How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080)

July 2nd, 2025

Canada

Date issued: 2 July 2025
Date implemented: 2 July 2025
Replaces: *How to Demonstrate Foreign Building Compliance with Drug Good Manufacturing Practices (GUI-0080)* (January 18, 2018)

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.

Également disponible en français sous le titre: Comment démontrer la conformité des bâtiments étrangers avec les bonnes pratiques de fabrication des médicaments (GUI-0080)

To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
Email: hc.publications-publications.sc@canada.ca

Publication date: July 2nd, 2025

Cat.: H139-89/2025E-PDF
ISBN: 978-0-660-76442-9
Pub.: 240968

Disclaimer

This document does not constitute legislation. In the event of any inconsistency or conflict between the legislation and this document, the legislation takes precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the legislation and the applicable administrative policies.

Table of Contents

About this document

1. Purpose

This guide is for Canadian importers who want to list and maintain a foreign building on their drug establishment licence (DEL).

It provides guidance on the type of information you should submit to support your DEL application. It will also help you understand how Part C, Division 2, Good Manufacturing Practices of the Food and Drug Regulations (FDR) applies to foreign buildings that supply Canadian importers with drugs for import into Canada or import into Canada for future export. This includes finished dosage forms (FDF), active pharmaceutical ingredients (API), and FDF and API intermediates.

2. Scope

These guidelines apply to importers of drugs for human and veterinary use from foreign buildings.

There may also be scenarios where a DEL holder must list a foreign building on their DEL for licensable activities not related to import. For example, DEL holders that use a foreign building solely as a third-party testing site must also follow the guidance in this document.

Foreign building licensable activities within scope:

- fabrication
- packaging/labelling
- testing

Drug categories within scope:

- pharmaceutical drugs
  - includes medical gases
- active ingredients
- vaccines
  - Schedule D to the FDA
- biological drugs
  - Schedule D to the FDA
- radiopharmaceutical drugs

    - Schedule C to the FDA
- prescription drugs
    - set out in the Prescription Drug List
- controlled drugs
    - defined in section G.01.001 of the FDR
- narcotics
    - defined in the Narcotic Control Regulations
- drugs containing cannabis
    - defined in subsection 2(1) of the Cannabis Act
- APIs set out in List A that are for veterinary use

For more information on drug categories, consult:

- Guidance on drug establishment licences (GUI-0002)

These guidelines also apply to foreign buildings that retain samples of a drug in dosage form on behalf of a Canadian importer or distributor. This is outlined in section C.02.025(1) of the FDR.

This document does not cover foreign buildings that perform activities with products that do not fall under Part C, Division 1A of the FDR. As well, it does not include foreign buildings that perform activities with:

- cannabis for medical and non-medical purposes
- cells, tissues and organs for transplantations
- excipients
    - non-medicinal components of a drug product
- drugs used in clinical trials
- drugs used for research and development
- medical devices
- natural health products as defined in the Natural Health Products Regulations
- veterinary vaccines and select veterinary immunomodulators that fall within the scope of the Canadian Food Inspection Agency (that is, veterinary products without a drug identification number (DIN))
- whole blood for transfusion

3. Introduction

When a drug is fabricated, packaged/labelled or tested outside of Canada, the foreign building where those activities occur must be listed on the Canadian importer's DEL. To be listed on the

DEL, the foreign building must be compliant with good manufacturing practices (GMP) requirements. These requirements are described in Part C, Divisions 2 to 4 of the FDR.

It's your responsibility as a Canadian importer to ensure that drugs fabricated, packaged/labelled or tested outside of Canada and imported for sale in Canada comply with GMP requirements.

This guidance document outlines:

- when and how to submit GMP evidence to support the compliance of a foreign building
- what GMP evidence must be submitted

Health Canada will assess the GMP evidence against the FDA and its associated regulations.

4. Listing Foreign Buildings On Your DEL

4.1 Drug Establishment License Annexes

All Canadian drug establishments must hold an active drug establishment licence (DEL) to fabricate, package/label, distribute, import, wholesale or test a drug. This is required under Part C, Division 1A of the Food and Drug Regulations (FDR).

For more information on how to comply with Part C, Division 1A of the FDR, consult:

- Guidance on drug establishment licences (GUI-0002)

The following sections describe the 3 different annexes where foreign buildings can be listed on a DEL. The type of annex where a foreign building is listed depends on the activities and the drug category associated with the foreign building:

1. Foreign building annex (FB annex)

This annex applies to foreign buildings that:

- fabricate, package/label or test finished dosage form (FDF) and FDF intermediates, including bulk process intermediates (BPIs)
- fabricate, package/label or test sterile active pharmaceutical ingredients (API), sterile API intermediates and sterile atypical APIs
- release test non-sterile APIs or non-sterile atypical APIs, where the testing results are used to release the API for use in fabricating an FDF

For guidance on adding foreign buildings to your FB annex, refer to Submitting an amendment to the FB annex.

Foreign buildings subcontracted to perform these activities must also be listed on the FB annex of your DEL:

- for example, a foreign building that performs testing on behalf of the foreign fabricator must be listed on the FB annex for the activity of test

Note: Health Canada considers the fabrication process of an FDF to include the release testing of the API as well as the final fabrication of the FDF. If the FDF fabricator performs the release testing of the API for use in the FDF fabrication:

- the testing is considered to be part of the FDF fabrication process
- the activity of release testing the API may be omitted from the licence

As well, in scenarios where the FDF fabricator is responsible for the full API release testing, the API fabricator does not need to be listed on the FB annex for release testing of the API.

2. Active pharmaceutical ingredient foreign building annex (API FB annex)

This annex applies to foreign buildings that:

- fabricate and package/label non-sterile APIs, non-sterile API intermediates and non-sterile atypical APIs
- test non-sterile APIs, non-sterile API intermediates and non-sterile atypical APIs
  - does not include release testing of non-sterile APIs or atypical APIs, where the testing results are used to release the API for use in FDF fabrication

For guidance on adding foreign buildings to your API FB annex, refer to Submitting an amendment to the API FB annex.

3. Alternate sample retention (ASR) annex

This annex applies to distributors and importers that retain samples of specific products at buildings outside of Canada. If the distributor and importer are different companies, only 1 of the 2 companies needs to list ASR buildings on their ASR annex depending on the responsibilities outlined in the quality agreement between those 2 companies.

The requirement for retaining samples:

- is outlined in section C.02.025 of the FDR

- ensures access to samples of finished drug products in the event of a quality concern

For guidance on adding a foreign building to your ASR annex, refer to Submitting an amendment to the ASR annex.

4.2 Mutual Recognition Agreements

Canada is a participant to several mutual recognition agreements (MRAs) covering drug good manufacturing practices (GMP) compliance programs. MRAs are created to ensure that the regulatory frameworks in place in each partner's jurisdiction are equivalent. Health Canada will consider a valid certificate of compliance (CoC) as evidence to support the GMP compliance of a foreign building located in an MRA country. We will exchange the CoC with our MRA partners only.

For when to use a CoC as GMP evidence to support an application for a foreign building located in an MRA country, refer to CoC to support compliance of foreign building.

APIs are temporarily excluded from certain MRAs, as not all MRA partners have an API GMP compliance program that has been assessed. We will be updating the list of countries with the updated MRAs (including APIs) as the scope of MRAs evolve.

Learn more about Health Canada's MRAs, including the specific MRA partners and their operational scope, consult mutual recognition agreements webpage.

Note: As per C.01A.015 of the FDR, you must notify us of any changes to a building's compliance status, permit, licence or other authorization issued by the regulatory authority that recognized the building.

For more information on C.01A.015 notifications, consult:

- Guidance on drug establishment licences (GUI-0002)

4.3 MRA Extra-Jurisdictional Inspection Outcomes

We have expanded the scope of certain MRAs to include the exchange of CoCs for GMP inspections of foreign buildings conducted by the MRA partner outside their jurisdiction (non-MRA countries). The expanded scope will:

- enhance cooperation and regulatory alignment between Canada and certain MRA partners
- reduce the regulatory burden for Canadian importers

We exchange extra-jurisdictional (EJ) CoCs directly with the MRA partner if the CoC is within the:

- validity period indicated by the issuing authority **and**
- operational scope of the MRA

We exchange EJ CoCs with certain MRA partners, including:

- MRA partners in the European Union (EU)
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Swissmedic
- Therapeutic Goods Administration (TGA)

For details on using an EJ CoC as GMP evidence to support an application for a foreign building located in a non-MRA country, refer to EJ CoC to support compliance of foreign building.

If the last Health Canada assessment of a foreign building was assigned a non-compliant rating, an EJ CoC cannot be submitted as GMP evidence to overcome the non-compliant rating. For the requirements to reassess a non-compliant rating, refer to Reassessing non-compliant ratings.

Note that remote and hybrid inspections are outside the operational scope of the MRA and are not eligible for the exchange of EJ CoCs. In these cases, we may consider inspection reports based on remote assessments using a risk-based approach. For information on when you may submit GMP evidence based on remote assessments, refer to Inspection report.

4.4 New Evidence Required By Date

A "new evidence required by" (NERBY) date is the date when updated GMP evidence must be submitted to Health Canada to renew a foreign building on the licence. The NERBY date acts as a checkpoint for us to verify the continued compliance of a foreign building that supplies products to Canada.

A NERBY date is assigned to foreign buildings based on location, the type of supporting GMP evidence reviewed and the type of annex on which the foreign building is listed (Table 1).

Table 1: Summary of when NERBY dates are assigned

DEL annex	Location of foreign building	NERBY date assigned (yes or no)

FB annex	Located in an MRA country (for activities or drug categories covered by the MRA)	No
FB annex	Located in an MRA country (for activities or drug categories not covered by the MRA or not inspected by the MRA partner) or Not located in an MRA country	Yes
API FB annex	Located outside of Canada	No
ASR annex	Located outside of Canada	No

A NERBY date is assigned to a foreign building using a risk-based approach. The typical NERBY date is 4 years from the start date of the inspection by a regulatory or qualified authority, qualified body or a Health Canada foreign onsite inspection. For example, if the start date of an inspection is January 14, 2023, the typical NERBY date will be January 14, 2027.

However, we may assign a shorter or longer NERBY date based on the risk profile of the foreign building.

When assigning a NERBY date to a foreign building, we consider the:

- existing compliance history of the building
- activities being performed
- category, type and dosage form of the drug
- inspection type
  - for example, onsite inspection or remote assessment
- type of GMP evidence available

If the foreign building on the FB annex of your licence is assigned a NERBY date, you must submit an application along with updated supporting GMP evidence to renew the NERBY date. You must do this before the assigned NERBY date to maintain the foreign building on the FB annex of your DEL.

If you submit an amendment application before the NERBY date, the foreign building will continue to be listed on the FB annex of your DEL while we review the application.

For more information, refer to Submitting an amendment to the FB annex.

We may extend a previously assigned NERBY date based on the circumstances described in a risk-based NERBY extension request.

If Health Canada becomes aware that the foreign building has GMP concerns, we may request new evidence from you before the NERBY date. Once we evaluate this new evidence, we may change the previously assigned NERBY date or propose other compliance and enforcement actions.

The foreign building may be removed from the FB annex if the NERBY date has expired and:

- an application to amend or extend the NERBY date is not received by the NERBY date
- the application to amend or extend the NERBY date is incomplete and responses to deficiency notices were not adequate **or**
- the evidence is deemed unacceptable or incomplete at any time during the assessment process and the deficiencies were not adequately addressed

To learn more about types of deficiencies and the pause-the clock policy, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

If a NERBY date is not assigned to a foreign building (refer to Table 1), you do not have to submit an application with new GMP evidence. However, you must ensure that any foreign building on your licence continues to comply with the GMP requirements.

4.5 Health Canada Assessment Outcomes

Health Canada will complete an assessment of a foreign building based on the supporting GMP evidence.

We will then assign a compliance rating:

- **Compliant:** issued when the evidence is acceptable and demonstrates compliance with Divisions 2 to 4 of the FDR
  - the foreign building will be added or maintained on your DEL
- **Non-compliant:** issued when the evidence is unacceptable and does not demonstrate compliance with Divisions 2 to 4 of the FDR

- the foreign building will not be added to your DEL or we may request that you remove the foreign building from your DEL

Terms and conditions (T&Cs) may be added to your DEL if other factors require additional oversight, such as:

- dosage form
- product sterility
- drug category
- medical necessity
- compliance history
- nature of the supporting GMP evidence
- activities conducted at the foreign building

For more information on T&Cs, refer to Compliance with terms and conditions.

5. Importer Responsibilities

Canadian drug establishment licence (DEL) holders have defined responsibilities under the Food and Drugs Act (FDA) and the Food and Drug Regulations (FDR) to ensure the safety, efficacy and quality of drugs imported or sold in Canada.

Importers who fail to comply with these responsibilities, which are outlined in this section, may be subject to compliance and enforcement action.

Learn more:

- Compliance and enforcement policy for health products (POL-0001)

5.1 Maintaining GMP Evidence Onsite

Importers must keep a copy of the good manufacturing practices (GMP) evidence used to support the GMP compliance of all foreign buildings listed on all of the annexes of their DEL at their Canadian site. This requirement is outlined in sections C.02.012, C.02.20, C.02.21 and C.02.24 of the FDR.

Maintaining and reviewing evidence onsite ensures that both the importer and Health Canada have oversight over the compliance of foreign buildings that supply product to Canada. It also ensures that the submitted GMP evidence covers the requested activities, drug categories and dosage forms in the DEL amendment application.

The evidence maintained and reviewed onsite should correspond to the type of evidence that is:

- submitted or attested to in your most recent DEL application for the building **or**
- indicated on your Table A: Foreign building conducting active pharmaceutical ingredient related licensable activities

For example, if an extra-jurisdictional certificate of compliance (EJ CoC) was the supporting evidence in your recent application for the foreign building, this evidence should be maintained onsite.

Importers can keep a copy of the redacted inspection report in cases where the report has confidential information. For example, the inspection report can include light redactions to hide customer names, employee names or product information. Redactions should be focused on confidential business information or a trade secret. Redactions of entire paragraphs are not acceptable.

The inspection report must be kept at the Canadian site for 1 year past the expiry date of the imported product, unless the licence indicates otherwise.

For more information on records, consult:

- Good manufacturing practices guide for drug products (GUI-0001)

During a domestic inspection of an importer, a Health Canada inspector may verify that GMP evidence for foreign buildings on the licence is kept onsite. If you are not able to provide an original or redacted copy of the GMP evidence upon request by the inspector onsite, the foreign building can submit the evidence directly to us after being requested to do so by an inspector.

The importer and foreign building should have a quality agreement in place (either with the subcontracted foreign building or the direct supplier). The agreement should include provisions that the applicable inspection reports be submitted to us by the foreign building within 2 business days of receiving the request. We will provide instructions on how to submit at the time of the request.

Importers should **always** keep a copy of the cover letter, closing letter or GMP certificate that corresponds to the inspection report. They should do so even if a quality agreement is in place that includes a provision to supply evidence directly to Health Canada upon request.

For information on the content of a quality agreement, consult Section C.02.012, under "Agreement" in:

- Good manufacturing practices guide for drug products (GUI-0001)

You should keep additional evidence onsite in scenarios where there are potential GMP issues for a foreign building on your licence. An example of this would be if the foreign building was the subject of a risk assessment by Health Canada for potential GMP issues.

For more information, refer to Foreign buildings with potential GMP issues.

5.2 Reporting Changes Related to a Foreign Building

Importers must inform Health Canada of any changes to the:

- foreign building's name (foreign establishment name) or address
- licensable activities, categories or dosage forms being conducted by a foreign building listed on your licence related to your imported products

This is set out in section C.01A.006 of the FDR. You must submit a DEL amendment application if any of the changes indicated in this section occur.

For more information, refer to Submitting an amendment for changes related to a foreign building on the DEL.

5.3 Compliance with Terms and Conditions

Health Canada may decide that we need to apply additional oversight to prevent risk to a person's health and safety. If we do so, we will add terms and conditions (T&Cs) to the licence or amend the T&Cs of the licence. This is set out in sections C.01A.008(4) and C.01A.012 of the FDR.

The importer must comply with all T&Cs listed on the DEL.

If you believe the T&Cs are no longer needed or should be amended, you must submit an application to us for the foreign building.

For information on submitting your application, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

Clearly indicate in the cover letter that you wish to have the T&Cs removed or updated and why. Your application will also require supporting GMP evidence that demonstrates the activities no longer require additional oversight and that the T&Cs can be removed or amended.

Upon GMP assessment, we may decide to maintain the same T&Cs if the updated evidence does not support their removal or amendment.

5.4 Retaining Samples of Imported Drug Product

Importers and distributors of drugs in dosage form must keep a sample of each lot or batch of a packaged/labelled drug in Canada for 1 year after the product has expired, unless otherwise specified on the licence. In some cases, we may permit a foreign building to be an alternate sample retention (ASR) building if specific requirements are met.

For more information, refer to Submitting an amendment to the ASR annex.

This requirement ensures that samples of finished drug products can be accessed if:

- Health Canada has a concern about their quality
- the importer or Health Canada needs to analyze a sample of the finished drug product

For details on the requirements of retention samples, consult section C.02.025, "Samples," in:

- Good manufacturing practices guide for drug products (GUI-0001)

6. Submitting DEL Amendment Applications

For a brief overview of the application types described in this section, refer to Application types and processes.

6.1 General Information for Submitting DEL Amendment Applications

This section outlines the general information that should be submitted for any DEL application.

For instructions on how to submit your application, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

These instructions apply to all applications described in this section.

You must inform Health Canada if:

- you plan to submit an application for a foreign building that performs activities with a critical product (a real or imminent drug supply shortage of a medically necessary drug as determined by Health Canada) **and**
- the application does not meet the standard requirements in this guidance

To determine next steps, email us at foreign.site-etranger@hc-sc.gc.ca.

If the foreign building that is part of your application is responsible for activities on products in shortage, consult:

- Guide to reporting drug shortages and discontinuations (GUI-0120)

6.1.1 Cover letter

Including a cover letter is strongly recommended when submitting all DEL applications. It should contain information that will help us review your application. Include the following information, where applicable:

- explanation of changes in the foreign building name or address from the last application
- explanation of discrepancies in the foreign building's name or address between FRM-0033 and the good manufacturing practice (GMP) evidence
- information on the criticality of the products
  - for example, a real or imminent drug supply shortage of a medically necessary drug
- justification for submitting older GMP evidence instead of the most recent evidence available
  - for example, an inspection report that is 2 years old instead of an inspection report that is 1 year old, by a regulatory or qualified authority, or qualified body
- references to previously assessed GMP evidence

For more information on what to include on your cover letter, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

6.1.2 FRM-0033

Make sure your application contains complete information in all applicable sections of the most recent and up-to-date version of FRM-0033.

For a copy of the recent FRM-0033 template and instructions on how to complete the form, consult:

- Drug establishment licence application form

6.2 Submitting An Amendment to the FB Annex

An application must be submitted to amend the foreign building (FB) annex (adding a new foreign building or renewing or amending an existing foreign building).

Include the cover letter and FRM-0033. Your application may need to be accompanied by supporting GMP evidence as well.

The rest of this section describes the type of supporting GMP evidence you can submit and how to submit it. The service standard for your application depends on the type of supporting evidence and whether it has been previously reviewed by Health Canada.

For more information on application service standards, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

6.2.1 Determining the type of GMP evidence

The type of GMP evidence needed to demonstrate the GMP compliance of foreign buildings is based on where the foreign building is located and whether it's covered by an MRA (Table 2). Some administrative amendment applications (for example, change in name or address of a foreign building or change to activities, categories or dosage forms) may require GMP evidence as well.

To determine when your administrative amendment application requires GMP evidence, refer to Submitting an amendment for changes related to a foreign building on the DEL.

Health Canada will evaluate the most recent GMP evidence available for the foreign building (recent evidence is within the last 3 years). In certain circumstances, we may consider a different validity period for GMP evidence. The GMP evidence must cover the scope of the activities, categories and dosage forms listed on your FRM-0033.

If you are not submitting the most recent GMP evidence (for example, evidence is within 3 years but is not the most recent) to support your application, you must indicate this and explain why in your cover letter.

Table 2: Recommended GMP evidence based on foreign building location and coverage by an MRA

MRA coverage	Foreign building located in an MRA country	Foreign building not located in an MRA country
Activities covered by an MRA (inspected by MRA partner)	CoC to support compliance of foreign building	EJ CoC to support compliance of foreign building

Activities not covered by an MRA (not inspected by MRA partner)	Full GMP evidence to support compliance of foreign building	Full GMP evidence to support compliance of foreign building

Note: To ensure service standards are met for application streams, Health Canada will only consider and review 1 type of GMP evidence for each foreign building included in your DEL application. If you need to submit a new type of GMP evidence, we will consider this as a change in scope of the current application and will require a new application.

Examples of a change in scope include a request:

- to add new activities, categories or dosage forms after we have sent the DEL screening completion notice **or**
- for an EJ CoC review after an application has been submitted for a full GMP evidence review

For more information on change in scope of applications, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

6.2.2 CoC to support compliance of foreign building

For an amendment to your FB annex where the foreign building is in an MRA country and the activities, drug categories and dosage forms are covered by the MRA, the supporting GMP evidence should be a CoC. You should:

- submit the cover letter and FRM-0033 (instructions outlined earlier in this document)
- indicate that a CoC is the supporting GMP evidence on the FRM-0033

The cover letter and FRM-0033 is Health Canada's prompt to request a CoC from the applicable MRA partner.

Keep a copy of the CoC at the domestic building (refer to Maintaining GMP evidence onsite). We exchange CoCs with our MRA partners only and will not send a copy of the CoC to importers.

Before submitting an application indicating a CoC as the supporting GMP evidence, make sure the CoC covers the requested activities, drug categories and dosage forms on FRM-0033.

6.2.3 EJ CoC to support compliance of a foreign building

For an amendment to your FB annex where the foreign building is located in a non-MRA country and was inspected by an MRA partner with whom Health Canada exchanges EJ CoCs, you should:

- submit the cover letter and FRM-0033 (instructions outlined earlier in this document)
- indicate the EJ CoC is the supporting GMP evidence on FRM-0033
- indicate the regulatory authority that inspected the foreign building on FRM-0033

The cover letter and FRM-0033 is Health Canada's prompt to request an EJ CoC from the applicable MRA partner. If the cover letter and FRM-0033 do not indicate these details, we will not request an EJ CoC from the MRA partner. We will assume that full GMP evidence will be submitted and route the application to the appropriate review stream.

If an EJ CoC becomes available while the application has already been routed to the full GMP evidence review stream or if you incorrectly submitted your application with EJ CoC as supporting evidence, you will be asked to withdraw the existing application. You will need to submit a new application under the appropriate review stream.

Keep a copy of the EJ CoC at the domestic building (refer to Maintaining GMP evidence onsite).

When the supporting evidence is an EJ CoC, the EJ CoC must:

- be within the period of validity indicated on the CoC by the issuing authority
- be within the operational scope of the MRA (including the inspection being conducted onsite)
- cover the requested activities, drug categories and dosage forms on FRM-0033

It's the importer's responsibility to submit a renewal application by the foreign building's NERBY date.

6.2.4 Full GMP evidence to support compliance of foreign building

For an amendment to your FB annex where the foreign building or its activities, categories or dosage forms are not covered by the MRA or not inspected by an MRA partner, you should submit full GMP evidence to demonstrate GMP compliance of a foreign building. This includes:

- the cover letter
- FRM-0033 (instructions outlined earlier in this document)
- full GMP evidence package:

- inspection report
- corrective actions
- site master file

The documents you need to submit in the GMP evidence package must meet specific requirements. To learn more about these requirements, refer to Recommended full GMP evidence package.

6.2.4.1 How to submit the full GMP evidence package

Health Canada strongly recommends that the importer submit GMP evidence when filing the application. Email the evidence to the Drug Establishment Licensing Unit at el.applications-le@hc-sc.gc.ca before you receive the DEL screening completion notice.

If you are not able to submit some of the recommended evidence, we will accept the evidence directly from the foreign building or by an organization on behalf of the foreign building. The evidence must be submitted:

- after the importer has filed an application (cover letter and FRM-0033) and has received an application number in the "acknowledgement of application acceptance" email from the Drug Establishment Licensing Unit
- to the Drug Establishment Licensing Unit at el.applications-le@hc-sc.gc.ca and the email clearly references the application number and DEL number

GMP evidence submitted separate from the application must be submitted before you receive the DEL screening completion notice. If GMP evidence is not submitted before we send out the DEL screening completion notice, we will send a GMP screening deficiency notice. This will count as 1 of your 2 opportunities to meet the GMP evidence requirements.

To learn more about deficiencies and the pause-the clock policy, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

To help with the submission process and review of the GMP evidence, we recommend that:

- documents be submitted as a portable document format (PDF)
- the PDF be able to recognize optical characters
- sections in the PDF be bookmarked
- the full GMP evidence be sent in multiple emails if the package is larger than 20 megabytes
    - include numbering in the subject line of your emails to ensure all emails are tracked

For responses to GMP screening deficiency notices, the DEL holder or the foreign building should submit the requested information to foreign.site-etranger@hc-sc.gc.ca and clearly reference the application number and DEL number.

Information submitted without referencing an application number or sent to the incorrect email address will not be accepted and may lead to the application being rejected in full or in part. The importer is responsible for making sure that we receive a complete response to a deficiency notice.

Applications are subject to the pause-the-clock policy and the clock will be paused when a deficiency is identified.

To learn more about types of deficiencies and the pause-the clock policy, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

6.2.5 A risk-based NERBY extension request

Importers may request an extension to a foreign building's NERBY date under certain scenarios. The request for a NERBY extension should be submitted as an application using FRM-0033. NERBY extensions help provide flexibility in scenarios where updated GMP evidence is not available at the time of submission.

If a foreign building on your licence has a NERBY date that is approaching but there is no new GMP evidence, you may ask for a risk-based extension of the NERBY date if an:

- inspection by a regulatory or qualified authority, or qualified body has taken place, but the issuance of the inspection report has been delayed
- inspection by a regulatory or qualified authority, or qualified body is scheduled to take place
- inspection by a regulatory or qualified authority, or qualified body has not taken place within the last 3 years
- inspection by a regulatory or qualified authority, or qualified body has not been planned

For Health Canada to consider extending the NERBY date, you must complete FRM-0559: NERBY extension request form and submit it with your application (FRM-0033 and cover letter). FRM-0559 requests additional information, which we use to determine if a risk-based NERBY extension can be granted.

Email foreign.site-etranger@hc-sc.gc.ca for a copy of the most recent version of FRM-0559.

When evaluating a risk-based NERBY extension, we consider:

- the reason for the extension request
- if previous extensions to the NERBY date were granted
- Health Canada compliance history of the building
  - for example, past instances of non-compliance from us
- the activity or activities taking place and the category and dosage forms being handled at the foreign building
  - for example, whether there are changes that are not supported by the most recently submitted GMP evidence
- nature of the drug or drugs
  - for example, medical necessity, real or imminent drug shortage of a medically necessary drug
- inspection method of the most recent inspection reviewed by us (onsite versus remote inspections)
- whether the foreign building is eligible to be supported by the submission of a corporate or consultant audit
- assurance that certain aspects of GMP operations and any changes made to quality assurance management, equipment or manufacturing processes since the last inspection meet GMP requirements

For a description of the NERBY extension assessment and outcomes, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

6.3 Submitting An Amendment to the API FB Annex

6.3.1 How to submit

To add a foreign building to your API FB annex that fabricates, packages/labels or tests non-sterile APIs, non-sterile atypical APIs or non-sterile API intermediates, email the application to el.applications-le@hc-sc.gc.ca.

Your application should include:

- cover letter (instructions outlined earlier)
- all applicable sections of the Drug establishment licence application: Forms and instructions (FRM-0033)
- a completed Table A: Foreign building conducting active pharmaceutical ingredient related licensable activities

- for a copy of the most recent version of the Table A form and instructions, email the Drug Establishment Licensing Unit at del.questions-leppp@hc-sc.gc.ca

You do not need to submit GMP evidence with your application. However, you must ensure foreign buildings on the API FB annex have an inspection report that demonstrates their compliance with Division 2 of the regulations. The inspection report you indicate in Table A must meet the requirements outlined in Inspection report.

Maintain and review a copy of the evidence that is referenced in Table A onsite at the domestic building.

An application is not required to maintain foreign buildings on the API FB annex as these buildings are not assigned a NERBY date.

For application considerations of a non-compliant site on your API FB annex, refer to Reassessing non-compliant ratings.

6.3.2 Considerations for atypical APIs

Importers of listed atypical APIs and finished dosage form (FDF) containing listed atypical APIs that are fabricated, packaged/labelled and tested can reference standards other than GMP in Table A.

For a copy of the most recent version of the Table A form and instructions, email the Drug Establishment Licensing Unit at del.questions-leppp@hc-sc.gc.ca.

Cases where antioxidants, preservatives or stabilizers are added to an atypical API to maintain the efficacy of the atypical API or for safety reasons would still be considered an atypical API.

Note: Before sale, each lot or batch of the atypical API must be tested against and comply with the specifications for that API. If there is a pharmacopeial standard for the atypical API (Schedule B, Food and Drugs Act), the API should be fabricated and tested against that standard.

6.3.3 Health Canada assessment

Health Canada will assess your application to make sure it's complete. As no GMP evidence needs to be submitted, deficiencies related to GMP evidence will not be sent for API FB annex applications. However, a deficiency notice will be sent if the Table A form is incomplete.

To learn more about other types of deficiencies related to the Table A form, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

During a domestic inspection, a Health Canada inspector will ensure importers have appropriate processes and oversight of API sites that are part of the supply chain. We use a risk-based approach to select foreign buildings on the API FB annex to review when confirming the availability of GMP evidence. This includes taking into consideration a number of factors, such as type of GMP evidence available (corporate audit or inspection by qualified or regulatory authority, or CoC/EJ CoC) and the foreign building's compliance history. At any time, we may also ask for evidence to demonstrate the foreign building's GMP compliance.

To help with verification, Table A should list all sites included on the importer's API FB annex. This includes referencing the most recent GMP evidence available for each foreign building.

For more information on maintaining evidence for foreign buildings on the API FB annex, refer to Maintaining GMP evidence onsite.

6.4 Submitting An Amendment to the ASR Annex

To add a foreign building responsible for retaining samples to your ASR annex or to retain samples for a new product at an existing foreign building on the ASR annex, email the application to el.applications-le@hc-sc.gc.ca. The application should include:

- a cover letter (instructions outlined earlier)
- all applicable sections of the Drug establishment licence application: Forms and instructions (FRM-0033)

You do not need to submit GMP evidence with your application.

For a foreign building to be eligible on the ASR annex, the samples that are retained must meet 1 of the following criteria:

- the drug is subject to testing under Health Canada's lot release program outlined in Guidance for sponsors: Lot release program for Schedule D (biologic) drugs
- there is a limited volume of the drug sold in Canada or small portions of many batches
- individual samples of the drug are very expensive
  - the total number of samples of complete batches to be retained (for example, high volume) is not a consideration for expense
- the drug product is a radiopharmaceutical
- the drug is a category IV monograph drug as specified in Annex 7 to the Good manufacturing practices guide - Selected non-prescription drugs (GUI-0066)
- the fabricator of the drug is in Canada
  - for example, the product is fabricated in Canada and then exported

You must attest that the retention sample meets at least 1 of these criteria in FRM-0033.

To allow a foreign building to be eligible on the ASR annex, as the importer or distributor (depending on who is responsible for maintaining retention samples), you must also attest in FRM-0033 that:

- the foreign building complies with Part C, Divisions 2 to 4 of the FDR
- sufficient numbers of samples of each lot or batch sold in Canada will be kept at the foreign building under the product's approved storage conditions with the container-closure authorized for sale in Canada
- samples will be sent within 2 business days of receiving a request from Health Canada in writing. Every reasonable effort will be made to provide the samples to Health Canada on an expedited basis if a situation arises where the health or safety of people in Canada is potentially at risk
- you will notify Health Canada immediately if the information in FRM-0033 or the DEL application becomes inaccurate at any time

6.5 Submitting an Amendment for Changes For A Foreign Building On the DEL

6.5.1 Change in foreign building name or address

To notify us of changes to the name or address of a foreign building on your DEL, email the application to el.applications-le@hc-sc.gc.ca. Include in your application:

- cover letter
- FRM-0033 (instructions outlined earlier)
  - updated name or address of the foreign building on FRM-0033

For foreign buildings located in a non-MRA country or foreign buildings in an MRA country not inspected by an MRA partner, the name and address should be consistent with the foreign building's site master file (SMF) (also known as a site reference file (SRF)). Submit the most recent SMF with your application.

For foreign buildings in an MRA country and inspected by an MRA partner, the name and address should be consistent with the name and address registered with the MRA partner and displayed on the CoC. If an updated CoC reflecting the new name or address is not available, indicate the change in your cover letter so Health Canada can confirm with the MRA partner.

You must submit your DEL amendment application with updated GMP evidence if a foreign building name or address changes due to a change in the physical location of the foreign building. The supporting GMP evidence must cover the new location of the foreign building whether the foreign building is in a non-MRA or an MRA country.

To determine what supporting GMP evidence should be submitted if a change in physical address occurred, refer to Submitting an amendment to the FB annex.

6.5.2 Change in licensable activities at a foreign building

To amend activities, categories or dosage forms of a foreign building on your FB annex, you must email the application to el.applications-le@hc-sc.gc.ca. Include in your application:

- cover letter
- FRM-0033 (instructions outlined earlier)
- GMP evidence

You may reference previously submitted GMP evidence to support your amendment. In this case, indicate in your cover letter that you are using previously submitted evidence to support the amendment. Make sure the referenced evidence is valid (within the last 3 years or a period considered acceptable by Health Canada) and supports any new licensable activities, categories and dosage forms. To determine what supporting GMP evidence should be submitted, refer to Submitting an amendment to the FB annex.

Note: If you are submitting an application for new licensable activities, categories or dosage forms at a foreign building already on your licence, you cannot import the applicable products until you receive a supplement to the FB annex or confirmation that your DEL has been updated. If a supplement to the FB annex or DEL was issued, it must authorize the new activities, categories and sterility statuses of dosage forms that have been added on your licence.

7. Recommended Full GMP Evidence

This section outlines the specific requirements of the recommended GMP evidence that you must submit to support an application that requires a full GMP evidence package. It also describes the GMP evidence you must maintain at your Canadian site for sites listed on your API FB annex.

The GMP evidence can have light redactions to hide confidential business information or trade secrets (for example, customer names, employee names or product information). Redactions of entire paragraphs in the evidence are not acceptable and will result in a deficiency.

The original GMP evidence documents should be available in either of Canada's official languages (English or French). If this is not possible, you should provide:

- a copy of the original information
- a translated copy in English or French **and**
- an attestation of the accuracy of the translation, signed by the certified translator

Electronic signatures are acceptable for all GMP evidence documents. For information on the appropriate controls for electronic signatures, consult:

- Good manufacturing practices guide for drug products (GUI-0001)

7.1 Inspection Report

Health Canada will accept the final and most recent inspection report (for example, within the last 3 years or a validity period considered acceptable by us). The inspection report must be signed and issued by the following authorities or partners:

- Health Canada (exit notice)
- regulatory authority
- qualified authority
- qualified bodies such as:
  - World Health Organization (WHO)
    - for foreign buildings listed on API FB annex and FB annex
    - Note: Some authorities may use a template similar to WHO's template. We only accept an inspection report that is signed and issued by WHO. Refer to WHO's Public Inspection Report database to confirm eligibility.
  - European Directorate for the Quality of Medicines and Healthcare (EDQM)
    - for foreign buildings listed on API FB annex or on the FB annex that conduct API related activities (for example, release testing sites)
- corporate or consultant audit
  - refer to Corporate or consultant audit reports

The inspection report should:

- be completed against GMP standards or a standard considered acceptable by Health Canada
- cover the foreign building's activities, categories and dosage forms that you are requesting in the DEL application

If the submitted evidence of GMP compliance of a foreign building is a Health Canada inspection report (exit notice), no other recommended evidence needs to be submitted.

We will accept, on a case-by-case basis, inspection reports issued by a regulatory or qualified authority, or a qualified body that conducted a product-specific inspection. For example, we will consider inspection reports that cover the same activities, product categories or dosage forms that you request in your application.

An onsite evaluation (OSE) conducted by Health Canada's Biologic and Radiopharmaceutical Drugs Directorate is **not** enough to demonstrate the GMP compliance of a foreign building. This type of evaluation does not cover all applicable sections of Part C, Division 2 of the Food and Drug Regulations (FDR).

Note: We may contact the issuing authority of the inspection report for more information if we identify any compliance concerns when reviewing the report. This may impact the timelines of your application.

For more information, consult:

- Applications and service standards for drug establishment licences (GUI-0127)

If you do not have an inspection report from 1 of these authorities and are importing a critical product, email us at foreign.site-etranger@hc-sc.gc.ca to evaluate options. (A real or imminent drug supply shortage of a medically necessary drug as determined by Health Canada is considered a critical product.)

7.1.1 Inspection reports based on remote inspections by a regulatory or qualified authority

Remote inspections have proven invaluable for protecting people's health under extenuating circumstances. However, some critical aspects of an onsite inspection may be missed when remote inspections are conducted.

Onsite components of inspections provide stronger oversight than solely remote inspections due to the challenges and limitations of remote inspections. For this reason, remote inspections from regulatory or qualified authorities or qualified bodies will be considered only for the following low-risk activities:

- packaging and labelling
    - for example, placing a drug in a container, other than its primary container, such as a carton or box, and placing an outer label on the drug's secondary container

- product types and activities that are eligible for a corporate or consultant audit

There may be cases where there is a critical and immediate need for updated GMP evidence and an onsite inspection is not feasible due to extenuating factors (such as travel restrictions, geo-political concerns, time constraints). In these cases, we may accept an inspection report based on a remote inspection by a regulatory or qualified authority, or qualified body.

You may submit the most recently available onsite inspection report to supplement the review of the remote inspection report if you:

- add a new foreign building to your DEL that has not been assessed by Health Canada previously **or**
- identify any changes in the foreign building's licensable activities since our last assessment

Hybrid inspections that contain an onsite component of the inspection will be considered for review for all product and activity types.

7.1.2 Submitting multiple inspection reports

If you are submitting multiple inspection reports to support different activities, categories and dosage forms, your cover letter should:

- indicate the reason for submitting multiple reports
- include a summary of which report covers which activity, category or dosage form
- explain the reason for not submitting the most recent inspection report

We will accept older GMP evidence (for example, evidence is within 3 years but is not the most recent) if it covers the activities, categories or dosage forms in the scope of the application and the newer evidence does not.

7.1.3 Corporate or consultant audit reports

If there are no inspection reports by a regulatory or qualified authority or qualified body, you may submit an onsite corporate or consultant audit report for the following specific activities and product types only:

- fabricate, package/label or test non-prescription/over-the-counter (OTC) drugs
- fabricate, package/label or test medical gases
- fabricate, package/label or test non-sterile ethical drugs

- sterilize packaging materials for drugs that will be aseptically filled without terminal sterilization

A self-audit report conducted by a member of the foreign building is not considered acceptable GMP evidence to support the building's compliance.

We recommend that you use the following template when performing the audit and preparing your application. It will help to reduce or eliminate the number of deficiency notices that we may issue:

- Good manufacturing practices: Audit report form (FRM-0211)

The following information must accompany the corporate or consultant audit report and be part of your application:

- a justification for submitting a consultant or corporate audit report, which clearly states the specific activity and product type that falls within the eligibility criteria for a consultant or corporate audit
  - include in your cover letter or audit report
- the resumé of the persons performing the audit, which should demonstrate that they are qualified to perform audits and have experience in and knowledge of one of the following as per section C.02.006 in Good manufacturing practices guide for drug products (GUI-0001):
  - Canadian GMPs
  - PIC/S GMP guidance documents
- observations noted during the audit that are risk-classified
  - consult Risk classification guide for drug good manufacturing practices observations (GUI-0023)
  - we will review the classification of observations
- audit report signed and dated by the auditor
- inspection report more than 3 years old from a regulatory authority or a qualified authority, if available
  - do not resubmit if the applicable inspection report was already submitted to support your previous application for the foreign building
  - provide the previous application number in your cover letter for us to access

7.1.4 Considerations for foreign building performing sterilization of packaging material

If there are no inspection reports by a regulatory or qualified authority or qualified body, you may submit:

- a corporate or consultant audit report completed against
  - ISO 13485:2016 – Medical devices
  - the ISO standard covering the applicable type of sterilization being performed by the foreign building
    - for example, ISO 11137-3:2017 Sterilization of health care products for sites performing gamma irradiation
- an ISO certificate, if available, as supplementary information

Along with the full audit report, you must also submit the additional information described in Corporate or consultant audit reports. The auditor's resumé should demonstrate their knowledge and experience in ISO standards and conducting ISO audits.

For foreign buildings responsible for sterilization of packaging material, indicate the activity as "fabricate" and the dosage form as "packaging material (S)" on Drug establishment licence application: Form and instructions (FRM-0033).

For more information on licensing the sterilization of packaging material, consult:

- Guidance on drug establishment licences (GUI-0002)

7.1.5 Considerations for foreign building campuses

When the foreign building is located within a campus, the cover letter should:

- confirm which buildings are conducting licensable activities and the type of activities being conducted at each building and their addresses
- confirm whether the inspection report covers each building conducting licensable activities
- indicate which buildings are covered by the site master file (SMF) **and**
- indicate whether each building operates under the same quality system

Where this information can be found in the GMP evidence, provide a reference to the page number in the cover letter.

Health Canada will review the campus as a whole if all the individual buildings operate under the same quality system. If this is the case, submit a FRM-0033 listing the address that represents the entire campus. The address should be the same as the address for the campus in the SMF.

Submit your application to us with separate FRM-0033s (or section 5 of FRM-0033) for each foreign building conducting licensable activities if:

- the building is a campus where the individual buildings operate under different quality systems **or**
- we have previously reviewed the campus by individual building conducting licensable activities

All FRM-0033s may be submitted in a single application. We will assess this information when we review the GMP evidence.

We reserve the right to review a campus as individual buildings, if necessary, regardless of the quality system (for example, if we identify potential GMP concerns for the individual buildings).

7.2 Corrective Actions

Submit a copy of the corrective actions signed and dated by a person responsible for the foreign building. The corrective actions should correspond to the observations cited in the submitted inspection report, if applicable.

If the corrective actions are contained in the final inspection report issued by the inspecting regulatory authority, a separate corrective action document is not needed. Clearly indicate in your cover letter if this is the case, to facilitate GMP assessment.

For a corporate or consultant audit, you must provide documentation indicating the auditor has reviewed the company's corrective actions and found them acceptable.

7.3 Site Master File

Submit a copy of the most recent, signed and dated SMF (also known as a site reference file (SRF)).

For information on how to include an SMF, consult:

- Explanatory notes for drug establishments on the preparation of a site master file (GUI-0005)

A quality manual may be submitted for foreign buildings that only test, provide secondary packaging and labelling services or sterilize packaging material.

7.4 Letter of Authorization

In certain cases, the GMP evidence package required to support your application may have been submitted to Health Canada as part of an application by another importer for the foreign building or by an organization on behalf of the foreign building. We will accept a letter of authorization (LoA) from the party (another importer or the foreign building) that previously submitted these documents to reference the GMP evidence.

DEL holders must maintain a copy of this evidence at their domestic building, even if using an LoA. For more information, refer to Maintaining GMP evidence onsite.

Submitting an LoA allows us to leverage existing GMP compliance, cross-reference this previous review and conduct an abbreviated assessment. If the existing GMP evidence supports your application, including all the requested activities, categories and dosage forms for the foreign building, the application will undergo a shorter review process.

You may submit the LoA with your application (cover letter and FRM-0033) if the LoA is issued either by:

- the foreign building to an importer directly
  - only applies if the foreign building submitted the evidence directly to us
- an importer to another importer
  - only applies if the importer providing the LoA has submitted the evidence directly to us

The LoA should also reference an inspection report that covers the activities, categories and dosage forms that you are requesting on FRM-0033.

If these conditions are met, the LoA must:

- be written on the letterhead of the issuing company
- clearly state that authorization is being provided to Health Canada
- clearly state the name and address of the foreign building
- specify which GMP evidence documents are being referenced
  - for example, authority, date, outcome, rating
- be signed and dated, with complete signature block including email address
- demonstrate the GMP evidence has been previously submitted to us
  - for example, providing the application number or copy of the acknowledgment of application acceptance email or GMP screening acceptance notice email

8. Requesting A Foreign Onsite Inspection

This section describes:

- when and how an importer can request for a foreign onsite inspection to support the addition, amendment or a renewal of a foreign building
- the assessment of the request
- the decision the importer can expect

8.1 When To Submit a Request For A Foreign Onsite Inspection

If there is no supporting GMP evidence and the foreign building is not eligible for a NERBY extension request, you may submit a request for Health Canada to conduct an inspection of the foreign building.

For more information on supporting GMP evidence, refer to:

- Submitting an amendment to the FB annex
- Submitting an amendment to the API FB annex

An onsite evaluation (OSE) conducted by Health Canada's Biologic and Radiopharmaceutical Drugs Directorate is **different from** an onsite inspection described in this section.

If a DEL application for the foreign building is in queue at the same time you requested an onsite inspection of that same foreign building, we may ask you to withdraw your DEL application.

8.2 How to Submit A Request for A Foreign Onsite Inspection

Email your application to foreign.site-etranger@hc-sc.gc.ca. Include the following:

- cover letter
- FRM-0213

Once we receive your application, we will send you an acknowledgment by email within 1 month. We will assess the information provided in the cover letter and FRM-0213 and may ask for clarification.

If recent GMP evidence becomes available while a request for an onsite inspection is pending, you should withdraw your request for an onsite inspection and submit the new GMP evidence to

us. Include the DEL application number in your email requesting withdrawal of the onsite inspection request to foreign.site-etranger@hc-sc.gc.ca.

For instructions on how to submit the evidence, refer to Submitting an amendment to the FB annex.

8.3 Health Canada Assessment

During our assessment, we consider the:

- nature of the product
  - for example, medical necessity, real or imminent drug supply shortage of a medically necessary drug as determined by Health Canada
- foreign building's compliance history
- plans by other trusted regulatory authorities to inspect or have recently inspected the foreign building
- licensable activities conducted by the foreign building
- categories of drugs and dosage forms fabricated by the foreign building
- activities, categories and dosage forms requested in FRM-0213

To help us with the assessment, include this information in your cover letter or in the Good manufacturing practices - Request for inspection of a foreign site form (FRM-0213). We usually complete an assessment within 2 to 3 months of acknowledging receipt, but this can be delayed if we do not receive responses to our requests for clarification quickly.

Our assessment of your request for inspection will result in 1 of 2 outcomes:

1. Decision to accept the inspection request:
   - an inspection may be conducted
   - an email will be sent accepting the inspection request
2. Decision to reject the inspection request:
   - an inspection will not be conducted at this time
   - an email will be sent declining the request and giving a reason for the decision

A Health Canada decision to accept a request for an onsite inspection does not contain a timeframe in which the inspection will be conducted. We take a risk-based approach when planning and scheduling inspections. It's the responsibility of the importer to work with their foreign buildings to obtain relevant evidence from within the last 3 years (or a validity period acceptable by Health Canada) on GMP compliance.

Note: In certain cases, we may inspect a foreign building remotely. When deciding whether a remote inspection is appropriate, we consider the:

- feasibility of an onsite inspection
- feasibility of a remote inspection
  - is the foreign building capable of hosting a remote inspection
- type of inspection required
- critical nature of the products fabricated by the foreign building
- type of activities conducted by the foreign building
- foreign building's compliance history

You will be notified of the inspection outcome if an inspection is conducted. For more information on outcomes of inspections conducted by Health Canada, refer to Health Canada assessment outcomes.

9. Potential GMP Issues, Reassessing NC Ratings

This section describes:

- how Health Canada monitors and responds to potential health and safety issues involving a foreign building
- what you must do for us to reassess a non-compliant foreign building

9.1 Foreign Buildings With Potential GMP Issues

Health Canada actively monitors for potential health and safety issues at foreign buildings that conduct licensable activities. We respond to these issues as soon as we become aware of them, from:

- our own inspections or reviews of good manufacturing practices (GMP) evidence
- adverse reaction reports
- notifications from companies
- notifications from regulatory or qualified authorities

We will initiate a review of the foreign building when we identify an issue with GMP compliance.

Visit the list of foreign buildings that we have reviewed or are reviewing:

- Inspection tracker: Drug manufacturing establishments

While we actively monitor for potential health and safety issues, importers are responsible for meeting the notification requirements.

Note: If you also hold a drug identification number (DIN), you must notify Health Canada if there is new safety information related to any serious risk of injury to human health involving regulatory issues in foreign countries. This is outlined in section C.01.050 of the Food and Drug Regulations (FDR).

Use this form to report:

- Notifying Health Canada of foreign actions in respect of a serious risk of injury to human health

For more information on notification requirements and risk notifications, consult:

- Guidance on drug establishment licences (GUI-0002)
- Notifying Health Canada of foreign actions: Guidance document for industry

Health Canada assessment

Once we are aware of a health and safety issue involving a foreign building, we issue a request for information to importers who have the building on their licence or have asked to add the building to their licence. Any reviews of active drug establishment licence (DEL) applications associated with the foreign building may be delayed during this review period.

DEL holders who are affected may withdraw their active DEL applications and resubmit later.

Canadian importers who receive a request for information must respond in a timely manner so we can review the foreign building's compliance status. Examples of information that may be requested include:

- an inspection report from a regulatory or qualified authority
- GMP observations corresponding to the inspection
- corrective actions
- risk assessments for all products imported or intended for import into Canada that are fabricated, packaged/labelled or tested at the foreign building
    - must demonstrate the impact of the GMP observations on the quality of the products and identify risks or mitigation measures

Once we complete our review, we inform the Canadian importers of 1 of 2 outcomes:

1. Health Canada has no remaining critical GMP concerns for the foreign building:

   - importers may continue or start to import from the foreign building on their DEL
2. Health Canada has remaining GMP concerns for the foreign building:
   - the foreign building will not be added to your DEL, or we may ask you to stop importing from the foreign building and remove the foreign building from the licence

Note: Depending on the risks identified during the review, other compliance and enforcement actions may be taken, for example:

- adding or amending terms and conditions (T&Cs) to the Canadian importer's licence
- shortening the "new evidence required by" (NERBY) date
- increasing the frequency of inspections
- recalling or issuing a stop sale order on a product

Learn more:

- Compliance and enforcement policy for health products (POL-0001)
- Drug good manufacturing practices (GMP) and drug establishment licence (DEL) enforcement policy (POL-0004)

9.2 Reassessing Non-Compliant Ratings

Health Canada must reassess foreign buildings with non-compliant ratings before they can be added to DELs. If the foreign building is already compliant, follow the instructions in Submitting DEL amendment applications. Before you submit your application, check the compliance status of your foreign building in the Drug and health product inspections database.

To add a foreign building with a non-compliant rating, you must submit a:

- DEL amendment application with new GMP evidence
- request for us to reassess the GMP compliance rating
- FRM-0033

To request a reassessment of a non-compliant foreign building on your FB annex or API FB annex:

- complete the applicable sections of FRM-0033
- follow the instructions in Full GMP evidence to support compliance of a foreign building

The new GMP evidence must include:

- an inspection report issued by a regulatory or qualified authority that is more recent than the inspection that resulted in the non-compliant rating **and**
- a document that shows how each GMP observation from the non-compliant inspection has been resolved and verified in the new inspection

The following is not sufficient GMP evidence to support the reassessment of a non-compliant foreign building:

- an extra-jurisdictional certificate of compliance (EJ CoC)
  - submit the full GMP evidence (inspection report) corresponding to the EJ CoC so that we can review the observations and corrective actions taken to ensure the issues that led to the non-compliant rating have been adequately addressed
- corporate or consultant audit reports
  - audits are accepted based on the risk profile of a foreign building
  - after a non-compliant rating or a regulatory or qualified authority has identified potential GMP issues, the risk profile of the foreign building has changed
  - due to the change in risk profile of the foreign building, we rely on our own onsite inspection or accept an inspection report from a trusted regulatory or qualified authority to reassess the GMP issues and ensure they have been adequately addressed

Importers cannot import until Health Canada confirms the foreign building is compliant with the FDR and is listed on their DEL.

Also, if the foreign building is intended to be listed on the API FB annex, you must submit an amendment to the API FB annex application after we have confirmed that the foreign building is compliant. The application should include the information described on this page as well as the information outlined in Submitting an amendment to the API FB annex.

10. Glossary, Definitions, Resources

10.1 Glossary

ASR: alternate sample retention
ALR: annual licence review
API: active pharmaceutical ingredient
API FB annex: active pharmaceutical ingredient foreign building annex
BPI: bulk process intermediate
C: compliant
CoC: certificate of compliance
DEL: drug establishment licence
DIN: drug identification number
EDQM: European Directorate for the Quality of Medicines and Healthcare
EJ: extra-jurisdictional
EU: European Union
FB: foreign building
FB annex: foreign building annex
FDA: Food and Drugs Act
FDF: finished dosage form
FDR: Food and Drug Regulations
GMP: good manufacturing practices
ISO: International Organization for Standardization
LoA: letter of authorization
MHRA: Medicines and Healthcare products Regulatory Agency
MRA: mutual recognition agreement
NC: non-compliant
NERBY: new evidence required by
OSE: onsite evaluation
OTC: over-the-counter
PIC/S: Pharmaceutical Inspection Cooperation Scheme
SMF: site master file
SRF: site reference file
WHO: World Health Organization
TGA: Therapeutic Goods Administration

10.2 Definitions

These definitions explain how terms are used in this document. If there is a conflict with a

definition in this document and a definition in the Food and Drugs Act (FDA) or Food and Drug Regulations (FDR), the definition in the act or regulations prevails.

Acknowledgment of application acceptance: A notice that an application has been accepted and an application number has been assigned.

Active ingredient: A drug that, when used as a raw material to fabricate a drug in dosage form, provides its intended effect. (FDR, section C.01A.001)

Active pharmaceutical ingredient (API): An active ingredient used to fabricate a pharmaceutical. (FDR, section C.01A.001)

Also includes an active ingredient used to fabricate a drug of non-biological origin listed in Schedule C to the FDA.

Active pharmaceutical ingredient foreign building annex (API FB annex): A list of foreign buildings that fabricate, package/label and/or test non-sterile APIs, non-sterile API intermediates and non-sterile atypical APIs. This annex is part of the drug establishment licence (DEL).

Active pharmaceutical ingredient (API) intermediate: A material (isolated or not) produced during the processing of an API that undergoes further molecular change or purification before it becomes a final API.

Alternate sample retention (ASR) annex: A list of foreign buildings that retain samples of imported product on behalf of the Canadian importer or distributor to comply with the C.02.025 requirement of the FDR. This annex is part of the DEL.

API set out in List A that is for veterinary use: A list of certain antimicrobial APIs that are important in human medicine. Health Canada has put a number of measures in place to help limit the development of resistance to these medically important antimicrobials.

ASR building: A foreign building that retains samples on behalf of an importer and distributor to comply with the C.02.025 requirement of the FDR.

Atypical active pharmaceutical ingredient: Active ingredients used in human pharmaceutical drugs, as well as pharmaceutical excipients or as ingredients in natural health products (NHPs), foods and cosmetics. These ingredients meet recognized standards other than good manufacturing practices (GMPs).

Bulk process intermediate (BPI): An active ingredient used to fabricate either a drug of biological origin that is listed in Schedule C to the FDA or a drug that is listed in Schedule D to the FDA. (FDR, section C.01A.001)

Certificate of compliance (CoC): A certificate issued by a regulatory authority attesting to the GMP compliance of a recognized building in that country. In Canada, a CoC is issued by Health Canada.

Corrective action: Steps taken by the regulated party to address the specified deficiencies (non-compliance with the law). Corrective action is taken to prevent a deficiency from happening again.

Compliance history: A foreign building's history of conformity with good manufacturing practices as outlined by legislative or regulatory requirements.

Compliant (C): At the time of the assessment, the foreign building has demonstrated that the activities it conducts comply with the act and its associated regulations. A "C" rating does not mean that there are no observations, corrective actions required or other compliance and enforcement actions taken.

Critical observation: Observation of a critical deviation from the FDR that describes a situation that may produce an immediate or latent health risk due to a lack of drug safety information. Observations that involve fraud, misrepresentation or falsification under the FDA and associated regulations are also considered critical.

Dosage form: A drug product that has been processed to the point to where it's now in a form that may be administered in individual doses (unless otherwise defined in the FDR). In this guidance document, this term is also referred to as a finished dosage form (FDF).

Drug: Any substance or mixture of substances fabricated, sold or represented for use in:

- diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals
- restoring, correcting or modifying organic functions in human beings or animals or
- disinfecting premises in which food is fabricated, prepared or kept

(FDA, section 2)

In Divisions 1A and 2 of the FDR, "drug" does not include:

- a dilute drug premix
- a medicated feed as defined in subsection 2(1) of the Feeds Regulations, 1983
- an active ingredient that is for veterinary use and is not an API
- an API for veterinary use that is not required to be sold pursuant to a prescription and is also a natural health product as defined in subsection 1(1) of the Natural Health Products Regulations

- a drug that is used only for the purposes of an experimental study in accordance with a certificate issued under section C.08.015 of the FDR

(FDR, section C.01A.001(2))

Drug establishment licence (DEL): A licence issued to a person in Canada to conduct licensable activities in a building that has been inspected and assessed as being in compliance with the requirements of Part C, Divisions 2 to 4 of the FDR.

DEL screening completion notice: A notice that the DEL screening of an application has been completed.

Drug identification number (DIN): An 8-digit number assigned by Health Canada to a drug in dosage form before it's marketed in Canada. It uniquely identifies any drugs sold in a dosage form in Canada. The DIN is located on the label of prescription and non-prescription drugs that have been evaluated and authorized for sale in Canada.

A DIN uniquely identifies the following drug characteristics:

- fabricator
- drug product name
- active ingredient or ingredients
- strength of active ingredient
- dosage form
- route(s) of administration
- species (for veterinary drugs only)

Ethical drug: A drug that, in accordance with federal legislation, does not require a prescription but is generally prescribed by a medical practitioner (for example, nitroglycerine).

Extra-jurisdictional (EJ) inspection: An inspection that occurs outside of the jurisdiction of a regulatory authority.

Extra-jurisdictional (EJ) certificate of compliance (CoC): A certificate issued by a regulatory authority attesting to the GMP compliance of a recognized building outside of the regulatory authority's jurisdiction.

Fabricate: To prepare and preserve a drug for the purposes of sale. This definition applies to Divisions 1A, 2, 3 and 4 of the FDR. (FDR, section C.01A.001)

Finished dosage form (FDF) intermediate: Any physical mix, starting when any 2 ingredients (for example, active ingredient, antioxidant, preservative, filler, binder, solvent) are first added to the drug lot being fabricated and before it becomes a drug in dosage form. Partially processed drug

product intermediates, in-process drugs or bulk drugs are examples of FDF intermediates. Atypical APIs with antioxidants, preservatives or stabilizers added are not considered FDF intermediates. These are classified as atypical APIs.

Foreign building: A building outside of Canada where the following licensable activities are conducted for drugs that are sold in Canada:

- fabrication
- packaging/labelling
- testing

Foreign building annex: A list of foreign buildings that have been assessed by Health Canada as being compliant with the requirements of Part C, Divisions 2 to 4 of the FDR. This annex is part of the DEL.

Foreign establishment name: The name of the foreign establishment that is or will be engaged in licensable activities (also referred to as foreign building name in this document).

Full GMP evidence: A GMP evidence package consisting of an inspection report, corrective actions (if applicable) and a site master file.

GMP screening acceptance notice: A notice that the GMP screening of evidence submitted for a foreign building has been deemed acceptable based on the requirements outlined in GUI-0080.

GMP screening deficiency notice: A notice that a deficiency has been identified with the GMP evidence and that the application review and clock have been paused. A response is required by the date specified in the request.

Hybrid inspection: An inspection conducted remotely (using technology to communicate, share and review documentation) and with a short, targeted onsite visit to evaluate critical aspects that cannot be assessed remotely.

Letter of authorization (LoA): A letter written and signed by the party who submitted GMP evidence documents that gives Health Canada authorization to process the importer's application.

Medical gas: Any gas or mixture of gases manufactured, sold, or represented for use as a drug. For information, consult Good manufacturing practices (GMP) for medical gases (GUI-0031). (FDR, section C.02.002)

MRA country: A country that is a participant to a mutual recognition agreement (MRA) with Canada. (FDR, section C.01A.001)

Mutual recognition agreement (MRA): An international agreement that provides for the mutual recognition of compliance certification for good manufacturing practices for drugs. (FDR, section C.01A.001)

New evidence required by (NERBY): The date when new supporting GMP evidence must be submitted to Health Canada as part of an application to renew a foreign building on a DEL.

Non-compliant (NC): At the time of the assessment, the foreign building has not demonstrated that the activities it conducts comply with the act and its associated regulations.

Over-the-counter (OTC): A drug that does not appear on a schedule or the Prescription Drug List or is not recommended to appear on any schedule.

Package/label: To put a drug or API in its immediate container and/or to affix the inner or outer label to the drug or API. This includes repackaging and relabelling previously packaged and labelled drugs. (FDR, section C.01A.001)

Pharmaceutical: A drug other than a drug listed in Schedule C or D to the FDA. This definition applies to Divisions 1A, 2, 3 and 4 of the FDR. (FDR, section C.01A.001)

Product category: In this guidance, includes pharmaceutical, active ingredient, vaccine, biologic, radiopharmaceutical, controlled drugs and narcotics or any other product category designated by the Minister.

Product type: In this guidance:

- Sterile: prescription, OTC, veterinary, category IV
- Non-sterile: prescription, OTC, medical gas, veterinary, category IV

Quality agreement: A formal document between parties (for example, the Canadian DEL holder and the contractor) that defines the responsibilities and duties of both parties for all aspects of a drug's quality.

For more guidance on the content of a quality agreement, consult Good manufacturing practices guide for drug products (GUI-0001).

Qualified authority: A regulatory authority that is part of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S).

Qualified body: Non-regulatory authorities that are associated partners to the Pharmaceutical Inspection Cooperation/Scheme (PIC/S).

Recognized building: A building that a regulatory authority (that is designated under subsection C.01A.019(1)) has recognized as meeting its good manufacturing practices standards to fabricate, package/label and/or test a drug. (FDR, subsection C.01A.001(1))

Regulatory authority: A government agency or other entity in an MRA country that:

- has a legal right to control the use or sale of drugs within that country and
- may take enforcement action to ensure that drugs marketed within its jurisdiction comply with legal requirements

(FDR, section C.01A.001)

Release testing of the API: Testing done to ensure the API meets the specifications of the ingredient. Each API must have proper specifications and test methods to help ensure that the API sold or used in further manufacturing is safe and meets its relevant standard (FDA, Schedule B)

Remote inspection: An inspection conducted remotely using technology to communicate, share and review documentation without having to undertake an onsite visit.

Terminal sterilization: The sterilizing of a drug in its final closed container.

Test: To perform the tests, including any examinations, evaluations and assessments, as specified in Part C, Division 2 of the FDR.

10.3 Resources

Laws and regulations

- Food and Drugs Act
- Food and Drug Regulations
- Controlled Drugs and Substances Act

Forms

- Drug Establishment Licence Application Form (FRM-0033)
- Good manufacturing practices: Audit Report Form (FRM-0211)
- Good manufacturing practices: Request for Inspection of a Foreign Site Form (FRM-0213)

Good manufacturing practices

- Risk classification of good manufacturing practices (GMP) observations (GUI-0023)
- Good manufacturing practices (GMP) guide for drug products (GUI-0001): Summary

- Explanatory notes for drug establishments on the preparation of a site master file (GUI-0005)
- Good manufacturing practices (GMP) for active pharmaceutical ingredients (APIs) guidelines (GUI-0104)

Other related documents

- Mutual recognition agreements
- Compliance and enforcement policy (POL-0001)
- Guide to reporting drug shortage and discontinuations (GUI-0120)
- Applications and service standards for drug establishment licences (GUI-0127)
- Drug good manufacturing practices (GMP) and drug establishment licence (DEL) enforcement policy (POL-0004)
- Fees for the review of human and veterinary drug establishment licence applications
- Guidance on drug establishment licences and drug establishment licensing fees (GUI-0002)
- Health Canada decision-making framework for identifying, assessing and managing health risks – August 1, 2000

International guidance documents

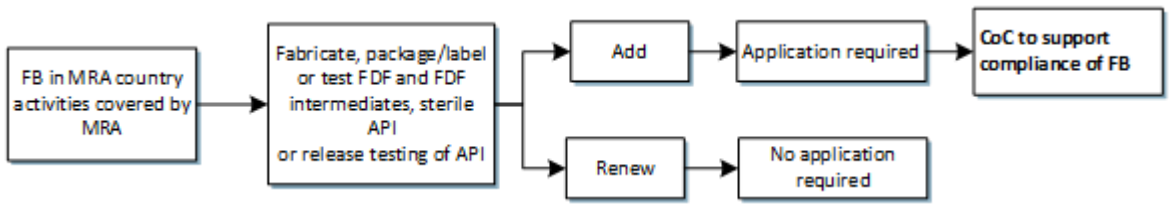
- Pharmaceutical Inspection Co-operation Scheme
- European Directorate for the Quality of Medicines & HealthCare

11. Application Types and Processes

This section contains diagrams that give an overview of the application types described in this guidance document. We have also provided a link to the appropriate section outlining the type of documentation that must be provided to support your application.

Figure 1. Flow charts of the application types with reference to applicable section in GUI-0080

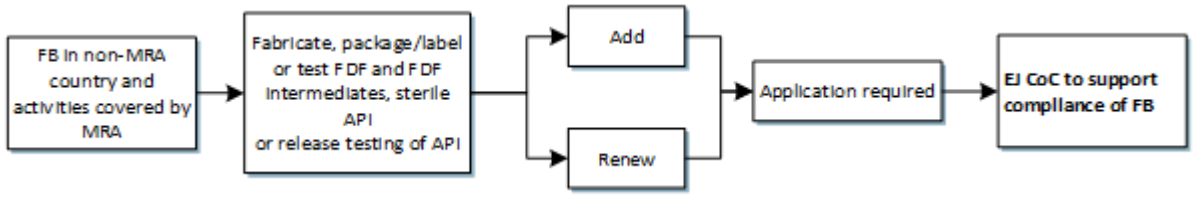
FB annex: Certificate of compliance



The flowchart outlines the process for a foreign building located in a country with a mutual recognition agreement (MRA) for activities covered by the MRA listed on the foreign building annex of a drug establishment licence (DEL). The foreign building is added to the FB annex for the activities of fabricate, package/label or test finished dosage form (FDF), FDF intermediates and sterile active pharmaceutical ingredients (APIs) or release testing of sterile and/or non-sterile APIs and atypical APIs.

You must apply to add this type of foreign building to a drug establishment licence. For information on the application process, refer to CoC to support compliance of foreign building. You do not need to apply to renew this type of foreign building.

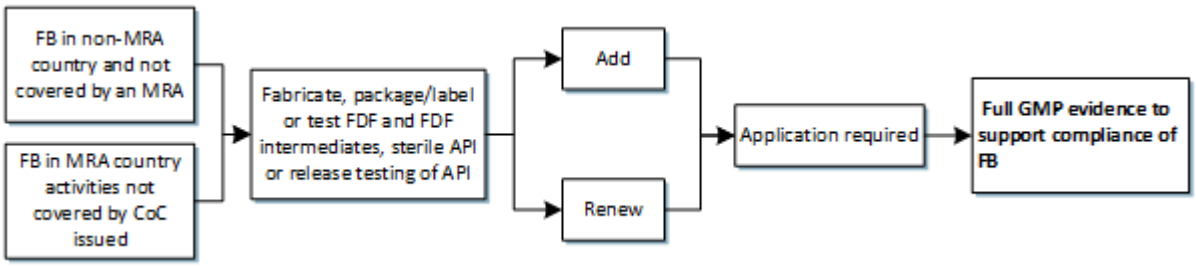
FB annex: Extra-jurisdictional certificate of compliance



The flowchart outlines the process for a foreign building located in a non-MRA country for activities covered by the MRA that should be listed on the foreign building annex of a DEL. The foreign building is added to the FB annex for the activities of fabricate, package/label or test FDF, FDF intermediates or sterile APIs, or release testing of sterile and/or non-sterile APIs and atypical APIs.

You must apply to add or renew this type of foreign building to a DEL. For information, refer to EJ CoC to support compliance of the foreign building.

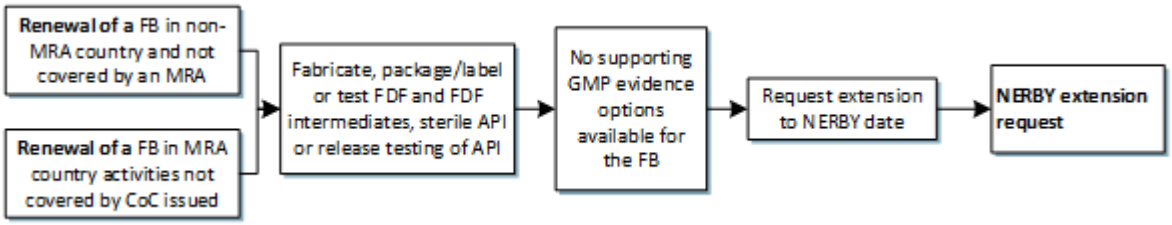
FB annex: Full good manufacturing practices evidence



The flowchart outlines the process for activities not covered by an MRA (inspected by an MRA partner) that should be listed on the foreign building annex of a DEL. This process also applies to foreign buildings located in both a non-MRA and MRA country. The foreign building is added to the FB annex for the activities of fabricate, package/label or test FDF, FDF intermediates, sterile APIs or sterile atypical APIs, or release testing of sterile or non-sterile APIs and atypical APIs.

You must apply to add or renew this type of foreign building to a DEL. For information on the application process, refer to Full GMP evidence to support compliance of foreign building.

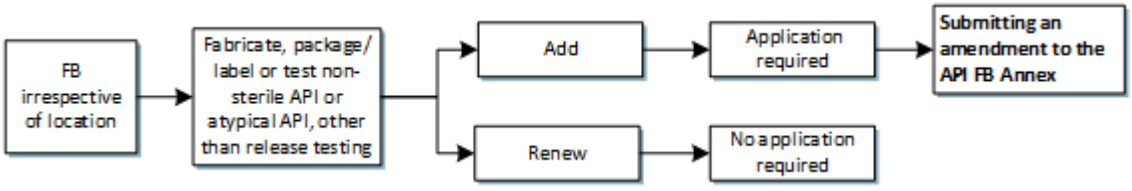
NERBY extension request



The flowchart outlines the process for renewing a foreign building located in an MRA country for activities not covered by the MRA (not inspected by an MRA partner). The process also applies to foreign buildings located in a non-MRA country that are listed on the foreign building annex of a DEL. The foreign building is added to the FB annex for the activities of fabricate, package/label or test FDF, FDF intermediates or sterile APIs, or release testing of sterile or non-sterile APIs and atypical APIs.

If there are no supporting GMP evidence options for the foreign building, you may submit a request to extend the NERBY date. For information, refer to A risk-based NERBY extension request.

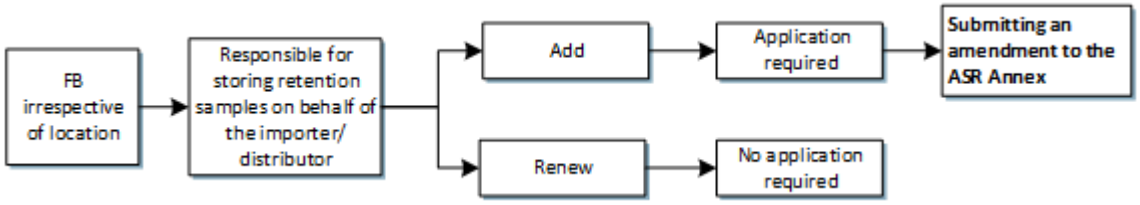
API FB annex



The flowchart outlines the process for a foreign building listed on the API foreign building annex of a DEL, whether it be located in an MRA country or a non-MRA country. The foreign building is added to the API FB annex for the activities of fabricate, package/label or test non-sterile APIs and atypical APIs, other than release testing.

You must apply to add this type of foreign building to a DEL. For information, refer to Submitting an amendment to the API foreign building annex. You do not need to apply to renew this type of foreign building.

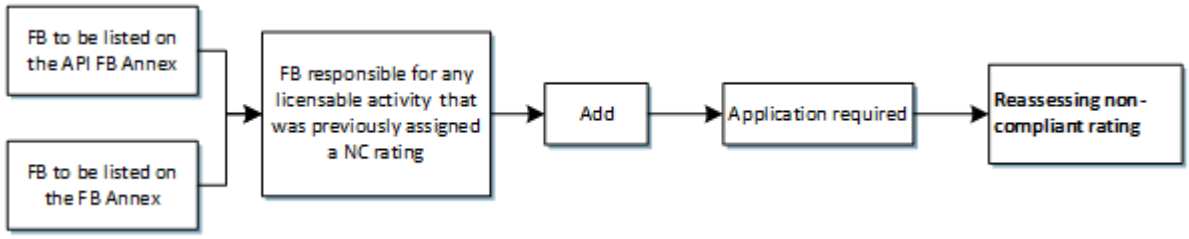
ASR annex



The flowchart outlines the process for a foreign building listed on the alternate sample retention (ASR) annex of a DEL, whether it be located in an MRA country or a non-MRA country. The foreign building is responsible for retaining samples on behalf of the importer or distributor (depending on who is retaining the samples).

You must apply to add this type of foreign building as an ASR building to a DEL. For information, refer to Submitting an amendment to the ASR annex. You do not need to apply to renew this type of foreign building.

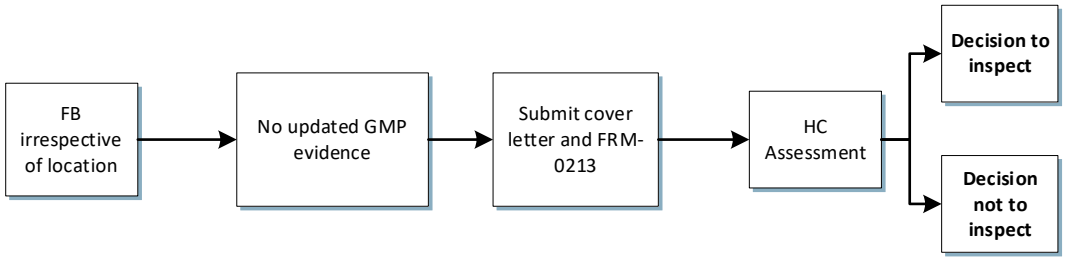
Reassessing non-compliant foreign buildings



The flowchart outlines the process for requesting Health Canada's assessment of updated GMP evidence for a foreign building that was assigned a non-compliant rating listed on either the API FB Annex or the FB Annex for any licensable activity.

You must apply to have updated GMP evidence reassessed. For more information, refer to the section on Reassessing non-compliant ratings.

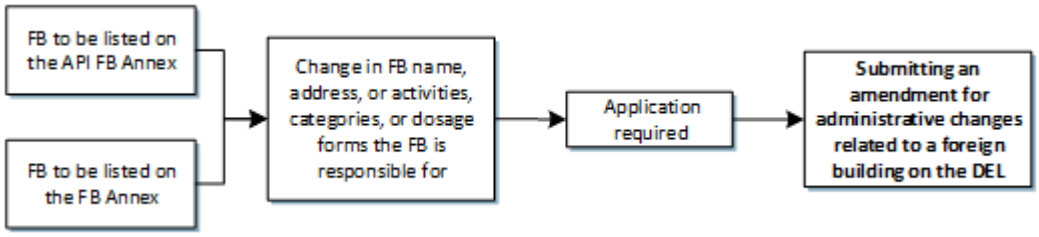
Requesting a foreign onsite inspection



The flowchart outlines the process for requesting a foreign onsite inspection of a foreign building that does not have updated GMP evidence whether it be located in an MRA country or a non-MRA country.

You must apply for a foreign onsite inspection request of a foreign building with a cover letter and FRM-0213. Health Canada will evaluate the information in the application and will decide if an inspection is necessary. For more information, consult Requesting a foreign onsite inspection.

Administrative changes related to a foreign building



The flowchart outlines the process for submitting an application to report an administrative change (such as a change in the foreign building name, address, or activities, categories, or dosage forms) related to a foreign building on the API FB Annex or the FB Annex.

If changes occur, you must submit an application to notify Health Canada. Refer to Submitting an amendment for changes related to a foreign building on the DEL.