market safety data on adverse events of special interest, such as VAERD, following authorization.

Internationally, regulators are in agreement on the safety assessment criteria. These criteria include defining:

- adverse events of special interest for close monitoring during clinical trials
- the size of the safety databases required

We will use these criteria when reviewing data submitted during the rolling review.

Assessing efficacy

Health Canada requires robust evidence of the vaccine's ability to prevent COVID-19 infection from well-conducted phase 3 clinical trials in humans. Ideally, we would like to see as high an efficacy as possible. However, as the virus that causes COVID-19 is new, we don't yet know how effective vaccines will be. We consider a target threshold of at least 50% efficacy to be reasonable for COVID-19 vaccines.

Clinical trials should demonstrate that the vaccine reduces the incidence of a symptomatic SARS-CoV-2 infection by at least 50% in people who are vaccinated, compared to a control group of people who don't receive the vaccine. Enough people should be enrolled so that the trial is sufficiently powered to exclude an efficacy result below 30%. The trial must have a sufficient number of participants with severe COVID-19 infection in the control group to show that the vaccine is effective.

This efficacy estimate is expected regardless of when the data are analyzed, including any pre-specified early looks at the data while the clinical trial is under way. Health Canada may issue terms and conditions requiring the sponsor to provide additional data confirming the duration of protection or other pertinent efficacy endpoints.

Although 50% efficacy is the target threshold, vaccines that don't reach this threshold may still be considered for authorization. We will review the safety and efficacy of each vaccine on a case-by-case basis. We will also consider the availability of other vaccines and treatments, public health needs, the status of the pandemic and the epidemiology of the disease in Canada.

When comparing a potential vaccine with a COVID-19 vaccine that has already met the efficacy criteria outlined above and been approved by a stringent regulatory authority, a non-inferiority trial design may be used with a non-inferiority margin of less than 10%. This means that the vaccine may show no more than 10% lower efficacy compared to the approved vaccine (lower bound of the confidence interval around the primary relative efficacy point estimate is $>-10\%$).

Critical efficacy results will be summarized in the labelling for the vaccine along with the dosing regimen and the patient populations used to demonstrate efficacy. Efficacy should be shown using the dosing regimen intended for authorization. The National Advisory Committee on Immunization (NACI) and public health officials use this information to develop vaccination programs.

Quality, manufacturing and lot release requirements

Establishment licensing

To bring a COVID-19 vaccine to market in Canada, a company must have an establishment licence to manufacture, package/label, test, import, distribute or wholesale a health product. An establishment licence is issued under the *Food and Drug Regulations*.

A company without such a licence must apply for one.

During the Drug Establishment Licence (DEL) application review process, a company must demonstrate compliance with good manufacturing practices (GMP). Depending on several criteria, including where the building is located, a company can demonstrate GMP compliance through:

- a Health Canada on-site inspection
- a certificate of GMP compliance issued by a partner with whom Health Canada has a mutual recognition agreement
- an inspection report from a regulatory authority, qualified authority, the WHO or, in some cases, a corporate/consultant auditor

The pandemic has created pressures on the drug supply chain and there is an urgent need for COVID-19 vaccines. Under the IO, Health Canada is issuing establishment licences more quickly. Licensing decisions are based on the materials submitted in the application.

Product quality

COVID-19 vaccines authorized under the IO must be manufactured under GMP conditions. These conditions are in line with international requirements, which are outlined in the International Council for Harmonization [Q7A guideline](#) and applicable [Health Canada guidance](#).

We require sufficient data to demonstrate that the manufacturing process is well controlled and consistent. This involves details on the manufacturing process for both the drug substance and drug product, including information on:

- source materials
- virus and cell banks
- in-process control testing based on specifications developed to evaluate critical process parameters

Data should be collected in a sufficient number of batches to demonstrate process consistency. Critical assays such as potency and impurities should be validated.

Authorization will also require establishment of stability parameters and expiry date on the drug product in its final container and formulation. Stability and expiry parameters should:

- indicate vaccine potency whenever possible and
- be from enough lots to be broadly representative of the product as a whole

Lot release

Biologic drugs in Canada are subject to lot release program requirements as outlined in section C.04.015 of Canada's *Food and Drug Regulations*. Vaccines are considered biologic drugs and are generally subject to the highest level of regulatory oversight since they're administered to healthy children and adults.

Health Canada's lot release program allows the application of a flexible, risk-based approach. This approach considers the evidence on manufacturing quality and controls as a whole, as well as testing from other international regulatory authorities. For example, Health Canada is an associate member of the European

Official Medicines Control Laboratory network, which supports the sharing of testing data among its members.

Health Canada's lot release program covers both the pre- and post-market stages for biologic drugs. Each lot of a biologic drug is subject to the lot release program before sale. We base the level of regulatory oversight (testing and/or protocol review) on the degree of risk linked to the product.

Health Canada has retained this requirement under section 13(1) of the IO. This section states that we have the authority to ask for information, material or samples to help us when deciding whether to grant, amend or suspend an authorization under the IO. The flexibilities offered in the IO make it possible for us to:

- address the current public health emergency appropriately
- take advantage of information gathered both pre- and post-authorization to develop a lot release strategy that adequately mitigates risks

Health Canada's COVID-19 vaccine lot release strategy

The IO gives Health Canada the ability to allow market access to vaccines that show promising clinical evidence of safety and efficacy and an adequate level of control over the manufacturing consistency and product stability.

Following authorization, clinical trials involving a sufficient number of participants will continue to be monitored. During this time, manufacturers will also continue to generate new information on the control and validation of their commercial manufacturing process, consistency of production and compliance with GMP. The lot release strategy for vaccines authorized under the IO must take into account these details in order to mitigate risks while allowing expedited access to address pandemic needs.

Health Canada's strategy includes the submission by the sponsor of a certificate of analysis for each lot before it's distributed on the Canadian market without the need to issue a lot release letter. This process will allow documentation of lots distributed in Canada and monitoring of product consistency. Following authorization, as part of our additional monitoring of product quality activities, we may ask for a summary of batch disposition information on a quarterly basis.

Normally, consistency testing would be conducted as part of the review process for full market authorization of a vaccine. To support expedited timelines under the IO process, Health Canada will use alternate approaches to ensure product quality. We will monitor product quality from time to time through key quality control tests. To further mitigate risks, Health Canada labs will also be reviewing the methodology used by the sponsor and the suitability of these tests for assessing product quality. During this period, we will begin the process for assay validation to support eventual lot release testing following transition of the vaccine to a full market authorization.

An important risk mitigation tool afforded to Health Canada through the IO will be the capacity to continue evaluating the quality of each vaccine throughout its lifecycle. Health Canada will be able to ask for additional information, such as an annual product report and/or product quality review. By using these tools, Health Canada can exercise more appropriate risk mitigation measures on a case-by-case basis at any time during the lifecycle of the vaccine. For example, Health Canada could implement more stringent lot release measures by placing a vaccine into Group 2 Lot Release in response to signals indicating increased risk.

Health Canada will communicate the requirements for lot release to each sponsor at the time of pre-submission discussions/meetings. We anticipate that considerations may need to be made on a case-by-case basis given the complexity of vaccine distribution (for example, prepositioning of lots before authorization). Decisions will be documented as part of the submission review process.

Vaccines authorized under the IO will transition to a market authorization through the new drug submission (NDS) process. At that time, the lot release requirements will be re-assessed. It is likely that methodologies and relevant quality management system processes will be in place at that time.

By implementing the flexible strategies outlined above, Health Canada can:

- mitigate the risk of potentially having lots distributed that don't comply with the approved specifications
- allow for expedited access to safe, effective and high-quality vaccines for Canadians

Labelling and post-market requirements

Brand name assessment

Health Canada will assess proposed brand names for COVID-19 vaccines to determine whether a vaccine's brand name could:

- mislead, such as:
 - imply it alone is effective but fails to provide evidence to support the claim
 - exaggerate the vaccine's effectiveness
 - minimize risk
 - make a claim of superiority
- be confused with another product authorized for use in Canada (with the aim of preventing medication errors)

Sponsors should refer to the criteria outlined in section 2.2 of our [guidance document on the review of drug brand names](#) before proposing a brand name for their vaccine.

The [information and application requirements for drugs authorized under the interim order](#) indicates that the requirement for a Look-alike Sound-alike (LASA) assessment does not apply to proposed COVID-19 products, including vaccines. Although not required, sponsors are invited to provide a LASA assessment as part of a brand name assessment, should one be available.

Inner and outer product labels

Sponsors of a COVID-19 vaccine are to comply with applicable labelling requirements outlined in the *Food and Drugs Act* and parts A and C of the Regulations. For vaccines, the requirements are found in A.01.014, A.01.015, C.01.004.1(2), C.01.005 to C.01.011 and C.04.019.

Although the plain language labelling requirements don't apply to drugs (including vaccines) that are filed under the IO, we recommend that sponsors consider applying plain language principles in their submissions, as a best practice.

Health Canada believes that labelling in both official languages is critical to the safe and effective administration of vaccines. Bilingual text should be present within the labelling information, where feasible.

For inquiries about the labelling requirements for proposed vaccines, sponsors are asked to contact the Office of Regulatory Affairs, Biologic and Radiopharmaceutical Drugs Directorate (BRDD), at hc.brdd.ora.sc@canada.ca. We will consider all concerns, proposals and/or other suggestions for meeting the labelling requirements outlined in the [Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19](#).

Risk management plan

Companies should submit a risk management plan (RMP) that focuses on the safety risks for a COVID-19 vaccine. For more information on RMPs, please see our [guidance document for submitting RMPs and follow-up commitments](#).

In addition, the Canadian addendum must demonstrate compatibility with Canadian regulatory requirements.

The addendum should contain the following sections:

Safety specifications

- include special events of interest, known and potential safety risks and special populations with limited information from (or that were excluded from) clinical trials
- address monitoring strategies in marginalized, remote and indigenous communities where data is available
- include timely updates of the list of safety concerns if a safety issue signal is observed from post-authorization surveillance

Pharmacovigilance plan

- consider activities in Canada during a pandemic related to collecting, collating, assessing and reporting spontaneous adverse events
- confirm expedited spontaneous reporting of adverse events (spontaneous reporting in Canada is different from other jurisdictions)
- discuss additional measures related to the detection of cases, such as:
 - fatal/life-threatening, serious unexpected, special events of interest
 - vaccination failure and errors
 - special populations
 - patients with comorbidities
 - potential interaction with other vaccines
 - concomitant treatments
- include additional post-market activities as required, such as:
 - registries
 - questionnaires
 - safety/effectiveness studies
 - timely and effective monitoring of the safety profile
- include monthly safety summary reports
- include rapid signal detection and communication of signals leading to a change in the balance of risks and benefits

Risk minimization plan

- include the following information:
 - robust labelling with warnings and precautions
 - educational materials
 - a plan for communicating and sharing safety information internationally in a timely and effective manner

Review process, communications and transparency

Review process

Decisions made about COVID-19 vaccines will follow processes established for rolling reviews under the IO. Health Canada will start rolling reviews to build towards a complete dossier for each vaccine. The dossier will include data to support the safety, efficacy and quality of the proposed vaccine.

In accordance with section 21.1 (3) of the *Food and Drugs Act*, we will share information on the safety and efficacy of a vaccine with the Public Health Agency of Canada and the National Advisory Committee on

Immunization (NACI). This collaboration will begin as early as possible to assist public health recommendations, as described in NACI's recently published [guidance](#).

With the sponsor's agreement, we may also collaborate with international regulatory partners to share analyses and perspectives and supplement the Health Canada review process.

Teams of medical and scientific experts at Health Canada will carry out the vaccine reviews. These people have experience in reviewing complex data and study results on the safety, efficacy and quality of a variety of vaccines. Review activities include developing strategies for the continued accumulation of data on vaccine safety and effectiveness following authorization through terms and conditions and/or pharmacovigilance activities, including post-market studies.

Collaborative review with international regulatory partners may be possible in cases where manufacturers file a rolling submission simultaneously with Health Canada and another jurisdiction with which there is a mutual collaborative agreement. While recommendations may be informed by discussions between regulatory partners during a collaborative review, authorization decisions by Health Canada will be based on a thorough assessment of the evidence. These decisions are independent of those made by international partners.

Authorization decisions will be based on the overall benefits and risks. We will also consider all of the data available, including the results that have been provided in the rolling submission and the current knowledge about the virus and disease, which will need to be continually monitored following authorization. Sources of knowledge include the scientific literature, public health and surveillance data, and collaborations with our international regulatory partners.

Vaccines are given to healthy individuals, so the tolerance for risk is much lower than that of other health products. The bar for safety is understandably higher.

While the IO contains provisions that allow the authorization of COVID-19 products based on the decision of a foreign regulator, this provision will not be used to authorize vaccines. For vaccines, we expect sponsors to file a detailed dossier with all the necessary data as provided to foreign regulatory authorities. Health Canada will review the data and information to ensure an independent decision considers the Canadian context and provides comprehensive labelling and other information to help public health officials develop guidelines for the deployment of COVID-19 vaccines in Canada.

Communications and transparency

Information about vaccines under review and those that are authorized will be posted on our website. Our [list of applications received](#) will include COVID-19 vaccines under review. Once authorized, COVID-19 vaccines will be included on our [list of authorized drugs](#). A [regulatory decision summary](#) will be published at the time of authorization. A [summary basis of decision](#) will follow, giving health care system partners and the public access to data and information supporting the authorization. Detailed clinical data will be published under the Public Release of Clinical Information initiative, in accordance with Health Canada's new guidance on the [public release of clinical information for drugs and medical devices in COVID-19 interim order applications](#).

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