

# GUI-0080 – How to demonstrate foreign building compliance with drug good manufacturing practices

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# Agenda

- Overview
- Purpose
- Scope
- Listing foreign buildings on a drug establishment licence (DEL)
- Process related to listing foreign buildings on a licence
- Submitting GMP evidence
- Application packages and GMP evidence
- Requesting an extension of the NERBY date
- Foreign building on-site assessments
- Questions

# Overview

- GUI-0080 has been revised and is now available on the Health Canada website as of January 18, 2018.
- The revisions to GUI-0080 were developed by Health Canada in consultation with stakeholders
- GUI-0080 has a new “look and feel” as this is in line with canada.ca posting requirements and includes:
  - New template for guidance documents
  - Visual call out boxes within document to high-light important information, tips or general knowledge items
  - Using plain language where possible



# Purpose

- GUI-0080 is targeted for Canadian importers who want to list a foreign building on their drug establishment licence (DEL).
- Outline to Canadian importers:
  - Who can submit GMP evidence
  - What GMP evidence must be submitted
  - When to submit GMP evidence
  - Where to submit applications and GMP evidence



# Scope

GUI-0080 applies to:

- Drugs for human use
- Drugs for veterinary use
  - Vet API new regulations come into force May 17, 2018
  - End of 14 month transition period July 17, 2019



Foreign buildings that conduct licensable activities for the drugs in the following product categories must be listed on the Canadian importers DEL:

| Activity    |
|-------------|
| Fabrication |
| Packaging   |
| Labeling    |
| Testing     |

| Product category            |
|-----------------------------|
| Pharmaceuticals (FDF & API) |
| Biologics (FDF & BPI)       |
| Medical gases               |
| Radiopharmaceuticals        |
| Vaccines                    |

## Scope continued

- GUI-0080 does **NOT** apply to:
  - Atypical APIs
  - Drugs used in clinical trials
  - Drugs used for research and development
  - Excipients
  - Natural health products





# **LISTING FOREIGN BUILDINGS ON A DRUG ESTABLISHMENT LICENCE (DEL)**

When do I list a foreign building on my Table A versus my Foreign Building annex?

Does my application need to include GMP evidence?

Do I need to submit an application **maintain** a foreign building on my DEL?



What is new evidence required by (NERBY) date?

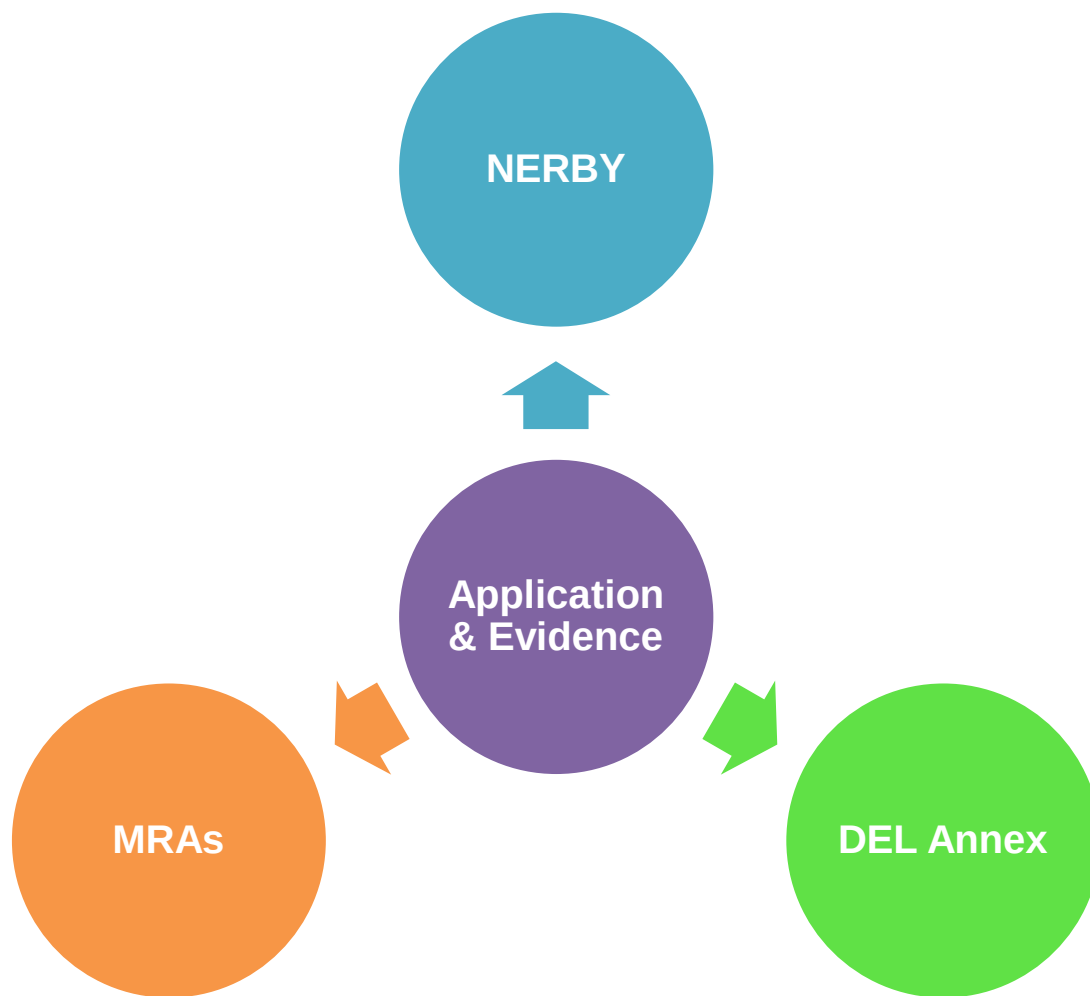
Why do some of my sites have a NERBY date will others don't?

How do MRAs impact my application process?

What does Health Canada do with the application when it is received?

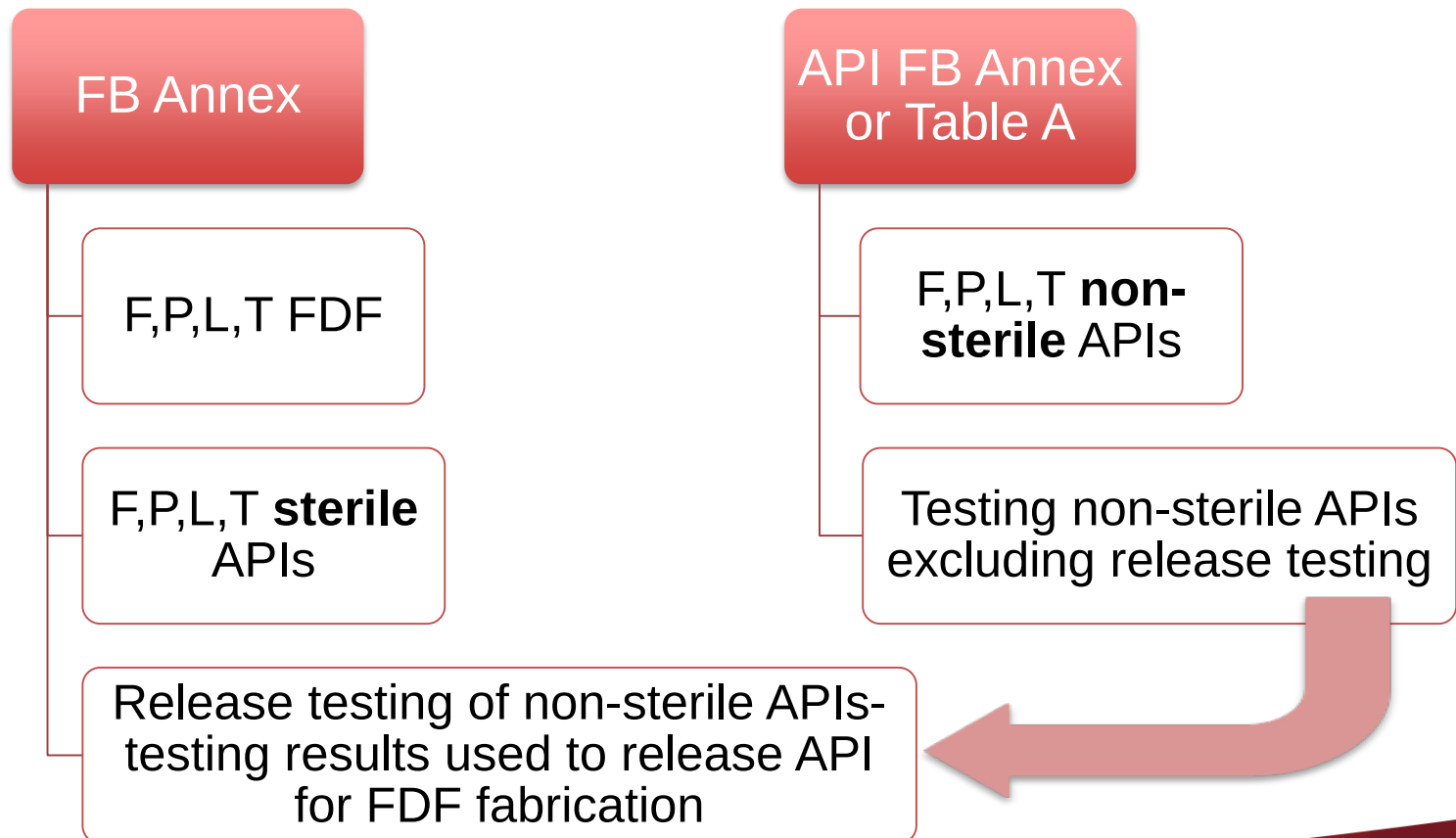
# Answers

To answer these questions we must go through **3** important factors



## Foreign buildings on a DEL

Foreign buildings are listed on two different parts of a DEL depending on activities and product type



# Mutual Recognition Agreements

- Health Canada is a partner in several mutual recognition agreements covering GMP compliance programs for drug products.
- Apply **only** to foreign buildings located within the MRA partners jurisdiction for products and categories covered by the MRA.
- Due to established equivalency Health Canada will accept reduced GMP evidence – Certificate of Compliance (CoC).

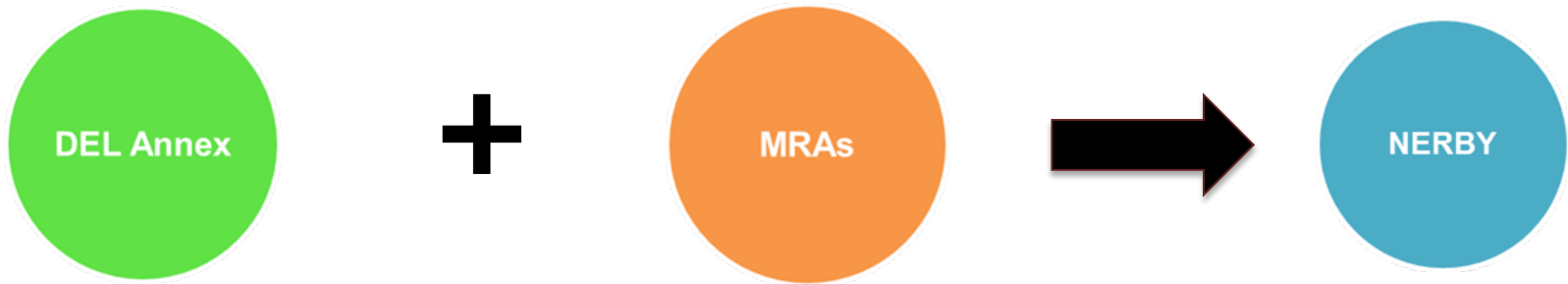


**APIs are currently excluded from MRAs, however, Health Canada is working to expand the scope of existing MRAs to include APIs.**



## New Evidence Required By (NERBY) Date

- Replaced Expiry date
- Applications have to be submitted **by** NERBY date
- As long as an application with the GMP evidence is filed by the NERBY date an importer can continue importation from the foreign building
- Length of a NERBY date is generally 3-4 years
- Assignment of NERBY date is determined by whether the foreign building is located in an MRA country and conducts activities covered by the MRA and the DEL Annex the foreign building is listed on.



FB listed on FB Annex + FB in MRA country & scope of MRA → **No** NERBY

FB listed on FB Annex + FB in MRA country but **NOT** scope of MRA → **Yes** NERBY

FB listed on FB Annex + FB in non MRA country → **Yes** NERBY

FB listed on API FB Annex/ Table A + Not applicable → **No** NERBY

FB has no NERBY date assigned → do **NOT** submit application to maintain FB

FB has NERBY date assigned → submit application to maintain FB



FB Annex + MRA country within scope of MRA → application to add foreign building is required without GMP evidence package

FB Annex + MRA country but **NOT** within scope of MRA → application to add or maintain foreign building is required with full GMP evidence package

FB listed on FB Annex + FB in non MRA country → application to add or maintain foreign building is required with full GMP evidence package

API FB Annex/ Table A → application to add foreign building is required with Table A



## **FB ANNEX FOREIGN BUILDING – MRA COUNTRY WITHIN SCOPE OF MRA**

# FB Annex – MRA country – scope within MRA

## Scenario 1

Importer

- Add foreign building
- Submit application with no GMP evidence package

Health  
Canada

- Request CoC from regulatory authority

MRA  
partner

- Provide CoC

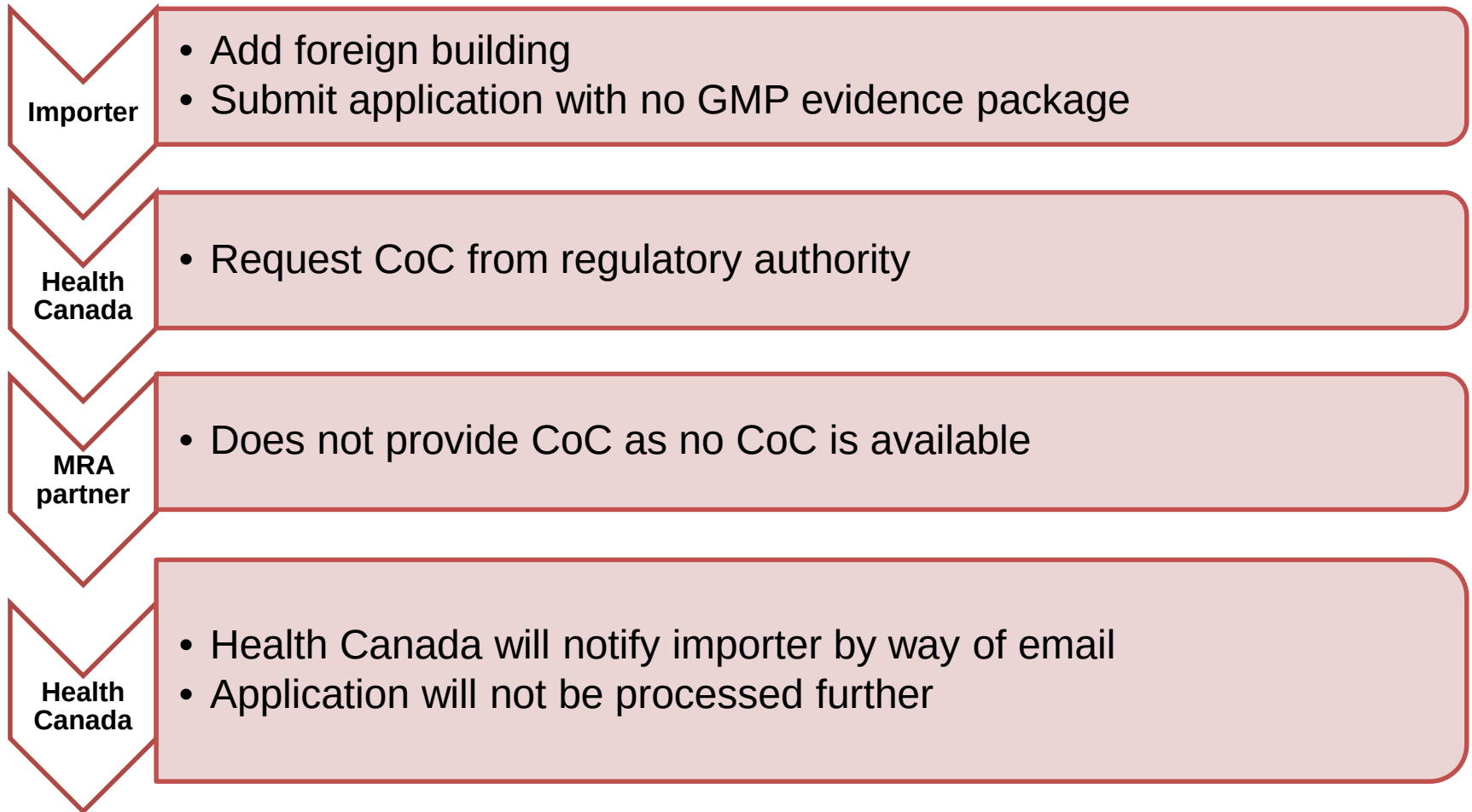
Health  
Canada

- Verify activities and dosage forms of CoC against application
- If all requested dosage forms and activities are covered, add foreign building to FB Annex of DEL
- In cases where some of the activities and dosage forms are not covered, importer will be notified.
- Issue an email including supplement to FB annex for dosage forms and activities covered by CoC

**Any activities or dosage forms requested by importer that are not covered by the CoC will require additional GMP evidence.**

# FB Annex – MRA country – scope within MRA continued

## Scenario 2



# FB Annex – MRA country – scope within MRA continued

## Important items to note



- No NERBY Date – no application to maintain
- Continue importation from foreign building unless Health Canada notifies the importer otherwise
- If scope of CoCs changes, the importer will be notified
- Canadian importer is ultimately responsible to **immediately** notify Health Canada if the foreign building located in an MRA country no longer holds a valid permit, licence or other authorization by the regulatory authority that recognised the building (C.01A.015)

# **FB ANNEX FOREIGN BUILDING – MRA COUNTRY NOT WITHIN SCOPE OF MRA**



## **FB ANNEX FOREIGN BUILDING – NOT IN MRA COUNTRY**

# FB Annex – MRA country – Not within scope MRA or FB Annex – Not in MRA country

## Importer

- Add or maintain foreign building
- Submit application and GMP package directly to Health Canada or submit GMP evidence through foreign building (slide # 32-33)

## Health Canada

- Initial Screening – accuracy and completeness of FRM-0033
- GMP Screening – Verification of GMP evidence package
- GMP assessment – Compliant, Non-Compliant and Terms and Conditions
- Communicate outcome
- Issue supplement to FB Annex or amend existing supplement

**FB Annex – MRA country – Not within scope MRA  
or  
FB Annex – Not in MRA country**

**Important items to note**



- NERBY Date is assigned
- New GMP evidence must be submitted by NERBY date to maintain foreign building on DEL.



# **API FB ANNEX-TABLE A FOREIGN BUILDING**

## API FB Annex or Table A

### Importer

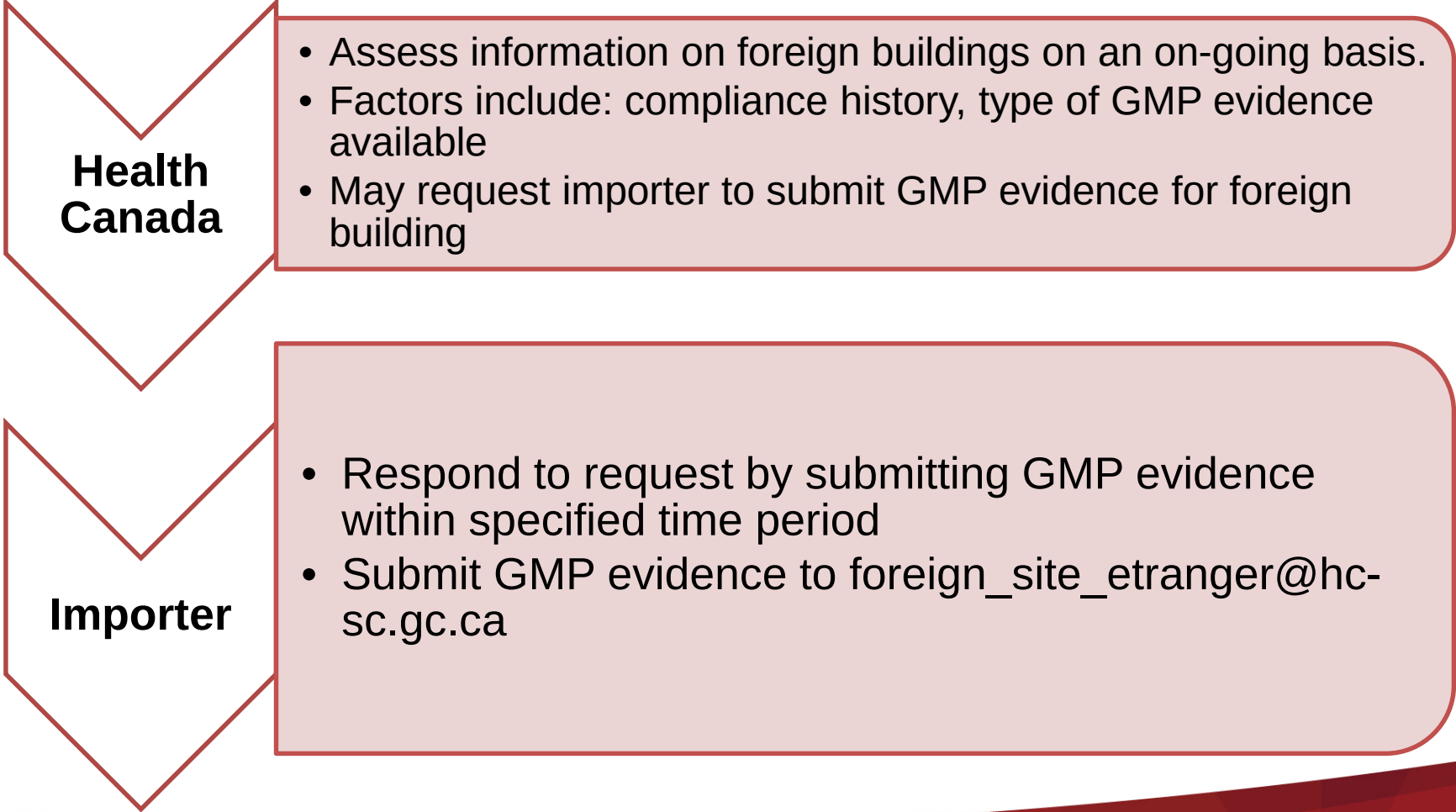
- Add foreign building
- Submit application with comprehensive Table A and without GMP evidence package

### Health Canada

- Verify Table A for accuracy and completeness
- Acknowledgement of Application acceptance along with API FB annex or approved Table A

## API FB Annex or Table A

Since no GMP evidence package is required when adding a FB to the API FB Annex or Table A:



### Health Canada

- Assess information on foreign buildings on an on-going basis.
- Factors include: compliance history, type of GMP evidence available
- May request importer to submit GMP evidence for foreign building

### Importer

- Respond to request by submitting GMP evidence within specified time period
- Submit GMP evidence to [foreign\\_site\\_etranger@hc-sc.gc.ca](mailto:foreign_site_etranger@hc-sc.gc.ca)

# API FB Annex or Table A - Important items to note



- NERBY Date is not assigned
- An importer must not add a foreign building to a drug establishment licence if the importer does not have evidence that demonstrates the foreign buildings compliance with Division 2 of the FDR.

# Documents issued by Health Canada – GMP Screening

Applications to add or maintain a foreign building on the FB annex of a DEL that undergo GMP screening of the GMP evidence.

- **Screening deficiency letter**- May be issued during the GMP screening portion if GMP evidence package is deficient.
- **Screening rejection letter** – May be issued if a response to the screening deficiency letter is not received in time period specified or is inadequate
- **Screening acceptance notice**- Will be issued If no deficiency is identified or all identified deficiencies are resolved.



Responses to deficiency letters must be submitted in the time period specified in the letter

## Documents issued by Health Canada- GMP assessment

After GMP screening, the applications undergo a GMP assessment by an inspector. During the assessment the following documents may be issued:

- **Request for other evidence** – May be issued by the inspector if additional information is required during the assessment (ex- quality agreements, SOPs).
- **Rejection letter** - May be issued if a response to the request for other evidence is not received or is inadequate.
- **Compliant email** - Will be issued if the assessment of the GMP evidence demonstrates that the foreign building is compliant with Division 2 of the FDR.
- **Supplement to FB Annex or amended FB Annex**- Issued by establishment licensing unit for foreign buildings on the FB annex of a DEL if GMP assessment results in compliant rating.

# Documents issued by Health Canada – Table A Verification

Applications to add a foreign building on the API FB annex of a DEL or Table A will undergo a verification

- **Screening deficiency notice** – May be issued during the verification of Table A if deficiencies are identified.
- **Rejection of application notice** - May be issued if a response to the screening deficiency notice is not received in time period specified or is inadequate.
- **Acknowledgement of application acceptance** - Will be issued if no deficiency is identified or if all identified deficiencies are resolved.
- **API FB Annex or approved Table A** - Will be issued if no deficiency is identified or all identified deficiencies are resolved.



# SUBMITTING GMP EVIDENCE

# What's New?

- Standard operating procedures (SOPs) and written quality agreements are no longer required to be submitted as part of application
- Guidance on how to submit GMP evidence to support an application
- Guidance on Letters of Authorization (LoA) for evidence already submitted to HC



# Where to submit?

- All submissions, unless otherwise specified, must be submitted to the Establishment Licencing group **ElapplicationLE@hc-sc.gc.ca**
- Electronic submissions through email are strongly recommended
- Information must be in English or French

# Who submits?

## A. Applications

- Applications **must** be submitted by Canadian importers and include a completed FRM-0033 and cover letter

## B. GMP Evidence

- GMP evidence **should** be submitted by Canadian importers
- GMP evidence **may be** submitted by a foreign building directly to Health Canada.

# GMP evidence submitted by foreign buildings to Health Canada

## Importer

- Files application to Health Canada (cover letter & FRM-0033)
- Clearly indicates foreign building will be submitting GMP evidence in cover letter

## Health Canada

- Creates application
- Issue application # to importer

## Foreign Building

- Submits GMP evidence after importer has filed application and cites application number with the GMP evidence

# Letters of Authorization (LoA)



- In certain instances, GMP evidence required to support an application may have already been submitted to Health Canada as part of an application by another importer or a the foreign building
- A **letter of authorization (LoA)** may be issued by the party (importer or foreign building) that has previously submitted GMP evidence to Health Canada
- The purpose of the LoA is to allow reference of GMP evidence previously submitted to support an application

# Letter of authorization (LoA)

An LoA must:

1. be provided on the letterhead of the issuing company
2. clearly state that authorization is being provided to Health Canada
3. clearly state the name and address of the foreign building
4. specify which GMP evidence documents are being referenced (this must include the date of the inspection)

# Letter of authorization (LoA)

An LoA must:

5. be signed and dated (with complete signature block including email address)
6. demonstrate that the GMP evidence has been previously submitted to Health Canada (i.e. application tracking number, copy of acknowledgement of application acceptance, or screening acceptance notice)



**LoAs must reference an inspection report that covers the activities and dosage forms being requested**

# Letter of authorization (LoA) - Important things to note

- LoAs must be issued by the party that previously submitted the documents to HC
- Although Health Canada may accept evidence and LoAs, directly from the foreign building, it is important for importers to continue to fulfill their requirements as outlined in the FDR.





# APPLICATION PACKAGES

# Application package contents

## A) Cover letter

Cover letters help ensure applications are processed efficiently and reduce the need for HC to issue deficiencies.

## B) FRM-0033

Importers must complete all applicable sections of the Drug Establishment Licence Application Form (FRM-0033) accurately before submitting an application to Health Canada.

## C) GMP evidence

Only when an application requires GMP evidence to be submitted

# GMP Evidence

## a) Inspection reports:

- Must cover the activities and dosage forms requested
- Must be from **within the last 3 years**
- Complete inspection reports must be issued by:
  - **Health Canada** (Exit Notice)
  - A **regulatory authority** (as per definition in Appendix A)
  - A **qualified authority** (as per definition in Appendix A)
  - A **corporate/consultant auditor**
  - World Health Organization (WHO) – **only** applicable for API FB Annex or Table A buildings
  - European Directorate for the Quality of Medicines (EDQM) – **only** applicable for API FB Annex or Table A buildings

# GMP Evidence

## b) Corporate/consultant audits

- When **no** inspection report by a regulatory/qualified authority within the last 3 years is available, a corporate or consultant audit report may be submitted.
- This is **ONLY** applicable for the following specific activities/product types:
  - fabricating, packaging/labeling or testing of drugs not listed on the prescription drug list and/or over the counter, medical gases or ethical drugs
  - sterilization of packaging materials for drugs that will be aseptically filled without terminal sterilization

# GMP Evidence

## b) Corporate/consultant audits continued

- The following information must accompany a corporate or consultant audit report as part of an application:
  - a justification for submitting a consultant or corporate audit report
  - the resume of the individual(s) performing the audit
  - any deficiencies are risk classified as per GUI-0023
  - the audit report signed and dated by the auditor
- If an inspection report more than 3 years old from a Regulatory Authority or a Qualified Authority is available, the report should accompany the consultant or corporate report

# Corporate/consultant audits - Important things to note

- A report of a self-audit conducted by the foreign building is not considered acceptable GMP evidence
- All applicable Canadian GMP requirements must be assessed
- FRM-0211 is available to conduct corporate/consultant audits and is recommended



# GMP Evidence

## c) Corrective actions

- **Must be signed by a responsible official** of the foreign building
- In the case of a corporate/consultant audit, documentation must be provided indicating that the auditor has reviewed the company's corrective actions and found them acceptable



# GMP Evidence

## d) Site Master File (SMF)

- Must be signed and date
- In the situation where an SMF is not available, an SRF or equivalent document(s) may be submitted that fulfills the requirements outlined in the PIC/S Annex 1: Explanatory Notes for Industry on the Preparation of a Site Master File

# GMP Evidence

## d) Site Master File continued

- If a **SMF** is not available, a **quality manual** may be submitted for:
  - Foreign building's that **only** conduct the activity of testing
  - Foreign building's that **only** perform secondary packaging
  - Foreign building's that **only** perform sterilization of packaging material

# GMP Evidence

## e) Other evidence

- Health Canada may ask for other evidence during the assessment
- Examples of other evidence may include but are not limited to:
  - standard operating procedures (SOP)
  - written quality agreements
  - annexes or appendices referred to in the corrective action response(s).

# Best practices when filing an application

- Address of the foreign building in GMP evidence provided must be in line with the address listed on the FRM-0033:
  - if different, clarification should be provided in cover letter
  - Health Canada Drug Health Product Inspection Database (DHPID) can be used for reference
- A complete inspection report must be submitted. A list of observations alone is not acceptable. If the complete inspection report is not yet available, an extension request of the NERBY date may be submitted.
- Evidence must only be submitted with your amendment for foreign buildings listed on the Foreign Building Annex of your DEL.



# **REQUESTING AN EXTENSION OF THE NERBY DATE**

# When can an extension of the NERBY date be requested?

When no inspection report is available, a request to extend the NERBY date of a foreign building may be submitted under the following circumstances:

- An inspection by a regulatory or qualified authority has taken place but there is a delay in the issuance of the inspection report.
- An inspection by a regulatory or qualified authority is expected or scheduled to take place.

# How to submit a request to extend the NERBY date?

- An extension request must be submitted **before the assigned NERBY date**. Extensions will **not** be granted for requests submitted after the NERBY date.
- A request should include the following:
  - cover letter
  - all applicable sections of the Drug Establishment Licence Application: Forms and Instructions (FRM-0033)



The request must be submitted to the establishment licencing unit (ELapplicationLE@hc-sc.gc.ca)

# What to include in an extension request?

The cover letter for this request should also include:

- the reason for the extension request
- dates of all recent inspections (within the last 4 years)
- confirmation that the foreign building has not undergone any recent inspections that resulted in critical observations or a non-compliant or unacceptable rating
- a listing of any changes in quality assurance management, equipment or manufacturing processes since the most recent inspection by a recognized/qualified authority

# What happens after submitting an extension request?

- The foreign building will continue to be considered GMP compliant and the importer may continue to import drugs from the foreign building in accordance with their DEL and the FDR
- Health Canada will assess the request for extension of the NERBY date.

# Extension request assessment

The following factors are taken into consideration:

- compliance history of the foreign building
- most recent inspection report, including:
  - date
  - result
  - repeat observations
- any major changes since last inspection to:
  - quality assurance (QA) management
  - manufacturing processes
  - equipment
- drug type
- licensable activities conducted at the foreign building

# Outcome of extension request assessment

## Extension granted

- This outcome will be communicated by email
- A supplement to the FB Annex will be issued with the extended NERBY date
- An application should be submitted as soon as the inspection report becomes available, irrespective of what the revised NERBY date is
- Health Canada may cancel any extension to a NERBY date previously granted, or may change a NERBY date previously assigned, if Health Canada has grounds to believe that the foreign building is not in compliance with GMP requirements.

# Outcome of extension request assessment

## Extension not granted

- This outcome will be communicated by email and will include the reason(s) for not granting an extension
- The foreign building may be removed from the FB Annex of an importer's DEL

# FOREIGN BUILDING ON-SITE ASSESSMENTS





## Foreign Building On-Site Inspections

- In the past a Health Canada on-site inspection was typically initiated by request from an importer or sponsor.
- In recent years, Health Canada's Drug GMP inspection program has adopted a more sophisticated risk based approach with respect to foreign buildings that manufacture drugs destined for the Canadian market.

### WHY?

- To be more agile and present globally while maintaining adequate oversight on domestic establishments

# Foreign Building On-Site Inspections

- To request a Health Canada on-site inspection Importers/Requestors must complete a: [Good Manufacturing Practices – Request for Assessment of a Foreign Building Form \(0213\)](#)
- Health Canada has recently updated FRM-0213
  - New form available on Health Canada website as of August 8, 2017
  - Includes APIs as a drug category
  - More options available with respect to types of testing
  - Requests more information that in turn facilitates the assessment of the request
- Once FRM-0213 is received and assessed, Health Canada will communicate the outcome of the assessment to the requestor.
- If Health Canada's assessment results in a decision to inspect to the foreign building, the Foreign Building on-site assessment service agreement form (FRM-0214) must be completed by the importer, Health Canada and the foreign building



## Foreign Building On-Site Inspections- continued

- For a Health Canada initiated on-site inspection, the following criteria are considered when selecting sites:
  - type of GMP evidence available (corporate audit or inspection by qualified or regulatory authority)
  - foreign buildings compliance history
  - possibility of a joint inspection with other qualified or regulatory authority
  - medical necessity of the drug product
  - foreign buildings with no available GMP evidence that are no longer eligible for a NERBY date extension
- Once the foreign buildings are selected, all importers with the foreign buildings listed on their Drug Establishment Licence (DEL) will receive a Health Canada notification of intent to inspect.

# Foreign Building On-Site Inspections- cont'd

Health Canada has recently revised its foreign on-site notification of intent to inspect template.



## Good Manufacturing Practices-Notification to Importers of Health Canada Assessment of Foreign Buildings

|                                                                                                                                                                                                                                                                                                                                                                                    |  |                                                    |          |                                                             |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----------------------------------------------------|----------|-------------------------------------------------------------|--|
|  Health Canada Santé Canada                                                                                                                                                                                                                                                                       |  | <i>Your Health and<br/>safety... our priority.</i> |          | <i>Votre santé et votre<br/>Sécurité... notre priorité.</i> |  |
| <b>Section 1: Introduction</b>                                                                                                                                                                                                                                                                                                                                                     |  |                                                    |          |                                                             |  |
| This is notification that Health Canada intends to conduct an on-site Good Manufacturing Practices (GMP) assessment of the following foreign building(s). Your acceptance of the assessment is being requested.                                                                                                                                                                    |  |                                                    |          |                                                             |  |
| <b>Section 2: Foreign Building Information</b>                                                                                                                                                                                                                                                                                                                                     |  |                                                    |          |                                                             |  |
| Company Name:                                                                                                                                                                                                                                                                                                                                                                      |  |                                                    |          |                                                             |  |
| Address:                                                                                                                                                                                                                                                                                                                                                                           |  | City:                                              | Country: | Postal Code:                                                |  |
| Office:                                                                                                                                                                                                                                                                                                                                                                            |  |                                                    |          |                                                             |  |
| Reason for Assessment:                                                                                                                                                                                                                                                                                                                                                             |  |                                                    |          |                                                             |  |
| <b>Section 3: Request</b>                                                                                                                                                                                                                                                                                                                                                          |  |                                                    |          |                                                             |  |
| <b><u>Assessment Information</u></b>                                                                                                                                                                                                                                                                                                                                               |  |                                                    |          |                                                             |  |
| Health Canada intends to conduct the assessment within Health Canada's 2017-2018 Fiscal Year (April 1- March 31). More information with respect to the potential assessment dates will be communicated at a later time. Health Canada schedules on-site assessments to take place when the foreign building is operating to allow the inspectors to observe production activities. |  |                                                    |          |                                                             |  |

## Foreign Building On-Site Inspections- cont'd

- In order for Health Canada to conduct an inspection, the Foreign Building on-site assessment service agreement form (FRM-0214) must be completed by the importer, foreign building and Health Canada.
- Health Canada has recently updated FRM-0214
  - Sets out clauses to differentiate between a requested on-site inspections
  - Clarifies the roles and responsibilities for all 3 parties
  - Updated section 6 for primary contact information
  - Provides the ability to specify importer's province under the applicable law and forum conveniens (section 10)
  - Created table to capture scope of assessment in appendix A of the form.
- FRM-0214 is sent to the importer
- It is expected that the importer will coordinate the completion of the form with the foreign building.
- Once both parties have signed the form it is sent back to Health Canada for signature and a fully signed copy will be sent back.



# Conclusion

- GUI-0080 is now available on [canada.ca](https://canada.ca) and is considered effective immediately
- Any questions with respect to GUI-0080 should be sent to the following email: [foreign\\_site\\_etranger@hc-sc.gc.ca](mailto:foreign_site_etranger@hc-sc.gc.ca)
- Thank you for your time and we hope that you found this webinar helpful!

