How to demonstrate foreign building compliance with drug good manufacturing practices

GUI-0080

January 18, 2017

Canada

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

Author:	Health Canada
Date issued:	January 18, 2017
Date implemented:	To be determined - draft for consultation
Replaces:	Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (August 1, 2009)

Ce document est aussi disponible en français.

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About this document

1. Purpose

This guide is for Canadian importers who want to list a foreign building on their drug establishment licence (DEL). It provides guidance on the type of information you should submit to support your DEL amendment 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 (finished dosage forms or active pharmaceutical ingredients including any intermediate steps) destined for the Canadian market.

2. Scope

These guidelines apply to foreign buildings that fabricate, package/label, or test the following:

- pharmaceuticals
    - finished dosage forms (FDF)
        - intended for use in human and veterinary drugs
    - active pharmaceutical ingredient (API)
        - intended for use in human drugs
        - imported solely for sale
        - imported for use in the fabrication of a human FDF
        - used in the fabrication of an FDF which is then imported
- radiopharmaceuticals
    - intended for use in human and veterinary drugs
- biologicals (including bulk process intermediates)
    - intended for use in human and veterinary drugs
- medical gases
    - intended for use in human and veterinary drugs

The scope of this document does not include:

- excipients
- natural health products
- APIs intended for veterinary use

3. Introduction

GMP evidence requirements

These guidelines interpret the good manufacturing practices (GMP) evidence requirements for importing drugs from foreign buildings into Canada. These guidelines were developed by Health Canada in consultation with stakeholders.

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 drug establishment license (DEL). For the foreign building to be listed on the DEL, it must be deemed compliant with GMP requirements (as described in Part C, Division 2 of the FDR).

You must submit evidence to support that a foreign building complies with GMP as part of your application as a Canadian DEL holder or authorized representative. Health Canada will assess the evidence against the *Food and Drugs Act* (the Act) and its associated regulations.

It is ultimately your responsibility as a Canadian importer to ensure that drugs manufactured outside of Canada and sold in Canada are manufactured in accordance with GMP, as outlined in section C.02.003 and C.02.003.3 of the regulations.

Important: You must notify Health Canada of any event that results in a foreign building contravening any of the applicable requirements of Division 2 of the FDR that may affect the quality, safety or efficacy of a drug. For more detailed information on how to submit this information, see: Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002)

How guidance documents work

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with rules and regulations. They also provide guidance to Health Canada staff, ensuring that the rules are enforced in a fair, consistent and effective way across Canada.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for flexibility in approach. So use this guide to help you develop specific approaches that meet your unique needs.

Guidance

4. Listing foreign buildings

If you want to add or maintain a foreign building on your drug establishment licence (DEL), you must submit an application. Health Canada must establish the foreign building's compliance with good manufacturing practices (GMP) before you can import any drugs. Health Canada will consider the application submitted and any other evidence it deems necessary to assess compliance.

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

1. Foreign building annex (FB Annex)

Foreign buildings are listed on your FB Annex if they:

- fabricate, package/label or test finished dosage forms (FDF)
- fabricate, package/label or test sterile active pharmaceutical ingredients (API)
- finished product test APIs (sterile and non-sterile)

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

Foreign buildings are listed on your API FB Annex if they:

- fabricate, package/label or test non-sterile APIs (not including finished product testing)

Until now, foreign buildings have been listed on your DEL with an expiry date. However, the New Evidence Required By (NERBY) date has replaced the expiry date on your DEL. You are no longer required to submit updated GMP evidence 250 days before the foreign building's expiry date. Instead, for certain foreign buildings, Health Canada's new policy is to submit an application to maintain the foreign building on your DEL by the assigned NERBY date.

Health Canada assigns the NERBY date using a risk-based approach. The NERBY date is often four years, calculated from the start date of the regulatory/qualified authority inspection submitted to demonstrate GMP compliance. Health Canada may issue a shortened or extended NERBY date for a foreign building based on several factors, including (but not limited to):

- the building's compliance history
- the category, type and dosage form of the drug (see Appendix A for definitions)

For more detailed information on how to submit an application, application types and the NERBY date, see: Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002).

The following table summarizes where foreign buildings are listed on a DEL (depending on the situation), and whether a NERBY date is assigned or not. If a NERBY date is not assigned to a foreign building, an application to maintain the foreign building on your DEL is not required.

Table 1.0: Listing foreign buildings on your DEL

DEL annex (FB or API FB)	Description (location/product type)	NERBY assigned (Y/N)
FB Annex	• FB located in MRA country for product categories and activities not covered under MRA	Y
	• FB located in non-MRA country	Y
FB Annex	• FB that fabricates, packages/labels or tests sterile APIs	Y
	• FB that conducts finished product testing of sterile or non-sterile APIs	Y
FB Annex	• FB located in MRA country for product categories and activities covered under MRA	N
API FB Annex	• FB that fabricates, packages/labels or tests non-sterile APIs (excluding finished product testing)	N

See Appendix D for a diagram of the Health Canada process for adding foreign buildings to a DEL.

4.1 Foreign building annex (FB Annex)

For a building to be listed on your FB Annex, the location of the foreign building influences what application is required and when it needs to be filed with Health Canada. Follow the appropriate instructions for buildings:

- located in an MRA country (for product categories/activities covered under the MRA)
- located in an MRA country (for product categories/activities **not** covered under the MRA)
- not located in an MRA country

Information: to find out whether the foreign building you want to add to your FB Annex is located in an MRA country (and whether the product categories and activities are covered under that MRA), please see: Mutual Recognition Agreements.

Health Canada is a partner in several mutual recognition agreements (MRAs) covering GMP compliance programs for drug/medicinal products. MRAs are established following a joint evaluation of the regulatory frameworks in place in each partner's jurisdiction for the purpose of establishing equivalency. The equivalency of the MRA partners' GMP compliance programs has been determined, therefore Health Canada will consider the Certificate of Compliance (CoC) as evidence to support the GMP compliance of a foreign building.

4.1.1 Foreign buildings located in an MRA country (for product categories /activities covered under the MRA)

To add or maintain a foreign building located in an MRA country (for product categories or activities covered by the MRA)on your DEL, include the following information in your application:

- cover letter
- all applicable sections of the Drug Establishment Licence Application: Forms and Instructions (FRM-0033)

For detailed information on how to submit an application, see: Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002).

Health Canada assessment

When adding or renewing a foreign building under the circumstances noted above, your application will undergo GMP screening and an assessment by Health Canada.

Health Canada will ask for the CoC directly from the applicable MRA partner, as needed. There are several possible outcomes resulting from the Health Canada request for a CoC:

1. The MRA partner provides Health Canada with the CoC. Health Canada validates the information to verify that the scope of the CoC aligns with the scope of the application. This entails verifying the dosage forms and activities (fabricated, packaged/labeled or tested) conducted by the foreign building.

    i. If the scope of the CoC aligns with the scope of your application, the foreign building will be considered compliant and will added to the FB Annex of your DEL. You will receive an email and a supplement to the FB Annex or an amended FB Annex will be issued, as applicable.

    ii. If the scope of the CoC does not align with the scope of your application, Health Canada will notify you and ask you to provide alternate evidence in support of your application (see section 5 of this document for recommended evidence requirements). If no alternate evidence is available, the application will be rejected.

2. The MRA partner informs Health Canada that a CoC cannot be issued (due to the foreign building no longer holding a valid permit, licence or other authorization). Health Canada will inform you and ask you to provide alternate evidence within the time period specified in the request.

    i. If no alternative evidence is provided, your application will be rejected. When new evidence becomes available, you should submit a new application (see section 5 of this document for recommended evidence requirements).

    ii. If alternative evidence is provided, your application will follow the process outlined in 4.1.2.

Since NERBY dates are not assigned to foreign buildings located in an MRA country for activities and product categories covered under the MRA, you do not need to apply to maintain the foreign building on your DEL. You may continue to import drugs from the foreign building unless we inform you otherwise. Meanwhile, Health Canada will continue to request CoCs from MRA partners. There are several outcomes resulting from Health Canada requests for a CoC:

1. The MRA partner provides Health Canada with a copy of the CoC (where the scope of the CoC continues to align with the dosage forms and activities conducted by the foreign building listed on the DEL). No further action is required by you.

2. The MRA partner provides Health Canada with a copy of the CoC (where the scope of the CoC no longer aligns with the dosage forms and activities conducted by the foreign

building listed on the DEL). Health Canada will notify you and provide you with an opportunity to submit a new application along with new evidence (see section 5 of this document for recommended evidence requirements).

3. The MRA partner informs Health Canada that a CoC cannot be issued (due to the foreign building no longer holding a valid permit, licence or other authorization). Health Canada will notify you (and other affected importers) and remove the foreign building from your FB Annex. You can no longer import from the foreign building. If you want to resume importing from the foreign building, you must submit a new application along with new evidence (see section 5 of this document for recommended evidence requirements).

4.1.2 Foreign buildings located in an MRA country (for product categories or activities **not** covered under the MRA) **or** foreign buildings not located in an MRA country

If a foreign building is located in an MRA country but the product categories/activities **are not** covered under the MRA, or if the foreign building is **not located** in an MRA country, include the following information in your application:

- cover letter
- Drug Establishment Licence Application: Forms and Instructions (FRM-0033)
- inspection report
- corrective actions
- site master file
- written agreement(s)

Important: If you submit a cover letter along with a Health Canada Inspection report (Exit Notice) as evidence of GMP compliance of a foreign building, none of the other recommended evidence must be submitted.

Health Canada assessment

When adding or renewing a foreign building under the circumstances noted above, your application will undergo GMP screening and an assessment by Health Canada.

The accuracy and completeness of applications is assessed during screening as per the requirements outlined in section 5 of this document. If any deficiencies are identified during screening, Health Canada will send you a screening deficiency email outlining the information

required. You must address all the deficiencies in one comprehensive response, within the time period specified in the request. If you fail to provide all requested information within the specified time period, or the submitted information is incomplete or deficient, Health Canada will send you a screening rejection email that outlines the reason(s) the application was rejected and you should submit a new application with the recommended evidence outlined in section 5 .

If no deficiencies are identified during the screening or if all the deficiencies are resolved, Health Canada will accept your application for assessment and will send you a screening acceptance notice.

Health Canada will conduct a GMP assessment to verify the information submitted demonstrates the foreign building's compliance with Division 2 of the FDR. We may issue a request for other evidence (see section 5.7 for more information) during the assessment. You will be required to provide the additional evidence as requested. If you fail to provide a complete response, or the response you provide is deemed insufficient for further assessment, Health Canada will issue a rejection email that outlines the reason(s) the application was rejected and you should submit a new application with new evidence.

After our assessment of the GMP evidence, we will assign a rating to the foreign building:

- Compliant (C) – Issued when the evidence is deemed acceptable and demonstrates GMP compliance with Division 2 of the FDR. The foreign building will be added or maintained on the FB Annex of your DEL.
- Non-Compliant (NC) – Issued when the evidence is not deemed acceptable and does not demonstrate GMP compliance with Division 2 of the FDR. The foreign building will not be added to the FB annex of your DEL, will be removed from the FB Annex of your DEL or will be maintained on the FB annex of your DEL with terms and conditions.

A C or NC rating with terms and conditions may be issued when other factors (such as the foreign building's compliance history, drug type, medical necessity, category, dosage form or activities conducted at the foreign building) require additional oversight. The foreign building will be added or maintained on the FB Annex of your DEL along with terms and conditions.

Information: As per section C.01A.011, it is the importer's responsibility to comply with the terms and conditions listed on the DEL.

Health Canada will communicate the outcome of the assessment to you by way of email and issue a supplement to the FB Annex (or an amended FB Annex).

A NERBY date will be assigned as a result of this Health Canada assessment.

4.2 Active pharmaceutical ingredient foreign building annex (API FB Annex)

APIs are not currently part of Health Canada's MRAs, so the location of the foreign building does not change the content required in your application to add or renew a foreign building on the API FB Annex of your DEL.

Include the following information in your application:

- cover letter
- all applicable sections of the Drug Establishment Licence Application: Forms and Instructions (FRM-0033) – including a completed Table A

Health Canada assessment

Health Canada will assess your application. We will review the information listed in Table A (of FRM-0033) for accuracy and completeness. If any deficiencies are identified, Health Canada will send you a screening deficiency email outlining the information required. You must address all the deficiencies in one comprehensive response, within the time period specified in the request. If you fail to provide all requested information within the specified time period, or the submitted information is incomplete or deficient, Health Canada will send you a screening rejection email that outlines the reason(s) the application was rejected and you should submit a new application.

Once all deficiencies are resolved and if no deficiencies are identified we will issue you an acknowledgement of acceptance email along with an API FB Annex or an approved Table A. For more detailed information on the API FB Annex, see Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002).

Health Canada assesses information related to foreign buildings that fabricate, package/label or test non-sterile APIs on an ongoing basis. Health Canada uses a risk-based approach to select foreign buildings for the assessment of GMP evidence.

We will contact you and ask you to submit GMP evidence. If you receive such a request, please submit the following information:

- cover letter
- inspection report
- corrective actions
- site master file
- written agreement

The cover letter for this application must include the tracking number of the latest application to add a foreign building to the API FB Annex.

Submit the information package as described above to: foreign_site_etranger@hc-sc.gc.ca account.

Health Canada will assess the evidence received in the same way as described above in section 4.1.2. You may continue to import drugs from the foreign building unless we inform you otherwise.

5. Providing recommended evidence

This section outlines the evidence you (the importer) should submit to Health Canada to demonstrate the GMP compliance of foreign buildings that fabricate, package/label or test drugs on your behalf.

If the original information is not available in either of the official languages (English or French), you must provide a copy of the original information and a translated copy in English or French, along with an attestation of the accuracy of the translation, signed by the translator.

If any of the required documentation is not available, include a written justification in your cover letter explaining why the required document type cannot be submitted. Health Canada will assess your justification and determine whether your application will be further assessed or rejected.

Important: The importer must be the one who submits all information as part of an application to Health Canada. This applies to the cover letter, FRM-0033 and evidence.

5.1 Cover letter

All applications should include a cover letter. For more information on the recommended content of the cover letter, see: Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002).

5.2 FRM-0033

You must complete all applicable sections of the Drug Establishment Licence Application Form (FRM-0033) accurately and according to the requirements of FDR C01A.005 before submitting your application to Health Canada. For more information on completing FRM-0033 and Table A, see: Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002).

5.3 Inspection report

Health Canada will accept the final and most recent (i.e. within the last 3 years), inspection report signed and issued by:

- Health Canada (Exit Notice)
- regulatory authority (refer to Appendix A for the definition)
- qualified authority (refer to Appendix A for the definition)
- World Health Organization (WHO) – applicable to non-sterile APIs only
- European Directorate for the Quality of Medicines (EDQM) – applicable to non-sterile APIs only
- corporate/consultant auditor (see section 5.3.1 for limitations)

Important: For non-sterile APIs only, if an inspection report within the last 3 years is not available for foreign buildings that fabricate, package/label or test (excluding finished product testing), you may submit the most recent inspection report available with a written justification and Health Canada may consider this on a case by case basis.

The inspection report must cover the activities and dosage forms that you are requesting to add or maintain on your DEL. If there are multiple current inspection reports available for a foreign building from different regulatory/qualified authorities, you should let Health Canada know. Submit the most current inspection report. In addition you should also submit a list of all inspections, including the final outcomes that have occurred in the last 4 years.

Important: An on-site evaluation (OSE), conducted by the Biologics and Genetic Therapeutics Directorate is not considered sufficient on its own to demonstrate the GMP compliance of a foreign building as it is not intended to cover all applicable sections of Part C, Division 2 of the FDR.

5.3.1 Corporate/consultant audits

If no inspections by regulatory/qualified authorities are available, you may submit a corporate or consultant audit report to Health Canada to demonstrate GMP compliance of a foreign building, but only for the following specific/activities:

- fabricating, packaging/labeling or testing of over the counter (OTC) products
- fabricating, packaging/labeling or testing of medical gases
- fabricating, packaging/labeling or testing of ethical drugs (on a case-by-case basis)
- sterilization of packaging materials for drugs that will be aseptically filled without terminal sterilization

Important: Health Canada strongly recommends that you contact the GMP Inspection Headquarters by sending an email to the foreign_site_etranger@hc-sc.gc.ca account before arranging for one of these audits, to ensure it would be considered acceptable GMP evidence for your situation.

The audit must be conducted against Canadian GMP guidelines and all applicable sections must be assessed. Use the form titled *Good Manufacturing Practices - Audit Report Form (FRM-0211)* to ensure all GMP requirements are assessed. If you chose to use an alternate form, it is your responsibility to ensure that all the sections outlined in FRM-0211 are covered.

Ensure the following information accompanies the corporate or consultant audit report as part of your application:

- a justification for submitting a consultant or corporate audit report (include in your cover letter)
- the resume of the individual(s) performing the audit, which clearly demonstrates their qualifications and experience (the individual(s) must have experience in and knowledge of GMP- see regulatory requirements for personnel in section C.02.006 of the *Good Manufacturing Practices (GMP) Guidelines (GUI-0001)*)
- any deficiencies, noted during the audit, are to be risk classified using this document: *Risk Classification of GMP Observations (GUI-0023)* (the classification of deficiencies will be reviewed by Health Canada)
- the audit report signed and dated by the auditor
- the most recent inspection report from a regulatory or qualified partner, unless the site has never been inspected

Important: A corporate or consultant report may be submitted in lieu of an inspection report from a source specified under section 5.3 for a **maximum** of two NERBYs. At which point, a corporate/consultant audit may not be accepted as evidence.

5.4 Corrective actions

Submit a copy of the corrective actions taken as a result of the inspection, signed by a responsible official of the foreign building.

In the case of a corporate/consultant audit, you must provide documentation indicating that the auditor has reviewed the company's corrective actions and found them acceptable.

5.5 Site master file

Submit a copy of the most recent, signed and dated site master file for foreign buildings that fabricate, package/label or test drugs.

For foreign buildings that only conduct the activity of testing, a quality manual may be accepted instead of a site master file.

For more guidance on site master files, see: PIC/S Annex 1: Explanatory Notes for Industry on the Preparation of a Site Master File.

5.6 Written agreement(s)

Submit the most recent, signed and dated copy of any written agreement(s) between you (the importer) and the foreign building(s) conducting the fabrication, packaging/labeling and testing. (This includes quality agreements and any other type of written agreement.)

These agreements should clearly identify all parties involved and their responsibilities to ensure compliance with all GMP requirements.

They should also establish the responsibilities of each party to avoid misunderstandings that could result in a product or operation of poor quality.

You should also provide a copy of all written agreements between all parties involved in different steps of the manufacturing process, even if you are not a party to these agreements. If written agreements between all parties are not available, please provide a document listing all parties involved, along with a description of their role in the supply chain.

For more guidance on the content of a written agreement, please see:

- Good Manufacturing Practices (GMP) Guidelines (GUI-0001)
- Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (GUI-0104)

5.7 Other evidence

Health Canada may ask you for other evidence during our assessment. You must provide this additional evidence within the time period specified in the request. If the evidence is not available, you must provide a written justification of why the evidence cannot be submitted. Health Canada will assess your justification and determine whether your application can be further assessed. If you application cannot be further assessed, Health Canada will provide written reasons as to why.

Important: It is the importer's responsibility to maintain all evidence of the foreign buildings' GMP compliance at their Canadian site (as outlined in sections C.02.012 and C.02.020–C.02.024 of the FDR).

6. Requesting an extension of the NERBY date

You may submit a request for a short extension of the NERBY date in certain circumstances, for example:

- 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 regulatory or qualified authority is scheduled to take place.

Submit your extension request no later than 90 calendar days before your assigned NERBY date. Extensions will not be granted for requests submitted after the NERBY date. Your request should include the following:

- cover letter
- all applicable sections of the Drug Establishment Licence Application: Forms and Instructions (FRM-0033)

The request(s) must be submitted in accordance with the Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002).

Your cover letter for this request should also include:

- a rationale for the extension request
- dates of all recent inspections (within the last 4 years) and information on any upcoming inspections by a recognized/qualified authority
- a statement attesting that the foreign building has not undergone any recent inspections resulting in critical observations or the issuance of a non-compliant or unacceptable rating
- information about all drugs imported from the foreign building, including for each drug (if applicable): activities, category, name and drug identification number (DIN), schedule, and dosage form
- a statement indicating whether there have been any changes in quality assurance personnel, equipment or manufacturing processes since the most recent inspection by a recognized/qualified authority (provide any relevant documentation)

Health Canada assessment

Health Canada will assess your request for extension of the NERBY date. Our assessment will take the following factors 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) personnel
    - manufacturing processes
    - Equipment

- drug type
- activities conducted at the foreign building

Our assessment can result in one of two outcomes:

1. **Extension granted** – Health Canada determined that the information provided supports an extension of the NERBY date. Therefore you may continue to import from the foreign building for the period of the extension. However, you should submit an application to Health Canada as soon as the inspection report becomes available, no matter what the revised NERBY date is.

2. **Extension not granted** – Health Canada determined that the information provided does not support an extension of the NERBY date. You must: (1) provide additional information to support the extension request, (2) choose an alternate site or (3) submit an application requesting a Health Canada inspection.

Important: Health Canada may cancel any extension to a NERBY date, previously granted, if Health Canada finds evidence of non-compliance after an extension has been granted. Health Canada will notify and provide a grace period before an extension is cancelled unless circumstances are such that the health and safety of consumers are at risk.

7. Requesting a Health Canada on-site inspection of a foreign building

You may submit an application requesting Health Canada to conduct an on-site inspection of a foreign building when there is no recent inspection report (i.e. within the last 3 years) or other acceptable evidence available. Your application should include:

- cover letter
- Good Manufacturing Practices- Request for Inspection of a Foreign Site Form (FRM-0213)

Make sure your cover letter includes the category of drug and whether the drug is Prescription or over-the-counter (OTC).

Submit your application(s) in accordance with the Guidance on how to apply for, amend and maintain a Drug Establishment Licence (GUI-0002).

Health Canada will issue a written acknowledgement within 28 calendar days of receiving your application.

Health Canada assessment

Upon receipt of a complete application, we will assess the information provided in the cover letter and FRM-0213. We may issue a request for clarification during our assessment. Send your responses to the clarification request(s) directly to the person and/or account outlined in the request within the timeframe indicated.

During our assessment, we will evaluate the following criteria:

- activities conducted
- all categories of drug(s) manufactured
- all dosage forms manufactured
- overall information about the drug (such as, but not limited to: product type, product category, product dosage form or medical necessity of product)
- compliance history of foreign building
- whether other qualified or regulatory authorities are planning on inspecting the same foreign building

Our assessment is typically conducted within 42 calendar days of the acknowledgement of receipt, but may be delayed if responses to clarification requests are not received promptly.

Health Canada's assessment can result in one of two outcomes:

1. Decision to inspect – Based on Health Canada's assessment, we have determined that an on-site inspection is required. We will send you an acceptance email stating that an inspector will contact you to make scheduling arrangements and request preparatory documents, contract and logistical arrangements.

2. Decision not to inspect – Based on Health Canada's assessment, we have determined that an on-site inspection is not required at this time. We will send you an email declining your request and providing you with further guidance.

Should an on-site inspection be conducted, there are two possible outcomes of the inspection:

- If the on-site inspection results in a compliant rating, the foreign building will be added or maintained on the FB or API FB Annex of the DEL.

- If the on-site inspection results in a **non-compliant rating**, the foreign building will not be added ,will be removed or will be maintained on the FB or API annex of your DEL with terms and conditions.

Appendices

Appendix A – Glossary

Acronyms

API: Active pharmaceutical ingredient

C: Compliant

CoC: Certificate of Compliance

DEL: Drug establishment licence

DIN: Drug identification number

EDQM: European Directorate for the Quality of Medicines & Health Care

FB: Foreign building

FDF: Finished dosage form

FDR: Food and Drug Regulations

GMP: Good manufacturing practices

MRA: Mutual recognition agreement

NC: Non-Compliant

NERBY: New Evidence Required By

PIC/S: Pharmaceutical Inspection Cooperation Scheme

WHO: World Health Organization

Terms

Information: These definitions explain how terms are used in this document. If there is a conflict with a definition in the *Food and Drugs Act* or *Food and Drug Regulations*, the definition in the Act/Regulations prevails.

Active ingredient – A drug that, when used as a raw material in the fabrication of a drug in dosage form, provides its intended effect. (*FDR* C.01A.001)

Active pharmaceutical ingredient (API) – An active ingredient that is used in the fabrication of a pharmaceutical. (*FDR* C.01A.001)

Active pharmaceutical ingredient foreign building annex (API FB Annex) – A listing of foreign buildings that manufacture non-sterile APIs. This annex is part of the drug establishment license (DEL).

Bulk process intermediate (BPI) – An active ingredient that is used in the fabrication of either a drug of biological origin that is listed in Schedule C to the Act or a drug that is listed in Schedule D to the Act. (*FDR* 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 buildings history of conformity with good manufacturing practices as outlined by legislative or regulatory requirements.

Compliant (C) – At the time of the inspection, the regulated party has demonstrated that the activities it conducts comply with the Food and Drugs Act and its associated Regulations. A "C" rating does not mean that there are no observations or corrective actions required.

Critical Observation - Observation describing a situation that is likely to result in a NC product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.

Dosage form – A drug that has been processed to the point to where it is now in a form that may be administered in individual doses (unless otherwise defined in the Food and Drug Regulations).

Drug – Any substance or mixture of substances manufactured, sold or represented for use in;

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,

(b) restoring, correcting or modifying organic functions in human beings or animals, or

(c) disinfection in premises in which food is manufactured, prepared or kept

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 complying with the requirements of Division 2 of the *Food and Drug Regulations*.

Drug identification number (DIN) – A drug identification number (DIN) is a computer-generated eight-digit number assigned by Health Canada to a drug prior to being marketed in Canada. It uniquely identifies any drugs sold in a dosage form in Canada. It is located on the label of prescription and over-the-counter drugs that have been evaluated and authorized for sale in Canada. A DIN uniquely identifies the following drug characteristics: manufacturer, drug product name, active ingredient(s), strength(s) of active ingredient(s), pharmaceutical form, and, route of administration.

Ethical drug – A drug that—according to federal legislation—does not require a prescription, but is generally prescribed by a medical practitioner (e.g. nitroglycerine).

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

Foreign building – A building outside of Canada where the following licensable activities are conducted for drugs that are sold in Canada: fabrication, packaging/labelling, and/or testing.

Foreign building annex – A listing of foreign buildings that have been assessed by Health Canada as being compliant with the requirements of Divisions 2 to 4 of the Food and Drug Regulations. This annex is part of the DEL. **Note**: Please note that a person cannot import any drugs nor sell any existing stock that has been fabricated, packaged/labelled or tested at a foreign building that does not appear on their DEL

Import – "To import into Canada a drug for the purpose of sale" (C.01A.001)

MRA country – A country that is a participant to a mutual recognition agreement with Canada. (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." (C.01A.001)

New evidence required by (NERBY) – The date by which new evidence is required to 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 inspection, the regulated party has not demonstrated that the activities it conducts comply with the *Food and Drugs Act* and its associated regulations.

Over-the-counter (OTC) – A non-prescription drug which still requires a market authorization.

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

Product category – For the purpose of this guidance**,** includes pharmaceutical, active ingredient, vaccine, biologic, radiopharmaceutical, controlled drugs and narcotics, or any other product category designated by the Minister.

Product type – For the purpose of this guidance:

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

Qualified authority – An authority listed as a member of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S).

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 that may take enforcement action to ensure that drugs marketed within its jurisdiction comply with legal requirements. (C.01A.001).

Test – To perform any examinations, evaluations and assessments as specified under Division 2 of the Food and Drug Regulations.

Written agreement – A formal document between the Canadian DEL holder and the contractor party that defines the responsibilities and duties of both parties for all aspects of a drug's quality. The intent is to avoid misunderstandings and guarantee that the quality of all activities performed is sufficient to result in a safe drug product.

Appendix B – References

Laws and regulations

Food and Drug Regulations
laws.justice.gc.ca/en/F-27/C.R.C.-C.870

Food and Drugs Act
laws.justice.gc.ca/en/F-27

Controlled Drugs and Substances Act
laws.justice.gc.ca/en/C-38.8

Forms

Drug Establishment Licence Application Form (FRM-0033)
hc-sc.gc.ca/dhp-mps/compli-conform/licences/form/frm-0033-eng.php

Good Manufacturing Practices – Audit Report Form (FRM-0211)
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/form/gui-0080-form-0211-eng.php

Good Manufacturing Practices – Request for Inspection of a Foreign Site Form (FRM-0213)
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/form/gui-0080-form-0213-eng.php

Good manufacturing practices

Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (APIs) Guidelines (GUI-0104)
hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingre-gui-0104-eng.php

Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2 (GUI-0001)
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php

Risk Classification of Good Manufacturing Practices (GMP) Observations (GUI-0023)
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0023-eng.php

Other related documents

Access to Therapeutic Drug Products: The Regulatory Process in Canada
http://publications.gc.ca/collections/collection_2007/hc-sc/H164-9-2006E.pdf

Compliance and Enforcement Policy (POL-0001)
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php

Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)
hc-sc.gc.ca/dhp-mps/compli-conform/licences/directives/gui-0002-eng.php

Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks – August 1, 2000
hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/risk-risques_tc-tm-eng.php

Mutual Recognition Agreements
hc-sc.gc.ca/dhp-mps/compli-conform/int/mra-arm/index-eng.php

International guidance documents

Pharmaceutical Inspection Co-operation Scheme
picscheme.org

PIC/S Annex 1: Explanatory Notes for Industry on the Preparation of a Site Master File
hc-sc.gc.ca/dhp-mps/compli-conform/licences/directives/gui_0005_tc-tm-eng.php

European Directorate for the Quality of Medicines & HealthCare
edqm.eu

Appendix C – Questions and answers

Here are comments received from industry members, and Health Canada's answers.

1. **What do I do if no new evidence is available by the NERBY date?**

   You may submit a request to extend the NERBY date if an inspection by a regulatory or qualified authority has taken place but there is a delay in the issuance of the inspection report or if an inspection by regulatory or qualified authority is scheduled to take place. If an extension is not granted, you may submit a request for a Health Canada on-site inspection.

2. **Is a certificate of GMP compliance (CoC) issued by a MRA country for a foreign building not located within their jurisdiction considered sufficient evidence for Health Canada to conduct their assessment?**

   No. A CoC issued by a MRA country for a foreign building located outside of their jurisdiction is not considered sufficient evidence. However, a copy of the CoC may be submitted along with the full inspection report.

3. **Would Health Canada conduct an on-site inspection of a foreign building if asked by a sponsor, to support the GMP compliance for a new drug submission?**

   Yes. Health Canada would consider conducting an on-site inspection of a foreign building to prove GMP compliance in support of a new drug submission. Health Canada will assess the need for an on-site inspection following the guidelines outlined in section 7 of this document.

4. **Why are foreign buildings that manufacture sterile APIs listed on the FB Annex and not on the API FB Annex of the DEL?**

   The FB Annex of a DEL lists all the foreign buildings that manufacture finished dosage forms (FDF). Since the sterilization of APIs (not terminally sterilized) is considered as an FDF manufacturing step, sterile APIs are listed on the FB Annex.

5. **Is GMP evidence only required for the foreign API sites imported from directly, or also for the API sites used by third party FDF fabrication/packaging/testing sites**?

   The API foreign buildings used by a third party FDF fabricator should be listed in Table A. Acceptable GMP compliance evidence must also be available for API buildings used by a third party FDF fabrication, packaging/labeling and testing sites. In other words, evidence must be available for all sites involved in the fabrication of the API, not just the last processing step.

As stated in section C.02.003 of the Food and Drug Regulations, no importer shall sell a drug unless it has been fabricated, packaged/labeled, tested and stored according to Division 2 of the Regulations (GMP requirements). Also, as stated in C.02.003.3, no person shall use an active ingredient in the fabrication of a drug unless it is fabricated, packaged/labeled, tested and stored according to GMP requirements.

6. Are there biological veterinary drugs?

Yes, there are veterinary drugs that are biological. The term “veterinary biologic” refers to veterinary vaccines and select classes of immunomodulators that fall within the scope of the Canadian Centre for Veterinary Biologics at the Canadian Food Inspection Agency. The term “biological veterinary drug” covers all other products that fall within the scope of this document.

Appendix D – Diagram of Health Canada process

The diagram below shows Health Canada's process for adding foreign buildings to drug establishment licences (DELs), depending on the situation