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Management of applications and performance for drug establishment licences (GUI-0127)

GUI-0127

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Canada

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Health Canada is the federal department responsible for helping Canadians maintain and improve their health. It is with this goal in mind that the Department executes its responsibilities as a regulator, a catalyst for innovation, a funder, and a trusted source of health information. The Department assesses the safety of drugs and many consumer products, helps improve the safety of food, and provides information to Canadians to help them make healthy decisions.

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Ce document est aussi disponible en français sous le titre :
Gestion des demandes et du rendement en matière de licences d'établissement de produits pharmaceutiques (GUI-0127)

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Disclaimer

This document does not constitute part of the Food and Drugs Act (the Act) or its regulations and in the event of any inconsistency or conflict between the Act or regulations and this document, the Act or the regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the regulations and the applicable administrative policies.

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The following icons are used in this document:

Important: Key or cautionary information to know.

Information: Supplementary information like quotes and legal references.

Tip: Things to do or understand.

About this document

1. Purpose

This document outlines:

- the responsibilities of applicants in the Drug Establishment Licence (DEL) application process, and
- how Health Canada manages DEL applications

This guide does not interpret the requirements under the *Food and Drugs Act* (the Act) or the Food and Drug Regulations (FDR). For a list of guides that interpret the various requirements under the Act or FDR, refer to Appendix A: References.

2. Scope

This document applies to all DEL applications submitted under Part C, Division 1A of the FDR. It covers:

- DEL application policies
- DEL application best practices; and
- processes and timelines used by Health Canada to manage DEL applications

Processes not directly related to a DEL application are excluded from this guide, in particular, regular Good Manufacturing Practices (GMP) inspections which verify the ongoing compliance of DEL holders with GMP requirements.

DEL application policies

The DEL application policies in this section apply to all DEL applications except applications that include a request for assessment of a foreign building by a Health Canada Inspector. For more information with regards to Health Canada's on-site assessment of a foreign building, please consult *How to Demonstrate Foreign Building Compliance with Drug Good Manufacturing Practices (GUI-0080).*

3. Service standard

The performance standard for processing a DEL application is 250 calendar days of Health Canada review time.

4. Pause-the-clock policy

Health Canada uses a “Clock” to measure performance against the 250 calendar day service standard.

4.1 Starting the clock

The clock starts on the date when Health Canada receives an application that is administratively complete. “Administratively complete” criteria are outlined in section 13.1.

The application “date of receipt” is one of the following:

- the date stamp on the email
- the date stamp on the fax
- the manual date stamp on an application received by mail

Once an application has been reviewed and found to be administratively complete, Health Canada issues an acknowledgment notice. This notice includes the application number and the date when the clock started.

4.2 Pausing and restarting the clock

The clock will be paused during the review process if the application meets any of the triggers described in section 4.2.1 to 4.2.4.

When a trigger is met, Health Canada sends an email to the Canadian building contact, informing them of the following:

- that the clock is paused,
- the reason for the pause, and,
- what the applicant needs to do to restart (i.e. un-pause) the clock.

The clock will be restarted on the day that the trigger is resolved. When the clock is restarted, the time with the applicant ends and the time with Health Canada resumes.

Health Canada records the date the clock was paused, not the time. Therefore, once Health Canada records the date when a response was received and the clock is restarted, the time paused is calculated in days. If a response is received the same day the clock is paused, the applicant time is calculated as zero days.

The following are descriptions of the four triggers that pause the clock and how each trigger can be resolved to restart the clock.

4.2.1 Deficiencies

An application is deficient when an application or part of an application cannot be further processed by Health Canada because:

- it does not meet regulatory requirements of the FDR or
- the intent/scope of the application is not clear

When a deficiency is identified, a deficiency notice is issued and the clock is paused. Detailed information on deficiency triggers are described in Appendix C: Deficiencies. Deficiencies may be identified at various steps in the review process.

When Health Canada has received a response to a deficiency notice, the clock will be restarted.

4.2.2 Applicant requests to delay an inspection

An inspection may be required to process an application. If an applicant requests to delay such an inspection, and Health Canada accepts the request, the clock will be paused.

The clock will restart when the inspection begins on-site.

4.2.3 Meeting request

An applicant may request to meet with Health Canada to discuss an application. If Health Canada cannot process the application further until the meeting takes place, the acceptance of the request by Health Canada will include a notification that the clock will be paused.

The clock will restart when the meeting ends.

4.2.4 Opportunity to be Heard (OTBH)

When Health Canada proposes to render a negative decision with respect to a DEL application, Health Canada issues a notice to the applicant to provide the applicant an opportunity to be heard. The notice includes the timeline for providing a response. The clock will be paused when this notice is sent.

When Health Canada receives a response to the notice, the clock will restart. If Health Canada does not receive a response, the clock will restart when the time set in the notice has passed. If an applicant does not wish to have an OTBH, Health Canada will restart the clock when the applicant's response is received.

4.3 Calculating the clock

Once a licensing decision has been issued for every request in the application, the clock stops. For example, if an application is requesting the addition of a foreign building and a domestic building to their DEL, the application clock is not stopped until a decision is issued for both buildings.

Health Canada's 250 calendar day service standard is calculated in days, by taking the difference between the date the clock was stopped and the date the clock was started, and then subtracting the time that the clock was paused (i.e. applicant time) to provide the total application time.

5. Rejection of deficient application

When a deficiency is identified, a first notice is issued to the applicant, providing them with 30 business days to respond. When a deficiency notice is issued the clock is paused, as described in section 4.2. If no response to the deficiency notice is received, or if the response that is received is inadequate, a second notice will be issued and an additional 30 business days will be provided to the applicant to respond.

If no response is received to address the deficiency after the second notice is issued, or if the response received is inadequate, the application will be rejected. The applicant can submit another application and restart the process.

6. New Evidence Required By (NERBY)

Every DEL holder is required to submit an Annual Licence Review (ALR) application by April 1 of each year, as per C.01A.009 of the FDR. This includes the requirement to submit GMP evidence for every foreign building listed on the DEL Foreign Building Annex. As explained in section 10 of *GUI-0002: Guidance on Drug Establishment Licences and Associated Fees*, in lieu of submitting GMP evidence as part of the ALR application, DEL holders have the option to sign an "Undertaking B" form provided in the ALR package. The signed form is the applicant's commitment to submit an amendment application containing acceptable GMP evidence, as described in GUI-0080, prior to the NERBY date indicated on the DEL.

The DEL holder can continue to import drugs from foreign buildings in compliance with the FDR and DEL requirements while the foreign building remains listed on their DEL. When the DEL holder submits an amendment application prior to the NERBY date requesting to update the NERBY date listed on the DEL, the foreign building will continue to be listed on the DEL Foreign Building Annex while Health Canada reviews the application. The DEL holder can also submit a request to extend the NERBY date following the instructions in section 6 of GUI-0080.

If an application to amend or extend the NERBY date is not received by the NERBY date, if the application is incomplete, or if the evidence is deemed unacceptable or incomplete at any time in the assessment process, the foreign building may be removed from the Foreign Building Annex.

Once a foreign building is removed from the DEL, the DEL holder is no longer authorized to import from this building and will be notified by Health Canada. To add the building back onto the DEL, the DEL holder must submit a complete application to Health Canada and the application will be subject to the 250 calendar day performance standard for processing a DEL application.

As outlined in GUI-0080, NERBY dates are generally not assigned to foreign buildings located in a Mutual Recognition Agreement (MRA) country.

7. Communication with applicants

Health Canada's primary mode of communication with DEL applicants is email. Health Canada considers the contact information provided in the DEL application to represent the approved contacts for the company. Correspondence related to pausing the clock will be directed to the Canadian building contact using the contact coordinates provided.

To make sure that applicants receive all correspondence related to their DEL application, applicants are responsible for:

- providing an accurate email address as part of their DEL application, and,
- keeping Health Canada up to date on any changes to their email address or other contact information.

DEL holders can update company contact information by filling out *FRM-0033 Drug Establishment Licence Application* and sending it to (hc.el.applications-le.sc@canada.ca).

Ensure contact lists are up to date to avoid missing deficiency notices or application rejections. Health Canada will only communicate licence-specific information to approved contacts provided by the applicant. Health Canada is not responsible for delays in applications or other issues stemming from outdated contact information.

8. Withholding services if fees are not paid

If fees that are due for a DEL application have not been paid by the required due date, Health Canada has the authority to withhold services, approvals, rights and/or privileges. Should Health Canada use this authority to stop the review of an application, the period of time where services are withheld does not count towards Health Canada's 250 calendar day service standard.

9. Issuance of decisions

9.1 Applications for a new DEL

Applications for new DELs should include every Canadian and foreign building for which a licence is requested. Where possible, Health Canada will issue each portion of the application, as it is ready.

Applications for a new DEL should not be separated on a per building basis.

9.2 Amendment applications

Health Canada only issues one decision per amendment application regardless of how many requests are included in the application.

For example, if an application contains amendments for several buildings, a decision will be issued only after the GMP inspection of all buildings is completed and a decision for all buildings is ready to be made.

Separating amendment applications helps to prevent situations where a decision on one building is held up by another, as a result of both buildings being included in the same application. See section 11 for more information on application best practices.

Application best practices

10. Preparing a DEL application

Deficiencies in DEL applications cause delays in processing. It is important that applicants understand the regulatory requirements for DEL applications, and carefully prepare an application by:

- reviewing the documents listed in Appendix A: References, in order to understand the DEL application regulatory requirements; and
- reading the instructions in FRM-0033, in order to complete the application properly

Prior to submitting an application, should further clarification of any aspect of the application be required, contact the appropriate generic email account:

- General DEL enquiries at: hc.del.questions-leppp.sc@canada.ca
- Fee related enquiries: hc.criu-ufrc.sc@canada.ca
- Foreign building GMP enquiries: hc.foreign.site-etranger.sc@canada.ca
- Domestic GMP enquiries: hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca

Cover Letter

Submitting a cover letter with an application to clarify what is being requested in the application can help with the efficient processing of the request, and can help avoid the issuance of deficiency letters. Health Canada recommends that applicants include the following information in a cover letter:

- DEL name and number (if assigned).
- Application Number(s) (if assigned). This is important when providing supplementary information to a pending submission.
- Clearly identify any important context including:
    - information about mergers and acquisitions
    - if the application is for a move
    - if an expedited review is requested
- Clearly identify what is requested in the application (e.g. to add a foreign building to the DEL that fabricates biologics and the addition of the drug category biologic to the domestic building):
    - List of the supporting documents being provided as part of the application.
    - If GMP evidence is being submitted as per GUI-0080 include a summary of the evidence being submitted.
- If specific guidance has been provided by Health Canada prior to filing an application, include a copy of the correspondence (if applicable).
- If a building (domestic or foreign) is performing any of the packaging/labelling activities below, provide a brief description of the packaging/labelling activities and include the answers to each of the following questions:
    - Does the building label the primary container?
    - Does the building enclose the primary container in a secondary container?
    - Does the building label the secondary container?
    - Does the building insert a leaflet in the secondary container?

Health Canada only expedites or prioritizes a DEL application if it can address a real or imminent drug supply shortage of a medically necessary drug, or if the drug has been accepted for priority review according the Health Canada's Priority review policy outlined in *Guidance for Industry - Priority Review of Drug Submissions*.

- A medically necessary drug is defined by Health Canada as a market-authorized drug in Canada which is used to prevent, treat or diagnose a serious or life-threatening disease or medical condition, for which there is no available alternative. Patient inconvenience alone is an insufficient reason to classify a drug as medically necessary.
- If the drug qualifies as medically necessary or if Health Canada has accepted the drug submission for a priority review, submit the DEL application as per section 11 and indicate "Request for EXPEDITED REVIEW: DEL# xxxxxxx; Establishment name" as the email subject line. The application must include a copy of the Health Canada acceptance letter for the priority review of the drug submissions or a duly filled FRM-0378 - Template for determination of medical necessity of a drug product *.

When requesting an expedited or priority review for a DEL application that has already been submitted to Health Canada, ensure that the request clearly indicates the application number.

* The FRM-0378 - Template for determination of medical necessity of a drug product, can be requested at: hc.del.questions-leppp.sc@canada.ca

11. Guidance on how to submit amendment applications for existing DEL

See below for best practices on submitting amendment applications for an existing DEL. These best practices will help applicants submit a DEL application in compliance with the FDR and limit the scope of the application for effective processing.

11.1 Administrative changes

Administrative changes to an existing DEL should always be submitted separately from other types of requests (e.g., separate from requests to add activities, drug categories, dosage form).

Administrative changes include changes to:

- mailing or billing address
- contact name, telephone number, fax number and email address
- warehouse information

11.2 Foreign buildings

Foreign Building Annex

Submit an application, per foreign building, if the purpose is to make any of the following changes on the DEL Foreign Building Annex:

- add a foreign building
- renew a foreign building NERBY date
- amend a foreign building

Applicants can request multiple changes for the same foreign building in the application but each application should only be for a single foreign building.

However, an exception is made to this requirement when GMP evidence is submitted via an inspection report that covers multiple buildings. In this case, every foreign building covered by that evidence can be grouped in a single application.

If adding or amending a foreign building, all drug categories, activities, sterility status and dosage forms requested for the foreign building must also be authorized at the domestic building that is performing the activity of import.

- When this is not the case, the application must also include a request to amend the associated domestic building to add the missing drug category, sterility status or dosage form under the activity of import.

Foreign Building Annex for Active Pharmaceutical Ingredients (API)

When submitting an application to amend the API Foreign Building Annex, a request can be included to add multiple foreign buildings in the same application.

For a drug imported as a finished dosage form, if the DEL holder is applying to add a new API foreign building to the DEL:

- The foreign building identified as the finished dosage form fabricator must be listed on the Foreign Building Annex.
- If this is not the case, then the DEL holder must apply to add the finished dosage form fabricator to the Foreign Building Annex.

Example:

Medicine Inc. holds DEL 3-009999 and would like to submit an application to add “Medicine API Inc. Mexico”. Medicine API Inc. Mexico is the API supplier for Medicine Inc. Germany.

DEL 3-009999 includes:

- The domestic activity of import pharmaceutical
- A Foreign Building Annex listing: Medicine Inc. USA
- An API Foreign Building Annex listing: Medicine API Inc. Germany

Medicine Inc. cannot submit an application to add the foreign building Medicine API Inc. Mexico to their DEL if the application indicates that the fabricator of the finished dosage form drug is Medicine Inc. Germany. This is because Medicine Inc. Germany is not listed on Medicine Inc. Foreign Building Annex.

Therefore, the application should also include a Section 5 form, which can be found in *FRM-0033 (Drug Establishment Licence Application)*, to add the finished dosage form fabricator Medicine Inc. Germany in order to add the foreign building Medicine API Inc. Mexico to their DEL.

11.3 Canadian buildings

Applications to amend or add a Canadian building to the DEL should be submitted for each building and separate from other applications, with the exceptions outlined below. Multiple changes can be requested for the same building in one application.

Adding the activity of import to a DEL

The application must include a request to add at least one foreign building and the *Table A: Foreign Buildings Conducting API-Related Licensable Activities* when submitting an amendment to:

- add the activity of import to an existing building on the DEL
- add a new building to the DEL with the activity of import

12. Submitting the DEL application

Submitting a DEL application electronically allows for the more efficient processing of the application. In order for the DEL process to start, applications must be submitted using **one** of the methods outlined below.

12.1 Filing by email

To submit a DEL application electronically, send the application and all supporting documents to: hc.el.applications-le.sc@canada.ca.

A system-generated auto-response will be sent, confirming that the application was delivered to Health Canada's establishment licencing inbox. It is recommended that applicants save both their sent email and the auto-response for future reference.

If an auto-response is not received, it means that the application remains undelivered. Please resubmit the application.

Best practices when an application needs to be sent using more than one email

If an application needs to be sent using more than one email, link the emails together using the subject line. Follow the best practices, below, to ensure that Health Canada can efficiently process the separated applications:

- Indicate in the email subject line that the application is in two parts. Example:
  - subject line for first email: Part 1 of 2 – DEL# 1234-A Renewal of Foreign Building
  - subject line for second email: Part 2 of 2 – DEL# 1234-A Password for Renewal of Foreign Building

Health Canada considers the receipt date for the application to be the date it received the **last** portion of the application.

12.2 Filing by mail or fax

If submitting an application by mail or fax, identify all applications and supporting documents in a cover letter.

Health Canada does not accept applications submitted on portable storage devices, such as:

- Universal Serial Bus (USB) memory stick
- External hard drive
- Secure digital (SD) card

Health Canada can accept applications submitted on a CD or DVD.

Mail or fax to:

Mail

Drug Establishment Licensing Unit
Jeanne Mance Building
200 Eglantine Driveway
Address Locator #1913B
Ottawa, Ontario
K1A 0K9

Fax

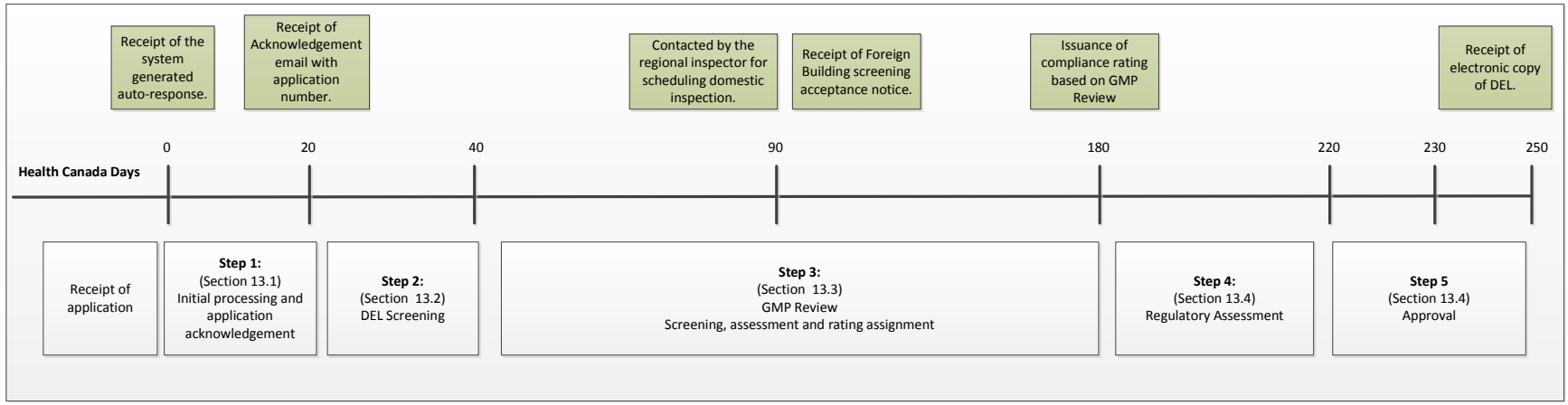
1 (613) 957-4147

How Health Canada manages DEL applications

13. Applications that are not for the annual review of the DEL

This section outlines an overview of the DEL application process. Although the process may vary depending on the type of application submitted, in general, an application will follow the steps in Diagram 1 upon receipt by Health Canada.

Diagram 1: DEL Application Timeline



13.1 Initial processing and application acknowledgement

13.1.1 Initial administrative review criteria

All DEL applications are reviewed to verify administrative completeness against the following criteria:

FRM-0033 Drug Establishment Licence Application: Forms and Instructions

- document is not corrupt
- if locked, confirm that a password has been received
- form is complete and signed
- presence of all indicated documents/emails
- verification/confirmation of changes requested
- additional information for foreign building name/address changes is provided (if applicable)
- if Table A was submitted, Section 5.1 of FRM-0033 is complete

Table A

Verify completeness against the following criteria:

- confirm correct version of Table A
- confirm that Table A is for one Canadian building
- validate that all mandatory fields are completed
- verify that there are no non-compliant foreign buildings listed

For more information regarding the mandatory Table A columns, please refer to the instructions in *Table A: Foreign Buildings Conducting API-Related Licensable Activities* from FRM-0033.

Amalgamations and changes of ownership

- review of application to ensure that all documents, as per guidance from Health Canada specific to the situation, are included

13.1.2 Application acknowledgement

Once the application is deemed administratively complete, an application number is assigned and the clock is started.

- All administratively complete applications will receive an application number as part of the Acknowledgement of Application email.
- HC aims to issue acknowledgement emails within 20 calendar days of receipt of the application.
- Applicants must reference this application number when contacting Health Canada about this application.

Applicants must not submit any additional information for an application until they have received an application number. Doing so will result in the additional information being rejected.

13.1.3 Processing of administrative applications

The following applications are considered to be administrative and do not require a full review. Processing of the application is completed during this step, however, these applications are only processed at this step if they are not combined with other requests.

Applicants are notified of completion as follows:

Cancellation Requests

Upon completion of the review of the cancellation request, the applicant will be notified either that the request is complete or that further information is required prior to the cancellation of the DEL.

Withdrawal Requests

Once the withdrawal request is processed, the applicant will receive an email notifying them that the withdrawal of the DEL application has been completed.

"Mailing, Billing and Head Office address and contact change" amendment applications

In lieu of an acknowledgement email for this type of application, an Amendment Completion Notice will be sent to the applicant. This notice acknowledges receipt of the application and indicates that the requested changes have been processed.

Warehouse amendment applications

In lieu of an acknowledgement email for this type of application, an Amendment Completion Notice will be sent to the applicant. This notice acknowledges receipt of the application, confirms that the requested changes have been processed and includes a copy of the updated warehouse annex, which is then mailed to the mailing address on file.

13.2 DEL screening

During the screening step, the application and cover letter are reviewed for completeness against the requirements outlined in GUI-0002.

Screening criteria

At the screening step, Health Canada verifies that the application is complete against application screening criteria, including, but not limited to the following:

- all listed documents are present
- FRM-0033 is complete and includes all required sections and documents
- for an application to change the name of the DEL holder, all supporting documentation is included (if applicable)
- for an application to amend a DEL where the amendment is specific to a foreign building:
    - The change is consistent with the authorised drug category, dosage form or sterility status under the activity of import; or the application includes a request to amend the activity of import to request a change to the missing component.
    - For example, if a foreign building is added that fabricates sterile pharmaceuticals, the domestic building must be licensed to import sterile pharmaceuticals or the application must include a request to add the activity of import for sterile pharmaceuticals to the domestic building.
- for applications including a foreign building located in a country with which Health Canada has a MRA:

- The foreign regulatory authority has issued an authorisation for the foreign building to conduct licensable activities included in the application.
- There are no discrepancies between the information in the application and the information in Health Canada's database.

If a deficiency is identified, Health Canada will send an email notification outlining the deficiency that needs to be addressed. The application clock will be paused, as per the pause-the-clock policy described in section 4.

It is the applicant's responsibility to provide a complete, clear and accurate application. Note that if an applicant requests to change the scope of an application after the DEL screening step of the process, Health Canada **may refuse** to accept changes to the scope of the application and a new application will need to be submitted.

13.3 GMP review

Once DEL screening is complete, the following parts of the application are assigned for GMP evaluation and assessment:

- requests for domestic inspections
- requests for Certificates of Compliance (CoC) from regulatory partners under the applicable MRA
- the evaluation and assessment of GMP evidence

13.3.1 Domestic building compliance with drug GMP

Once past DEL screening, an application for a new domestic building or an amendment to a domestic building is assigned for a drug GMP inspection. However, depending on the nature of the application request, a domestic building that has been previously inspected may not require an inspection.

Health Canada aims to contact the applicant within 90 calendar days of receiving the application in order to set the date for an inspection.

- Applicants are responsible for being ready and available for a GMP inspection.
- Health Canada inspectors can inspect the premises of an applicant at any time following receipt of an application.

Any request from the company to delay the proposed date of inspection is subject to approval by Health Canada inspectors and will result in a pause to the application clock.

The scope and duration of the inspection is dependent on:

- The activities being assessed
- Drug categories and dosage forms of products being handled on site

Applicants can refer to the Drug GMP documents listed in Appendix A: References to understand the Division 2 regulatory requirements that apply to their activities.

Not ready for the inspection?

If an applicant is not ready for an inspection when they are contacted by an inspector, the applicant can request a withdrawal of their application. If the application is not withdrawn, an inspection will be conducted. Lack of readiness may result in a Non-Compliant (NC) rating. Inspection ratings are posted on the Drug and Health Products Inspections database on the Government of Canada website.

Inspection rating following an inspection

An inspection rating indicates whether a site is Compliant (C) or Non-Compliant (NC) with GMP requirements.

The inspector aims to issue the inspection report with a compliance rating within 180 calendar days from the receipt date of the application. The following information is posted to the Drug and Health Products Inspections database on the Government of Canada website:

- inspection rating
- summary of the observations noted during the inspection
- inspection outcome and measures taken by Health Canada

13.3.2 Foreign building compliance with drug GMP

Once past DEL screening, applications that include a request to add, renew or amend a foreign building to the DEL will be sent for GMP evidence screening, and then for a GMP evidence assessment.

If a foreign building is located in an MRA country, GMP evidence may not be required if the drug categories and activities are included within the scope of the MRA and a CoC is available. Health Canada will request the CoC from the MRA partner.

Health Canada reviews the GMP evidence for completeness and accuracy, as per GUI-0080.

If an importer is unable to submit GMP evidence in support of its application, Health Canada will accept the evidence directly from the foreign building as outlined in GUI-0080. If the foreign building has not submitted the evidence to Health Canada by the time that the GMP screening step has begun, the application will be considered deficient and a Screening Deficiency Notice (SDN) will be sent.

GMP evidence screening

GMP evidence is reviewed for completeness, based on the requirements outlined in GUI-0080. Once the evidence is deemed acceptable for further assessment, the applicant will be sent a Screening Acceptance Notice (SAN).

If GMP evidence deficiencies are identified, Health Canada will send the applicant a SDN outlining the missing or inadequate information. The application clock will be paused. Once the evidence is deemed acceptable for further assessment, the applicant will be sent a SAN, on average, 90 calendar days from the date of receipt of the application.

If Health Canada does not receive a reply to the SDN or the response is incomplete or deficient, Health Canada will email the applicant a Screening Rejection Notice (SRN). This means the application will be rejected. The applicant may resubmit an application once they have all the required information.

GMP Evidence Assessment

During the assessment of GMP evidence, Health Canada determines whether the submitted evidence demonstrates compliance with Divisions 2 to 4 of the FDR for the drug categories, activities and dosage form(s) requested in FRM-0033.

If GMP evidence deficiencies are identified, Health Canada will send the applicant an email outlining the missing or inadequate information. The application clock will be paused. Examples of GMP evidence deficiencies can be found in Appendix C: Deficiencies.

Once the complete GMP evidence package has been assessed, a rating will be assigned, based on the outcome of the assessment, and communicated via a GMP Compliance Notification.

The GMP Compliance Notification is not an authorization for importation. Importation may only commence from a foreign building upon issuance of a new or amended DEL with the foreign building listed.

As outlined in section 6, if the foreign building is currently listed on the DEL, activities may continue in accordance with those listed on the DEL.

Requesting and assessing a CoC

Health Canada has several MRAs with regulatory agencies in other countries. If the foreign building is located in a MRA country (for drug categories or activities included in the scope of the MRA), Health Canada will request a CoC directly from the MRA partner.

The list of countries with the updated MRAs is available at the Mutual Recognition Agreements website.

There are several possible outcomes resulting from Health Canada's request for a CoC:

- The MRA partner provides Health Canada with the CoC. The information in the CoC is then compared to the scope indicated in the application. If the scope of the CoC includes the dosage forms, activities and categories requested by the applicant, the foreign building will be added to the Foreign Building Annex of the importer's DEL.
- The MRA partner provides Health Canada with the CoC but the scope of the CoC does not include the activities, categories and/or dosage forms requested in the application. The DEL applicant would be notified of the activities, categories and/or dosage forms that are covered by the CoC and, therefore, reflected on their licence. A new application, including GMP evidence, will be required to add/ maintain the activities and/or dosage forms not covered by the CoC to the foreign building on the importer's DEL.
- The MRA partner informs Health Canada that a CoC cannot be issued because the foreign building no longer holds a valid permit, licence or other authorization. In this scenario, Health Canada, will notify the applicant that their application has been rejected.

For more information regarding CoCs, please consult GUI-0080.

13.4 Regulatory assessment and approval

During the regulatory assessment and licensing recommendation step, the application is reviewed against the requirements of the FDR and guidance outlined in GUI-0002. Applications recommended for licence issuance or amendment are sent for final approval.

When conducting the regulatory assessment of the application, the following actions are taken:

- review the application and ensure discrepancies and/or deficiencies are addressed
- review the GMP inspection report rating, scope, and recommendations
- ensure alignment between the application, assessment, recommendation, and regulations
- identify if terms and conditions are recommended

If a deficiency is identified, Health Canada will send an email notification outlining the deficiency that needs to be addressed. The application clock will be paused.

Based on the regulatory assessment, a licensing recommendation is made. The final approval of a licensing recommendation is made by the Director of the Health Product Inspection and Licensing Division of the Health Product Compliance Directorate.

A recommendation will be made when all requests included in an amendment application are ready for processing. For more information regarding Health Canada's recommended application scope see section 9.

When a final licensing decision is rendered, the decision is issued to the applicant by email and via Canada Post to the mailing address on file.

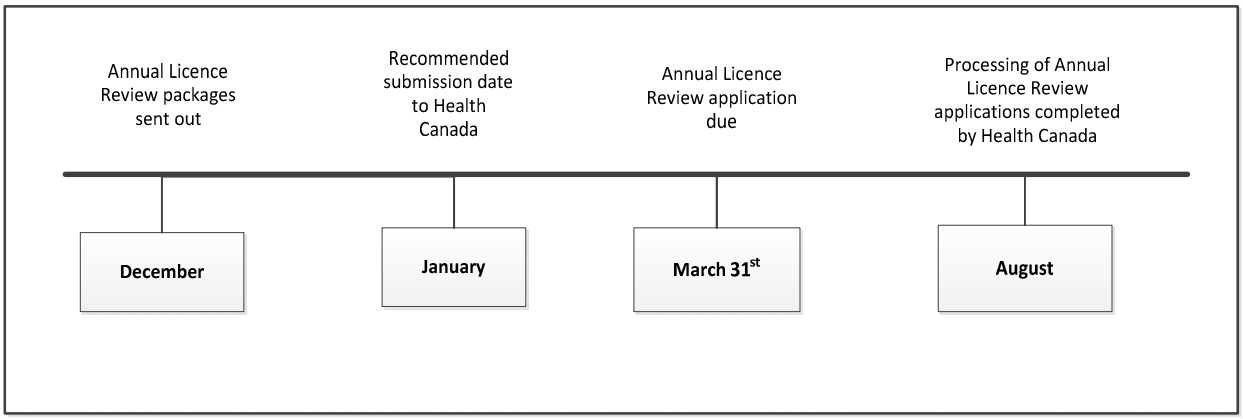
Applicants are responsible for notifying Health Canada of any change in contact information, including mailing addresses, to prevent issues in obtaining documentation. Health Canada is not responsible for issues regarding the receipt of hard copy documents that may result from companies failing to provide appropriate and up to date address information.

14. Applications for the annual review of the DEL

This section describes how Health Canada manages applications through the Annual Licence Review (ALR) process.

Every DEL holder must submit an ALR application before April 1 of every year. Because a high number of applications are received within a short period of time, and because there is more variability in the time required to process ALR applications, the process below differs from that of general applications, and Health Canada has established milestones for completing the review tasks, as outlined below.

Diagram 2: ALR timeline



14.1 Initial processing

Health Canada verifies that the application is complete based on, but not limited to, the following screening criteria:

- all required documents and forms are included
- electronic documents can be opened and are not corrupt or locked
- the ALR application form contains all the required pages
- all required signatures are present

14.2 Application acknowledgement

If the ALR application is deemed complete as per the screening criteria, an application number is created and the administrative information (i.e. contact information, mailing and billing address, etc) is processed.

The application number will be sent as part of the Acknowledgement of Application email. Applicants should refer to this application number when contacting Health Canada about their application.

Applicants should not submit additional information for the same application until they have received an application number.

14.3 Acknowledgement with deficiencies

If ALR application deficiencies are identified, Health Canada will email the applicant a Notice of Application Deficiency. The application clock will be paused.

14.4 ALR review and completion

This review verifies that only acceptable changes have been made as part of the ALR application. The approved changes will be updated and reflected in the Health Canada database.

Upon completion of the ALR assessment, applicants receive an email notification informing them that annual review of the DEL is complete and the regulatory requirements of C.01A.009 to maintain the DEL have been met.

A revised licence is issued only if a change was made during ALR that impacted the information appearing on the domestic building section of the licence.

Appendix A: References

Laws and regulations

Food and Drugs Act (the Act)
laws.justice.gc.ca/eng/acts/F-27/

Food and Drug Regulations (FDR)
laws.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html

Service Fees Act
laws-lois.justice.gc.ca/eng/acts/S-8.4/

Forms

Drug Establishment Licence Application: Forms and Instructions (FRM-0033)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/forms/drug-establishment-licence-application-instructions-0033.html

Good manufacturing practices

Good Manufacturing Practices Guide for Drug Products (GUI-0001)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001.html

Risk classification guide for drug good manufacturing practices observations (GUI-0023)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/risk-classification-drug-gmp-observations-0023.html

Good Manufacturing Practices for Medical Gases (GUI-0031)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0031.html

Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (GUI-0104)
https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/compliance-enforcement/manufacturing-active-pharmaceutical-ingredients-gui-0104.html

How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/guidance-evidence-demonstrate-drug-compliance-foreign-sites-0080.html

GMP Inspection Policy for Canadian Drug Establishments (POL-0011)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/policies-standards/inspection-policy-canadian-drug-establishments.html

Drug Establishment Good Manufacturing Practices – Pre-Application Package (Importers, Distributors and Wholesalers)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/application-package-importers-distributors-wholesalers.html

DEL related documents

Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/guidance-drug-establishment-licences-drug-establishment-licensing-fees-0002.html

Guidance Document Alternate Sample Retention Site Guidelines (GUI-0014)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/forms/alternate-sample-retention-site-guidelines-0014.html

Other documents

Compliance and Enforcement Policy (POL-0001)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/policies-standards/compliance-enforcement-health-products.html

Drug Good Manufacturing Practices (GMP) and Establishment Licencing (EL) Enforcement Directive (POL-0004)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/drug-good-manufacturing-practices-establishment-licensing-enforcement-directive-0004.html

Guidance for Industry - Priority Review of Drug Submissions
https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/priority-review/drug-submissions.html

Appendix B: Glossary

Acronyms

ALR	Annual Licence Review
API	Active Pharmaceutical Ingredient
CoC	Certificate of Compliance
DEL	Drug Establishment Licence
FDA	The Act
FDR	Food and Drug Regulations
GMP	Good Manufacturing Practices
HPIL	Health Product Inspection and Licensing (Division)
MRA	Mutual Recognition Agreement
OTBH	Opportunity to be heard
ROEB	Regulatory Operations and Enforcement Branch
SAN	Screening Acceptance Notice
SDN	Screening Deficiency Notice

Terms

Active pharmaceutical ingredient (API) - An active ingredient that is used in the fabrication of a pharmaceutical. (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.

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 FDR).

Drug establishment licence (DEL) - A licence that allows a person to conduct licensable activities in a building in Canada.

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.

Inspection - Assessment of compliance against any of the applicable requirements of the *Food and Drugs Act* and its associated regulations by a designated inspector.

Licensable activity - Activities that require a licence (DEL). The six activities are fabricating, packaging/labelling, importing, distributing, wholesaling and testing.

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

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. (FDR C.01A.001)

Appendix C: Deficiencies

In cases where the application requirements listed in the FDR are not met, a deficiency notice is issued to the applicant. A deficiency occurs when an application cannot be further processed by Health Canada because it does not meet regulatory requirements or the intent/scope of the application is not clear. Examples of deficiencies include but are not limited to:

- Lack of clarity regarding application scope. For example, an application is submitted to renew a foreign building, but the activities listed on FRM-0033 are different from those currently approved for the foreign building. It is unclear if the applicant wishes to add new activities for the foreign building or just renew the foreign building for the current approved activities. The best practice to ensure that submitted applications are not found deficient is to clearly outline the scope of the request in a cover letter.
- The required API information is not included in the application (Table A).
- The application does not include GMP evidence that meets the requirements in GUI-0080. Some examples are:
    - lack of evidence (including when the foreign building is sending the evidence on the importer's behalf)
    - missing dates, signatures or required documents
    - evidence is heavily redacted and conclusions cannot be drawn with respect to GMP compliance
    - the foreign building inspection was not conducted against Canadian GMP standards as indicated in GUI-0001
    - during the assessment, supporting GMP evidence does not cover the activity, category or dosage forms requested
    - there is more recent evidence available for the foreign building, than what has been provided
    - foreign building address listed on FRM-0033 does not match the address on the inspection report provided