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# GMP

Drug Establishment Good Manufacturing Practices

## Pre-Application Package

Importers, Distributors and Wholesalers

[www.healthcanada.gc.ca/gmp](http://www.healthcanada.gc.ca/gmp)

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# Greetings

Health Canada is pleased to provide you with our new pre-application package to assist your organization in preparing for an initial drug GMP inspection by the Inspectorate.

This package is intended to be used prior to the submission of a Drug Establishment Licence Application for the activities of Wholesaling, Importation and Distribution, in order to ensure that your establishment has the minimum requirements for GMP Compliance in place prior to an inspection.

In order to conduct activities relating to the fabrication, packaging/labelling, testing, distribution, importation or wholesaling of a category of drugs listed in Table II of Section C.01A.008 of the *Food and Drug Regulations*, you must comply with the requirements of Division 2 of the *Food and Drug Regulations*, which covers Good Manufacturing Practices (GMPs). As evidence of this compliance, an Establishment Licence is required. Division 1A of Part C of the *Food and Drug Regulations* outlines the requirements for Establishment Licences.

These activities are defined as follows:

**Wholesale** - "To sell any of the following drugs, other than at retail sale, where the seller's name does not appear on the label of the drugs:

- (a) a drug listed in Schedule C or D to the *Act* or in Schedule F to these *Regulations* or a controlled drug as defined in subsection G.01.001 (1);

or

- (b) a narcotic as defined in the *Narcotic Control Regulations*." (C.01A.001)

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

**Distributor or Manufacturer** - "A person, including an association or partnership, who under their own name, or under a trade, design or word mark, trade name or other name, word, or mark controlled by them, sells a food or drug." (A.01.010)

Divisions 1A and 2 to 4 apply to the following distributors (C.01A.003):

- (a) a distributor of a drug listed in Schedule C or D to the *Act* or in Schedule F to these *Regulations*, a controlled drug as defined in subsection G.01.001 (1) or a narcotic as defined in the *Narcotic Control Regulations* who does not hold the drug identification number for the drug or narcotic; and
- (b) a distributor of a drug for which that distributor holds the drug identification number.



# Contents

The following information is contained in this package:

- Inspection Overview (page 4);
- A table describing which regulations apply to each licensable activity to aid your organization in preparing for an inspection (page 5);
- Checklists of minimum requirements that should be in place prior to the submission of your Drug Establishment Licence Application for each of the licensable activities (pages 7-9);
- References to other applicable guidance documents and tools available (pages 11-12);
- Feedback request (page 13)

# Inspection Overview

The initial inspection of an establishment conducting licensable activities is triggered by the receipt of a Drug Establishment Licence Application. You are advised to submit your application once your establishment is ready to begin licensable activities for products subject to Division 1A of the *Food and Drug Regulations* or once you have received drug marketing authorization. The Drug Establishment Licence Application and Instructions can be found on Health Canada's website at [www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/index-eng.php).

The Inspectorate endeavours to schedule an initial on-site inspection within 3 months of the date of the receipt of a complete Drug Establishment Licence Application by the Establishment Licensing Unit (ELU). Inspections are conducted to assess compliance with Division 2 Part C of the *Food and Drug Regulations* – with legislative authority for the regulations stemming from the *Food and Drugs Act*.

The scope of the inspection is dependent on the licensable activities being assessed. An on-site inspection could last anywhere from 1-5 days depending on the activity being conducted, as well as the category and dosage form class of products involved. It is important to note that it is expected that all documentation be available on site at your establishment.

To get a sense of which Division 2 regulations would apply to you, please refer to the *GMP Regulations Applicable to Licensable Activities* table included in this package. It is also recommended that you refer to **Good Manufacturing Practices (GMP) Guidelines – 2009 Edition (GUI-0001) version 2**, applicable GMP Annexes and the **Guidance on Drug Establishment Licences (GUI-0002)** for further information.

An inspection will typically feature:

- An Opening Meeting, review of an Inspection Plan which may include inspection schedule, products or operations to be reviewed, procedures/records that may be reviewed, completion of Establishment Profile which includes information on the establishment's key personnel, activities conducted, etc;
- A Premises Tour may be conducted. A representative number of products may also be selected for documentation review.
- Assessment Phase, review of procedures, operations, records and interviews with personnel to assess compliance with requirements.
- Documentation Review, a fact finding and spot checking of procedures and records.
- A Closing Meeting, a summary of the on-site inspection at the close of inspection where draft observations may be verbally communicated to the establishment.
- An Exit Meeting, where the inspector will present the draft Inspection Exit Notice and go over any observations that have been made.

During an inspection, the inspector will record all deviations to Division 2 Part C of the *Food and Drug Regulations* as observations. You/Your establishment will be given the opportunity to correct observations as they are made during an inspection, where possible. Following the inspection, you/your establishment will be expected to submit a corrective action plan to address the observations noted. A defined timeframe for the submission of your establishment's response may be imposed and may vary according to the severity of the observations noted in the report.

For foreign market authorization holders, evidence that the Importer is a legal business entity in Canada (eg. Business Registration) may be requested by Health Canada. It is important to note that under C01.004.1 the Importer assumes all regulatory responsibilities.

# GMP Regulations Applicable to Licensable Activities

Section	Regulation	Importer* (MRA and non-MRAs)	Distributor	Wholesaler
1. Premises	C.02.004	✓	✓	✓
2. Equipment	C.02.005			
3. Personnel	C.02.006	✓	✓	✓
4. Sanitation	C.02.007			
	C.02.008			
5. Raw Material Testing	C.02.009			
	C.02.010			
6. Manufacturing Control	C.02.011	✓	✓	
	C.02.012	✓	✓	✓
7. Quality Control	C.02.013	✓	✓	✓
	C.02.014	✓	✓	✓
	C.02.015	✓	✓	✓
8. Packaging Material Testing	C.02.016			
	C.02.017			
9. Finished Product Testing	C.02.018	✓	✓	
	C.02.019	✓	✓	
10. Records	C.02.020	✓	✓	
	C.02.021	✓	✓	✓
	C.02.022	✓	✓	✓
	C.02.023	✓	✓	✓
	C.02.024	✓	✓	✓
11. Samples	C.02.025	✓	✓	
	C.02.026	✓	✓	
12. Stability	C.02.027	✓	✓	
	C.02.028	✓	✓	
13. Sterile Products	C.02.029			

\* For further information on Mutual Recognition Agreements, please refer to: [www.hc-sc.gc.ca/dhp-mps/compli-conform/int/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/int/index-eng.php)

For the extent to which these requirements apply to your products, please refer to the relevant guidance documents.

# Preparing your Establishment for a First Inspection

You/Your establishment should ensure that the following systems are in place prior to applying for an Establishment Licence. If, following an assessment of your Drug Establishment Licence Application, Health Canada determines that your site is not ready for an inspection, your Licence Application will be refused.

Following the implementation of the amendments to the *User Fees Act* ([www.tbs-sct.gc.ca/fm-gf/ktopics-dossiersc/fms-sgf/uf-fu/menu-eng.asp](http://www.tbs-sct.gc.ca/fm-gf/ktopics-dossiersc/fms-sgf/uf-fu/menu-eng.asp)), the refusal of a Drug Establishment Licence Application will result in the forfeiture of the Licence Application Fees. In addition, if the GMP compliance of an applicant's site cannot be assessed due to the site's lack of readiness or if the inspection results in a non-compliant rating, this will result in the refusal to issue the licence and a forfeiture of fees.

The assessment of your establishment's compliance may include, but may not be limited to, the requirements listed on pages 7-9, as applicable; however you should be aware that depending on the activities conducted or the products handled on site, other *Regulations* may apply.

# Wholesalers – Pre-Application Checklist

## Premises (C.02.004):

- Warehouse has been temperature mapped (protocols for seasonal mapping should be available)
- Warehouse is temperature monitored at points representing the worst-case scenarios
- Sanitation program
- Pest control program
- Areas for returned, rejected, quarantined, recalled products have been identified

## Personnel (C.02.006):

- The qualified individual in charge of the quality control department has been identified
- GMP and SOP training has been provided to all personnel involved in GMP activities

## Transportation (C.02.015):

- Transportation providers or containers or packaging configurations are qualified
- Transportation procedures have been qualified to ensure that appropriate conditions/temperatures are maintained under probable extremes of ambient temperature
- Maintenance of transportation conditions should be supported by written agreements between transportation providers and your establishment
- Refrigerators, walk-in coolers and freezers are qualified, mapped and temperature monitored, if applicable. Preventative maintenance program is in place
- All monitoring devices have been calibrated (including devices located in fridge & freezers)

## Records (C.02.022):

- Computerized systems used for inventory control and recall have been validated, if applicable

## The following Standard Operating Procedures (SOPs) must be in place:

- Review of SOPs
- Ordering
- Shipping and receiving
- Picking and packing (packing procedure for products requiring special storage condition if applicable)
- Rejected/damaged goods
- Temperature monitoring and appropriate follow up to any temperature excursions
- Calibration of temperature sensors
- Preventative maintenance program for refrigerators and freezers
- Complaint handling
- Change control
- Recall(s)
- Distribution and inventory control
- Deviation handling
- Training
- Product release
- Transportation (incoming and outgoing)
- Handling of returned/rejected/expired goods
- Refrigerators/freezers maintenance records - if Receipt Storage
- Technical / quality / GMP agreements
- Self-inspection
- Record retention

## Additional requirements:

- Quality agreements are in place with suppliers/ transportation carriers identifying at minimum, the respective responsibility of each party with respect to: complaints, recalls, returns and transportation.
- Quality agreements are in place with the transportation providers
- A copy of all the proposed suppliers' ELs have been maintained

# Distributors – Pre-Application Checklist

In addition to the requirements for wholesalers, distributors are also required to have the following available for all products:

- Master Production Documents (MPDs)\*
- Test method validation and method transfer (for both confirmatory and stability testing)
- Process validation/process validation protocol (GUI-0042)
- Quality agreements with drug suppliers, and contractors, such as warehouses, packager/labeller, testing laboratories, wholesalers and QC consultants (if applicable)
- Retention samples
- Release of finished product
- Deviation(s)
- Stability program
  - shelf life data
  - on-going stability program for drugs marketed in Canada
  - stability protocols

**\*Note:** MPDs are defined in the Good Manufacturing Practices (GMP) Guidelines - 2009 Edition (GUI-0001) version 2 as documents that include specifications for raw material, for packaging material and for packaged dosage form; master formula (including composition and instructions as described in the definition above), sampling procedures, and critical processing related SOPs, whether or not these SOPs are specifically referenced in the master formula.

## Additional required SOPs:

- Testing program
- Review and approval of batch manufacturing record
- Review and approval of Master Production Documents
- Stability program
- Out Of Specification (OOS) investigations
- Goods receiving and sampling
- Retain samples
- Methods validation and transfer
- Annual product quality review

# Importers – Pre-Application Checklist

In addition to the requirements for wholesalers and distributors, importers are also required to have the following available for all products:

- Inclusion of all foreign suppliers on the importers Drug Establishment Licence
- Retention samples - Pre-approval from Health Canada is required if a firm wishes to use an alternative site for retention samples. An 'Alternate Sample Retention Site Application Form' must be completed by the establishment and submitted for approval.

**Note:** It is expected that information demonstrating the GMP compliance of those foreign establishments conducting activities on your (your establishment's) behalf will be submitted with a Drug Establishment Licence Application. An outline of the types of information that should be submitted to demonstrate the GMP compliance of a foreign drug establishment can be found in the Inspectorate policy document entitled "*Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)*", available on the Health Canada website.

## Additional requirements:

- Testing program – different requirements exist for products imported from countries with which Canada has Mutual Recognition Agreements (MRA) and products imported from countries with which no Mutual Recognition Agreements exist (Non-MRA).
- Review of batch records – this requirement applies to products imported from countries with which Canada does not have Mutual Recognition Agreements (Non-MRA).

# Pre-Inspection Information Request

The following Pre-inspection Information Request represents a sample of the information that you may be requested to provide the inspector in preparation for an inspection; however, depending on the licensable activity being evaluated, other information may be requested. An assessment of your firm's readiness for inspection could be evaluated by means of a phone interview.

## Wholesalers

- A copy of the current organizational chart
- A copy of the SOP index
- A list of prospective pharmaceutical clients
- The names and addresses of all perspective prospective drug suppliers.
- Nature of activities
- A list of product(s) that will be sourced from each supplier indicating the following:
  - DIN(s) available/assigned
  - Category i.e. Schedule C, D, F, G, narcotic or OTC
  - Dosage form class (SVP, LVP, solution, powder, tablets, capsules etc)
  - Special transportation and storage requirements

## Importer/Distributor

- A copy of the current organizational chart identifying the responsible Quality Control person(s)
- A copy of the SOP index
- A floor plan of the facility
- A list of prospective pharmaceutical clients
- A copy of Notice of Authorization Form in the event that a Quality Control Consultant is acting on behalf of the establishment
- Nature of activities
- Names and addresses of all drug "suppliers" (all domestic and foreign manufacturers, contract packagers, contract testing laboratories and contract sterilization facilities; any domestic contract warehousing operations should be identified)
- A list of product(s) sourced from each supplier indicating the following:
  - DIN # and DIN owner
  - Category i.e. Schedule C, D, F, G, narcotic or OTC
  - Active ingredient and strength
  - Dosage form class (i.e. SVP, LVP, solution, powder, tablet, capsule, etc.)
  - Special transportation and storage requirements
  - Process validation type and status (prospective, retrospective or concurrent/completed/in-process/not performed - if incomplete anticipated completion dates)
  - Test method validation / method transfer studies completion
  - Use of reduced testing
  - Unique identifier for products imported from Non-MRA countries
  - Drugs granted Alternate Sample Retention Site

# Additional Reference Material

In addition to the information provided in this package, we recommend that you review Health Canada's guidance and policy documents regarding good manufacturing practices and establishment licensing which can be found at [www.healthcanada.gc.ca/gmp](http://www.healthcanada.gc.ca/gmp) and <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/index-eng.php>.

## Reference Documentation

Acts and regulations of Canada are available on the Department of Justice Web Site [www.justice.gc.ca](http://www.justice.gc.ca).

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

## Good Manufacturing Practices

Guides (GUI), Policies (POL) and Forms (FRM) that relate to GMPs are available on Health Canada's Web Site in the Compliance and Enforcement section under Good Manufacturing Practices. [www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/index-eng.php)

- Good Manufacturing Practices Guidelines 2009 Edition (GUI-0001)
- Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines – Veterinary Drugs (GUI-0012)
- Alternate Sample Retention Site Guidelines (GUI-0014)
- Risk Classification of Good Manufacturing Practices Observations (GUI-0023)
- Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines – Schedule C Drugs (GUI-0026)
- Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)
- Good Manufacturing Practices Guidelines for Medical Gases (GUI-0031)
- Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/ Labellers, Distributors and Importers (GUI-0042)
- Annex 11 to the Current Edition of the Good Manufacturing Practices Guidelines – Computerised Systems (GUI-0050)
- Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines – Selected Category IV Monograph Drugs (GUI-0066)
- Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)
- Guidance on Evidence to Demonstrate Drug Good Manufacturing Practices Compliance of Foreign Sites (GUI-0080)
- Good Manufacturing Practices (GMP) and Establishment Licensing Enforcement Directive (POL-0004)
- GMP Inspection Policy for Canadian Drug Establishments (POL-0011)

## Additional Reference Material (continued)

### Establishment Licences

- Guidance on Drug Establishment Licences (GUI-0002)
- Good Manufacturing Practices (GMP) and Establishment Licensing Enforcement Directive (POL-0004)
- Drug Establishment Licence Application: Form and Instructions
- Fee Reduction Request form for Drug Establishment Licence

A Questions and Answers document is available on our website at:  
<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/question/index-eng.php>.

Should this list not address your question, please forward your question via e-mail to:  
[gmp\\_questions\\_bpf@hc-sc.gc.ca](mailto:gmp_questions_bpf@hc-sc.gc.ca), or by fax to 613-957-6709.

## Tell Us What You Think

The Inspectorate is committed to continuous improvement in the delivery of its programs and services. Our new pre-application information package is just one way we are working towards helping the health products industry with information and guidance towards achieving world class excellence in safety and quality standards.

To help us develop better and more effective tools in support of our shared goals, please do not hesitate to tell us what you think.

- Did you find the new pre-application package helpful?
- Did the new pre-application package answer most of your questions related to the drug GMP inspection process for wholesalers, importers and distributors?
- Do you have any suggestions on other information or tools that you believe could help you better prepare for a drug GMP inspection?

Contact us with any comments or questions related to this package by email at: [gmp\\_questions\\_bpf@hc-sc.gc.ca](mailto:gmp_questions_bpf@hc-sc.gc.ca) or fax at 613-957-6709, with a subject heading of “Pre-Application Package”.