Health Canada Santé Canada

Guidance Document: Annual update of seasonal influenza vaccines

Date adopted	2015-01-12
Effective date	2015-01-30
Administrative changes date	2024-06-04
Revised date	2016-03-17

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
Ligne directrice : Mise à jour annuelle des vaccins contre la grippe saisonnière

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Publication date: August 2024

Cat.: H164-381/2024E-PDF
ISBN: 978-0-660-73175-9
Pub.: 240490

Document change log

Date	Change	Location (section, paragraph)	Nature of and/or reason for change
2024-06-04	Added: and/or starting material • changes to the seed banks and/or starting material that are required to produce vaccine for the upcoming influenza season	1.2 Scope and Application	Administrative
2024-06-04	Deleted: ~~For seasons with multiple strain changes~~ Revised sentence: Sponsors may provide BRDD's ORA with a proposed submission filing schedule if it will facilitate timely review of the submission.	2.2 Key timelines	Administrative
2024-06-04	Updating reference to Guidance on evaluation fees for human drugs and disinfectants (formerly Guidance Fees for the Review of Human and Disinfectant Drug Submissions and Applications)	2.4 Annual update submission	Administrative
2024-06-04	Updating reference to Management of Drug Submissions and Applications guidance document (formerly Management of Drug Submissions guidance document)	2.4 Annual update submission	Administrative
2024-06-04	Deleted: ~~for live attenuated influenza vaccines~~ Added: drug substance Added: 3.2.S.7 • Real-time stability data for the drug substance and drug product (3.2.S.7 and 3.2.P.8, Stability)	2.4.1 Quality Requirements	Administrative
2024-06-04	Link updated to new version of the Certified Product Information Document-Biologics (CPID-B)	2.4.1 Quality Requirements	Administrative

2024-06-04	Added text to the following paragraph: Sponsors are reminded to include annotated copies of the updated Certified Product Information Document-Biologics (CPID-B) within Module 1… New additional text: …where process changes have been made. However, the CPID should avoid including strain-specific details unless the process requires it.	2.4.1 Quality Requirements	Administrative
2024-06-04	Deleted: ~~Sponsors should also inform ORA of any intended changes to the seed banks for planning purposes.~~	2.4.1 Quality Requirements	Administrative
2024-06-04	Added: to the labelling material Sponsors should confirm within the cover letter that no other changes are being made to the labelling material.	2.4.2 Product monograph and labelling requirements	Administrative
2024-06-04	Deleted: ~~included~~ Added: revised Only text related to the annual update should be revised.	2.4.2 Product monograph and labelling requirements	Administrative
2024-06-04	New paragraph: If there are any changes outside of the annual update that may impact the design elements of the inner and outer labels, the sponsor should reference the *Questions and Answers: Plain Language Labelling Regulations for Prescription Drugs* for the appropriate filing category.	2.4.2 Product monograph and labelling requirements	Administrative
2024-06-04	New text added to table header **Suggested text**: **Suggested text related to seasons and strains**	Table 2. Product labelling for seasonal influenza vaccines	Administrative

2024-06-04	BGTD's Viral Vaccines Division updated to BRDD's Vaccines Quality Division	2.5 Lot Release	Administrative
2024-06-04	Deleted: • ~~Anticipated lot release date by BGTD~~	2.5 Lot Release	Administrative
2024-06-04	Updating reference to Reporting Adverse Reactions to Marketed Health Products - Guidance Document for Industry	2.6. Pharmacovigilance Activities for Seasonal Influenza Vaccines	Administrative
2024-06-04	Added: Upon request Updated: Bureau and Directorate names Upon request, reports covering intervals of 6 to 12 months should be sent to the attention of the Bureau of Biologics, Radiopharmaceuticals and Self-Care Products (BBRS), of the Marketed Health Products Directorate (MHPD) through the Office of Submissions and Intellectual Property within 70 days of the data-lock point.	2.6. Pharmacovigilance Activities for Seasonal Influenza Vaccines	Administrative
2024-06-04	Added: Refer to the most up-to-date version of the Health Canada *Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products – Guidance Document for Industry* for more details.	2.6. Pharmacovigilance Activities for Seasonal Influenza Vaccines	Administrative
2024-06-04	Deleted: ~~preferably~~ Deleted: ~~ICH E2E~~ Deleted: ~~Notice Regarding Implementation of Risk Management Planning~~ Added: the Health Canada *Guidance Document – Submission of Risk Management Plans and Follow-up Commitments*	2.6. Pharmacovigilance Activities for Seasonal Influenza Vaccines	Administrative

2024-06-04	Updating email addresses Updating Division and Directorate information Biologic and Radiopharmaceutical Drugs Directorate contact information (formerly Biologic and Genetic Therapies Directorate) Vaccines Quality Division (formerly Viral Vaccines Division) Centre for Vaccines, Clinical Trials and Biostatistics (formerly Centre for Biologics Evaluation) Bureau of Biologics, Radiopharmaceuticals and Self-care products (formerly Marketed Biologicals, Biotechnology and Natural Health Products Bureau) Updating MHPD Phone and Fax numbers	Contact information	Administrative

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 program 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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1. Introduction

Influenza virus vaccines are usually modified annually to protect against circulating strains. Every February, the World Health Organization (WHO) recommends which influenza virus strains should be used for vaccine production in the northern hemisphere. Immediately following the recommendation, manufacturers begin vaccine production. The challenge is the short timeframe between the WHO recommendation and the start of the next influenza season. These tight timelines necessitate well planned regulatory submission and evaluation processes and close collaboration between the vaccine industry and Health Canada's Biologic and Radiopharmaceutical Drugs Directorate (BRDD).

1.1 Policy objectives

Health Canada aims to:

(i) support the timely authorization of annual updates to seasonal influenza vaccines by using a special market authorization process with expedited timelines, and

(ii) ensure sponsors understand the process and have the information they need to file annual update submissions.

1.2 Scope and application

This guidance document applies to sponsors seeking authorization for annual updates to influenza vaccines. The document covers the process, data requirements, and associated timelines for the submission, review, and lot release of seasonal influenza vaccines in Canada.

The material covered in this document only applies to changes associated with the annual update to seasonal influenza vaccines, specifically

- changes to the virus strain(s)
- changes to the seed banks and/or starting material that are required to produce vaccine for the upcoming influenza season, and
- changes to the product labelling to reflect strain changes and the season of use

All other changes require separate submission(s) and regular timelines apply. Refer to Health Canada's *Post Notice of Compliance Changes* guidance documents for more information.

New influenza vaccines that have not yet received authorization for sale in Canada require a New Drug Submission and shall follow the regular market authorization process.

The timelines in this guidance are specific to the authorization and release of influenza vaccines for the northern hemisphere. Sponsors interested in seeking authorization of an annual update to influenza vaccines for the southern hemisphere should contact BRDD's Office of Regulatory Affairs (ORA).

2. Guidance for implementation

2.1 Overview of the process

To support authorization of annual updates to influenza vaccines, sponsors file quality (chemistry and manufacturing) data related to production of the vaccine with the new strain(s), when applicable, as well as updated labelling information. If the conclusion of BRDD's evaluation is favourable, a market authorization letter is issued.

Vaccines in Canada are subject to BRDD's lot release program. To expedite the process for seasonal influenza vaccines, BRDD's lot release testing is performed in parallel with the sponsor's quality control testing. It is important to note that lots will only be released by BRDD once the market authorization letter is issued.

2.2 Key timelines

The annual update submission and review process is characterized by tight timelines. BRDD needs to receive critical information by specific dates in order to plan and perform regulatory evaluation and lot release activities. Table 1 outlines the key dates and activities associated with annual update submissions. The dates provided should be viewed as maximum deadlines and sponsors are encouraged to provide information as soon as it becomes available. The activities presented in Table 1 are described in more detail throughout the guidance document. Sponsors may provide BRDD's ORA with a proposed submission filing schedule if it will facilitate timely review of the submission. The proposal should be submitted no later than May 1st.

Table 1. Key dates and activities associated with annual update submissions

Activity	**Deadline**
Pre-influenza season submission meeting (Optional)	Meeting requests should be sent 1 month in advance of proposed meeting date
Sponsors to notify BRDD of the strains, reassortants and reagents they are using, and an approximation of the number of lots to be released by BRDD	May 1st
Sponsors to have filed complete annual update submission	July 31st
Sponsors to submit lot release schedules	July 31st
Sponsors to submit complete Batch Release Protocols	14 days in advance of anticipated lot release date

2.3 Pre-influenza season submission meetings

Sponsors may request a pre-influenza season meeting. These meetings provide an opportunity for sponsors to seek advice on any issues or proposed changes for the upcoming season and to present BRDD with an update on their development and lot release plans.

Meeting requests should be sent to BRDD's ORA in writing no less than 1 month prior to the proposed meeting date and should include the following information:

- The purpose of the meeting
- A brief description of the issues to be discussed at the meeting, and
- Two or more proposed dates and times for the meeting

BRDD will aim to inform the sponsor of the confirmed meeting date at least two weeks in advance of the meeting. Sponsors should provide the following information at least 1 week in advance of the meeting:

- Agenda
- List of participants
- Purpose of the meeting
- Background information, including any presentations being made, and
- A list of any questions/issues to be raised by the sponsor

2.4 Annual update submission

Strain changes should be filed as a Supplemental New Drug Submission (SNDS). For details on the applicable fees, sponsors may refer to the Health Canada Guidance on evaluation fees for human drugs and disinfectants that are published annually.

Due to the severe time constraints associated with the annual update and to ensure availability of influenza vaccines in time for the influenza season, the target performance standards provided in Health Canada's Management of Drug Submissions and Applications guidance document are not applied in practice to these submissions.

The submission should follow the Common Technical Document (CTD) format and only relevant sections of the CTD should be provided.

2.4.1 Quality Requirements

Sponsors should refer to the most up-to-date version of the European Medicines Agency (EMA) *Guideline on Influenza Vaccines - Quality Module* for guidance on the quality data requirements for seasonal influenza vaccines.

The following information should also be included in the submission within the identified section of the CTD:

- Qualification of reference antiserum report(s) (3.2.S.4.3, Validation of Analytical Procedures)
- Accelerated stability data for the drug product (3.2.P.8, Stability)[1]
- Real-time stability data for the drug substance and drug product (3.2.S.7 and 3.2.P.8, Stability)

[1] Not applicable to live attenuated influenza vaccines

Sponsors are reminded to include annotated copies of the updated Certified Product Information Document-Biologics (CPID-B) within Module 1 where process changes have been made. However, the CPID should avoid including strain-specific details unless the process requires it.

If the WHO does not recommend a change to the strains from one year to the next, but changes to the seed banks are necessary to produce vaccine for that particular season (e.g. the creation of a new Master Seed Bank or Working Seed Bank), the sponsor should refer to the Health Canada Post-Notice of Compliance Changes guidance documents for the type of submission and supporting data that would be required. The timelines presented in section 2.2 of this guidance document would apply.

2.4.2 Product monograph and labelling requirements

Updated product labelling should be filed in the annual update submission. However, BRDD recognizes that sponsors may wish to seek approval of the updated labelling in advance of the quality documentation being available in order to initiate printing labels. In this case, sponsors should file the product labelling update as a notifiable change submission. A cross-reference to the submitted/approved notifiable change should be included in the cover letter of the annual update SNDS.

If the WHO does not recommend a change to the strains, sponsors would only need to file their product labelling update as a notifiable change. Sponsors should confirm within the cover letter that no other changes are being made to the labelling material. If deemed acceptable, a market authorization letter would then be issued to enable lot release.

Revised labelling material (inner labels, outer labels, and a revised Product Monograph) should be submitted in Module 1. Only text related to the annual update should be revised.

If there are any changes outside of the annual update that may impact the design elements of the inner and outer labels, the sponsor should reference the *Questions and Answers: Plain Language Labelling Regulations for Prescription Drugs* for the appropriate filing category.

To avoid any confusion, the labelling should include information about the influenza virus strains and the season of use. In addition to meeting labelling requirements set out in the *Food and Drugs Act* and the *Food and Drug Regulations*, the information in Table 2 should be included in the product labelling for seasonal influenza vaccines.

Table 2. Product labelling for seasonal influenza vaccines

Product labelling	**Suggested text related to seasons and strains**
Inner label	The season of use should be stated. For example: "yyyy/yyyy season"
Outer label	WHO recommended strains should be included in the outer label. For example: "A/Victoria/361/2011 (H3N2) - like strain The season of use should be stated. For example: "yyyy/yyyy season"

Product labelling	Suggested text related to seasons and strains
Product Monograph	A statement indicating compliance with WHO recommendations should be included in Parts I and III of the product monograph. For example: "This vaccine complies with the WHO (World Health Organization) recommendation (Northern hemisphere) for the [year/year] season" For inactivated vaccines, the WHO recommended strains, followed by actual strains should be included in Part II of the product monograph. For example: "A/Victoria/361/2011 (H3N2) - like strain (A/Victoria/361/2011, IVR-165)"

2.4.3 Clinical requirements

Routine clinical trials are not required to support authorization of the annual strain change. Enhanced safety surveillance as well as routine surveillance throughout the product life-cycle are used to monitor the safety and effectiveness of seasonal influenza vaccines. Refer to section 2.6 for more information.

2.5 Lot Release

Sponsors should notify BRDD of the strains, reassortants and reagents they are using as soon as the information is available. An approximation of the number of expected lots to be released by BRDD should also be provided. If the information is not available by May 1st, sponsors should provide an expected timeline for when the information will be provided.

This information should be sent directly to BRDD's Vaccines Quality Division via email. Refer to section 3 for contact information.

Sponsors are also asked to submit a lot release schedule to BRDD's Vaccines Quality Division no later than July 31st to enable BRDD to plan its evaluation and lot release activities. At a minimum, the schedule should include the following information:

- Company name
- Product name
- Product description
- Season [year/year]
- Final package lot numbers
- Date samples are to be submitted to BRDD
- Date Batch Release Protocols to be submitted to BRDD

Any updates to the schedule should be communicated to BRDD's Vaccines Quality Division as soon as they become available.

Sponsors should submit vaccine samples to BRDD for parallel testing to avoid any delays. This parallel testing should be reflected in the sponsor's lot release schedule.

One of the first vaccine lots submitted for release for a given influenza season is designated as BRDD's assay monitoring control. As such, additional samples for this lot must be sent to

BRDD as part of the first sample shipment. If the same testing reagents are used for different vaccines from the same manufacturer, one presentation of one vaccine lot can be selected as the monitoring control. The number of containers required is dependent on the presentation of the vaccine selected. The additional sample requirements are as follows:

- Additional samples must correspond to a total volume equal to 3mL times the number of final vaccine lots intended for lot release in Canada. For example, if 20 lots are intended for release to the Canadian market then the number of samples required for the monitoring control should be equal to a total of 60mL. These quantities are in addition to the number of samples typically required for lot release of this lot.

Complete batch release protocols should be submitted to BRDD's Vaccines Quality Division no later than 14 days prior to the anticipated release date.

A market authorization letter must be issued by BRDD prior to the release of any lots of vaccine. Upon release by BRDD, the sponsor will receive a formal lot release letter authorizing the sale of the lot in Canada. More information on BRDD's lot release program can be found in the Health Canada *Guidance for Sponsors: Lot Release program for Schedule D (Biologic) Drugs*.

Refer to Table 1 in section 2.2 for recommended deadlines associated with lot release activities. Sponsors should aim to submit the requested information as early in the season as possible.

2.6 Pharmacovigilance Activities for Seasonal Influenza Vaccines

Post-market surveillance is essential to monitor the safety and effectiveness of vaccines. Canada has a combination of passive and active surveillance systems in place to monitor the safety of influenza vaccines during the influenza season. These include the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), IMPACT (Canada's Immunization Monitoring Program ACTive), and the Canada Vigilance Program. Sponsors have a regulatory responsibility to report certain adverse events following immunization to Health Canada's Canada Vigilance Program. Refer to the most up-to-date version of the Health Canada *Reporting Adverse Reactions to Marketed Health Products - Guidance Document for Industry* for more details.

Periodic Benefit Risk Evaluation Report

Effective monitoring and risk mitigation also require integration with an increasingly global vaccine supply network. Manufacturers are reminded to prepare an annual summary report of serious and non-serious adverse drug reactions following immunization with a critical analysis and conclusion of the effect on the risks and benefits of the vaccine (Section C.01.018 of the *Food and Drug Regulations*). The report should include all adverse reactions received during the preceding influenza season, and should be in the format of a Periodic Benefit-Risk Evaluation Report (PBRER) (ICH E2C(R2)). Upon request, reports covering intervals of 6 to 12 months should be sent to the attention of the Bureau of Biologics,

Radiopharmaceuticals and Self-Care Products (BBRS), of the Marketed Health Products Directorate (MHPD) through the Office of Submissions and Intellectual Property within 70 days of the data-lock point. PBRERs are submitted as clinical study reports within section 5.3.6 of the CTD. Refer to the most up-to-date version of the Health Canada *Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products – Guidance Document for Industry* for more details.

Risk Management Plans

Sponsors should implement surveillance programs to monitor the safety and effectiveness of their influenza vaccines. For newly identified risks, sponsors should provide information on their proposed pharmacovigilance plan and risk mitigation strategies to the MHPD in the format of a Risk Management Plan (RMP) or amended RMP as per the Health Canada *Guidance Document – Submission of Risk Management Plans and Follow-up Commitments*. Sponsors are encouraged to seek advice on proposed surveillance plans. Summaries of surveillance studies should be included in the PBRER. If a study is supported by the company but conducted by an outside agency, it should be listed under the proposed pharmacovigilance activities in the RMP.

3. Contact information

Submission inquiries should be directed to BRDD's ORA:

Office of Regulatory Affairs
Biologic and Radiopharmaceutical Drugs Directorate
Health Canada
Phone: 613-957-1722
Email: brdd.ora@hc-sc.gc.ca

Lot release schedules and batch release protocols should be sent directly to BRDD's Vaccines Quality Division:

Vaccines Quality Division
Centre for Vaccines, Clinical Trials and Biostatistics
Biologic and Radiopharmaceutical Drugs Directorate
Health Canada
Email: hep.inf@hc-sc.gc.ca

Inquiries related to pharmacovigilance activities and risk management plans should be directed to MHPD:

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