

Natural and Non-prescription Health Products Directorate (NNHPD) – Natural Health Products Good Manufacturing Practices (NHP GMP)

Webinar

February 2021



Overview

- GMP – A short summary
- The 4 “P” of GMP:
 - Places,
 - People,
 - Processes (and procedures),
 - Product
- More information about GMP

Goal of Good Manufacturing Practices

- GMPs are ongoing measures intended to:
 - ensure an effective overall approach to product quality control and risk management
 - produce safe and effective NHPs
 - ensure a product consistency between different batches / throughout years
- GMPs are often summarized by their 4 key elements: Places, People, Processes (and Procedures) and Product.

Goal of Good Manufacturing Practices

- GMPs answer questions such as:
 - Has my equipment been properly calibrated?
 - Can I trace the manufacturing process from beginning to end with controlled documents?
 - How is my staff properly trained and knows the processes and procedures within my company?
 - How are my products tested?
 - How can I demonstrate all of this to an auditor?

Good Manufacturing Practices: A Responsibility set in the Regulations

- Per section 43 of the *Natural Health Products Regulations (NHPR)*:

No person shall sell a Natural Health Product (NHP) unless it is manufactured, packaged, labelled, distributed or stored in accordance with Good Manufacturing Practices (GMP).
- If importing NHPs, the same requirements apply:

It is the final responsibility of the importer to ensure that the NHP is manufactured, packaged, labelled, imported, distributed or stored in accordance with GMP or equivalent and that the product meets its specifications before being released for sale regardless who is the Product Licence holder (i.e. “NPN owner”).

Good Manufacturing Practices: A Responsibility set in the Regulations

- This presentation:
 - represents current guidance documentation (2015);
 - addresses manufacturers, packagers, labellers and/or importers of NHPs for sale in Canada to facilitate compliance with GMP requirements.

Note: The Natural and Non-prescription Health Products Directorate (NNHPD) recognizes that there are various ways of meeting GMPs and producing safe and effective NHPs. Thus, alternative means of complying with the Regulations may be considered by the NNHPD when an appropriate rationale or justification is provided.

Overview

- GMP – A short summary
- The 4 “P” of GMP:
 - **Places** (Premises and Equipment),
 - People,
 - Processes (and procedures),
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NHPR Section 45

Premises

(1) Every natural health product shall be manufactured, packaged, labelled and stored in premises that are designed, constructed and maintained in a manner that permits the activity to be conducted under sanitary conditions, and in particular that

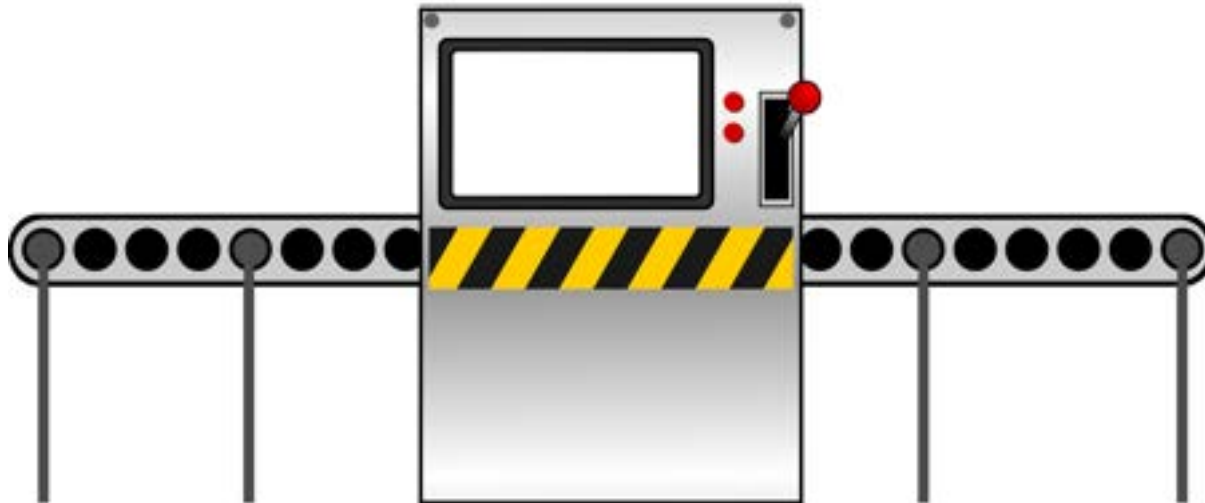
- (a) permits the premises to be kept clean and orderly;*
- (b) permits the effective cleaning of all surfaces in the premises;*
- (c) permits the natural health product to be stored or processed appropriately;*
- (d) prevents the contamination of the natural health product; and*
- (e) prevents the addition of an extraneous substance to the natural health product.*

(2) Every natural health product shall be stored under conditions that will maintain the quality and safety of the natural health product.

Premises

GOAL: to keep facilities organized and clean, preventing mix-ups, adulteration or cross contamination during production

- Production vs. Non-Production Areas
 - Should be clearly separated and designated
 - Manufacturing, packaging and testing areas may be further segregated



Premises – Production Areas

- Production Areas
 - Design facilities to facilitate maintenance, cleaning and waste disposal
 - Institute controls to minimize mix-ups/adulteration
 - Seal doors, windows and all surfaces
 - Ensure doors, windows and all surfaces have no cracks or holes
 - Ensure all surfaces permit cleaning and are made of materials that do not shed particles
 - Restrict direct entry from outdoors to production areas during operations

Premises – Production Areas

- Production Areas
 - Remove and prevent pests from entering
 - Ensure floor drains are screened and trapped
 - Control humidity and temperature where products require
 - Provide adequate filtration, ventilation and lighting
 - Use explosion proof bulbs/fixtures
 - Identify outlets for liquids and gases

Premises – Storage Areas

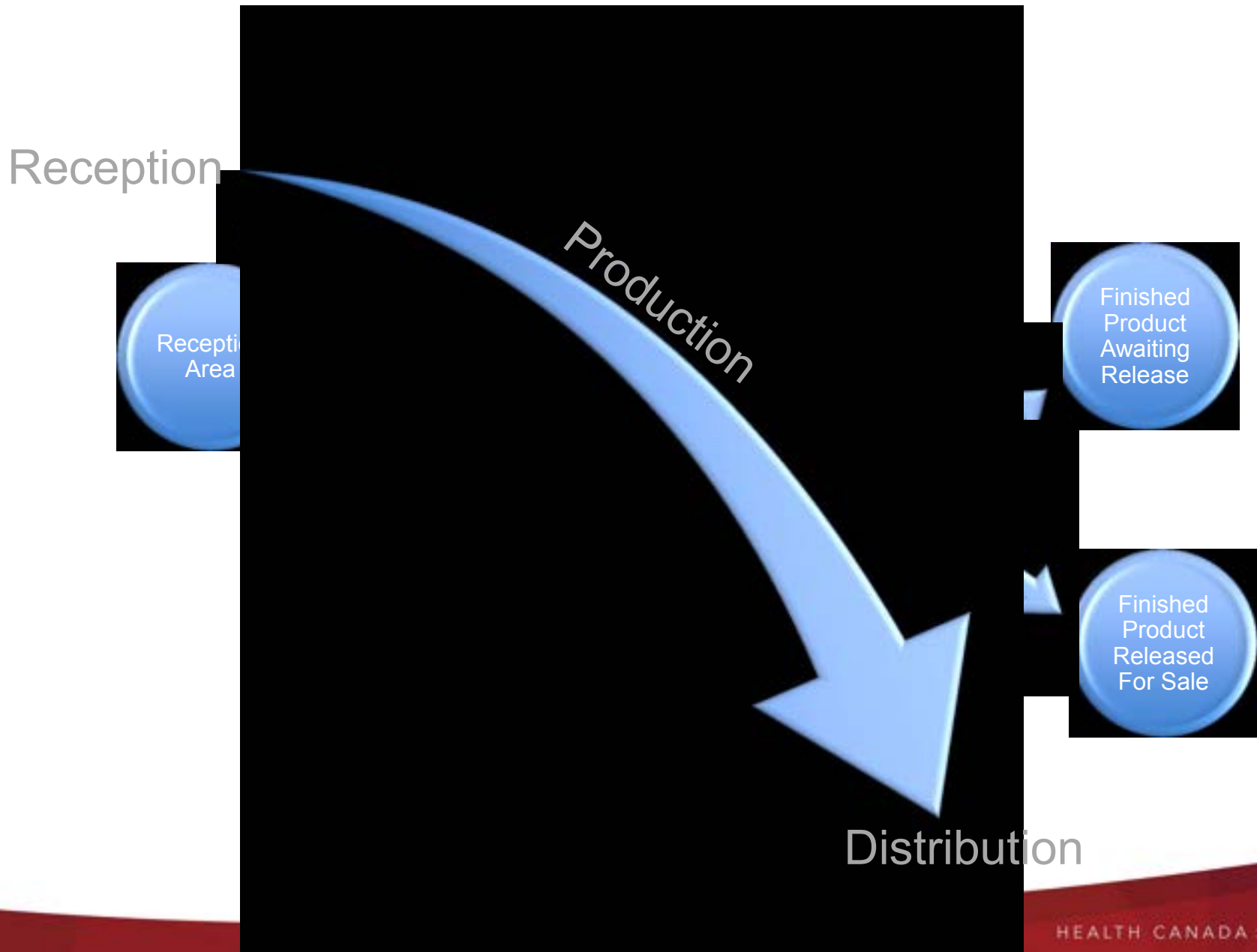
- Protect materials in storage from chemical and/or microbial contamination, and deterioration
- Physical **quarantine** areas should be clearly marked

Table 1: Example of storage areas within a facility*

Manufacturer	Importer
Reception area	Reception area
Miscellaneous products (ex: cleaning agents)	Miscellaneous products (ex: cleaning agents)
Released raw materials	-
In-process materials	-
Finished products awaiting release	Finished products awaiting release
Finished products released for sale	Finished products released for sale
Quarantine area	Quarantine area
Sample storage	Sample storage (if not at the foreign site)

* For example purpose only

Figure 1: Example of storage areas within a manufacturing facility



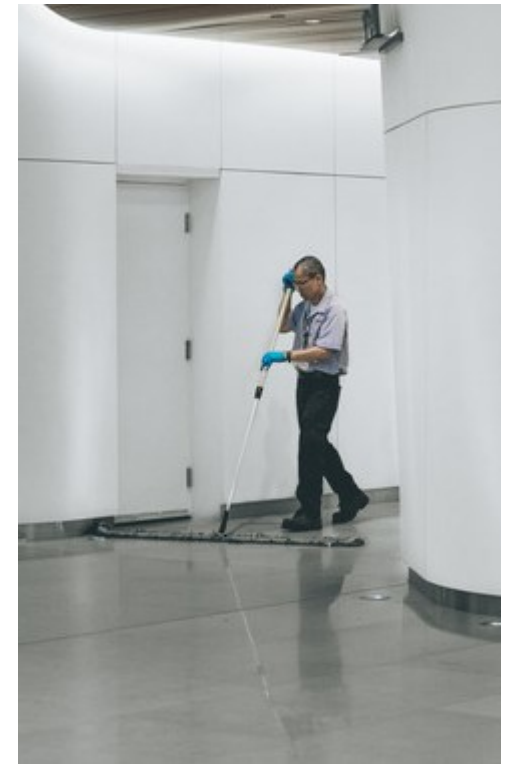
Premises – Non-Production Areas

- Non-Production Areas
 - Permit good sanitary practices
 - Separate toilets, wash stations, change rooms and break areas from the production areas
 - Ensure water supply meets the Canadian Drinking Water Guidelines, WHO guidelines for Drinking Water Quality, etc.
 - Install refuse receptacles and follow waste disposal practices



GMP Evidence for Premises

- Examples of evidence may include but are not limited to:
 - Detailed floor plan showing production and non-production areas
 - Ventilation filters change record
 - Water quality test record
 - Daily temp., humidity, light control records
 - Facility maintenance records
 - Pest control logs or inspection reports
 - Janitorial duty schedule, cleaning records
 - Relevant standard operating procedures (SOPs)



NHPR Section 46

Equipment

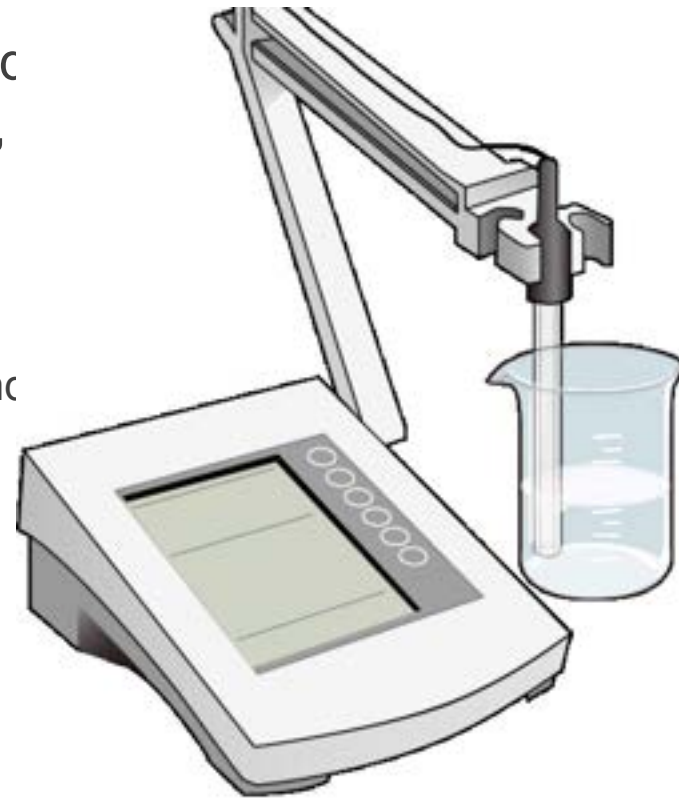
Every natural health product shall be manufactured, packaged, labelled and stored using equipment that is designed, constructed, maintained, operated and arranged in a manner that

- (a) permits the effective cleaning of its surfaces;*
- (b) permits it to function in accordance with its intended use;*
- (c) prevents it from contaminating the natural health product; and*
- (d) prevents it from adding an extraneous substance to the natural health product.*

Equipment

GOAL: prevent the contamination of NHPs by other products, dust, cleaning agents or by foreign materials (e.g. rust, lubricant)

- Production equipment is designed, constructed, installed, and maintained to facilitate cleaning, sanitizing (where appropriate), and its inspection and the surrounding areas. Specifically, this means the following:
 - establishing and following procedures for cleaning and maintaining equipment and utensils used to manufacture products;
 - avoiding temporary repairs (e.g. with tape); and
 - clearly labelling defective equipment as such.
- Each piece of production equipment is operated according to its SOP.



Equipment

GOAL: prevent the contamination of NHPs by other products, dust, cleaning agents or by foreign materials (e.g. rust, lubricant)

- Production equipment and utensils in direct contact with materials and products are constructed of smooth, non-reactive and non-toxic materials, and are designed to withstand repeated cleaning.
- Avoid the possibility of lubricant or other maintenance materials contaminating the products by ensuring proper equipment design.
- Properly maintain instruments, including laboratory equipment, to ensure that they remain accurate, and retain records.



GMP Evidence for Equipment

- Examples of evidence may include but are not limited to:
 - Preventative maintenance schedule for equipment.
 - Equipment cleaning and maintenance logs.
 - Equipment usage logs.
 - Calibration records for essential equipment.
 - Relevant SOPs and associated blank record templates.



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NHPR Section 47

Personnel

Every natural health product shall be manufactured, packaged, labelled and stored by personnel who are qualified by education, training or experience to perform their respective tasks.

Personnel

GOAL: To have the appropriate personnel with sufficient training to manufacture, package, label, import, or store NHPs of high quality.

The operations involved in the preparation (or handling) of quality NHPs requires:

- Attention to details (e.g. Good Documentation Practices (GDP), identify deviations from procedures)
- Constant monitoring

Inadequate personnel qualification or training often leads to GMP issues.



Personnel

To meet the requirement:

- Individuals in charge of manufacturing and quality assurance have adequate education, training, and/or practical experience to control and/or supervise the activities.
- All personnel have appropriate education (including on-going GMP or other training) and/or have the practical experience necessary to perform their assigned duties.
- It is important to maintain records of education and training and update when needed.

GMP Evidence for Personnel

- Evidence may include but is not limited to:
 - Job descriptions.
 - Resume, C.V., or copy of educational degrees (shows the person meets their job description).
 - Employee training schedule and/or attendance records (demonstrating on-going relevant training).
 - Certificates of completion (i.e. GMP).
 - Relevant SOPs and associated blank record templates related to personnel

NHPR Section 51

Quality Assurance

- (1) Every manufacturer, packager, labeller, importer and distributor shall
 - (a) have a quality assurance person who
 - (i) is responsible for assuring the quality of the natural health product before it is made available for sale, and*
 - (ii) has training, experience and technical knowledge relating to the activity conducted and the requirements of this Part; and**
 - (b) investigate and record every complaint received in respect of the quality of the natural health product and, if necessary, take corrective action.**
- (2) Every natural health product shall be manufactured, packaged and labelled using only material that, prior to its use in the activity, has been approved for that use by a quality assurance person.*
- (3) Every natural health product shall be manufactured, packaged, labelled and stored using methods and procedures that, prior to their implementation, have been approved by a quality assurance person.*
- (4) Every lot or batch of a natural health product shall be approved by a quality assurance person before it is made available for sale.*
- (5) Every natural health product that is sold and subsequently returned to its manufacturer, packager, labeller, importer or distributor, as the case may be, shall be approved by a quality assurance person before that natural health product may be made available for resale.*

Quality Assurance

GOAL: to ensure every batch of product is of satisfactory quality and suitable for sale

The Quality Assurance Person (QAP) is responsible for ensuring:

- Products are properly tested
- Products meet specifications prior to release
- Specifications are correct
- Release of products before sale
- Quality Technical Agreements are signed and maintained
- Corrective And Preventative Action plans (CAPA) are developed and implemented



Quality Assurance

QAP responsibilities related to testing:

- Ensure that laboratories (in-house and contract) are capable of performing all tasks assigned to them
- Maintain laboratory records of tests and investigations
- Approve or reject all specifications, test methods, controls and results



GMP Evidence for Quality Assurance

- Evidence may include but is not limited to:
 - Approved finished product specification by the QAP
 - Master production documents and batch records
 - Finished product specification change control log
 - Certificates of analysis for raw materials and/or finished products
 - Records for Out of Specification (OOS) results which includes **investigations into root causes**
 - SOPs/templates related to quality assurance
 - Organization structure which clearly demonstrates independence of function (e.g. from activities such as manufacturing)

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NHPR Sections 48

Sanitation Program

Every natural health product shall be manufactured, packaged, labelled and stored in accordance with a sanitation program that sets out

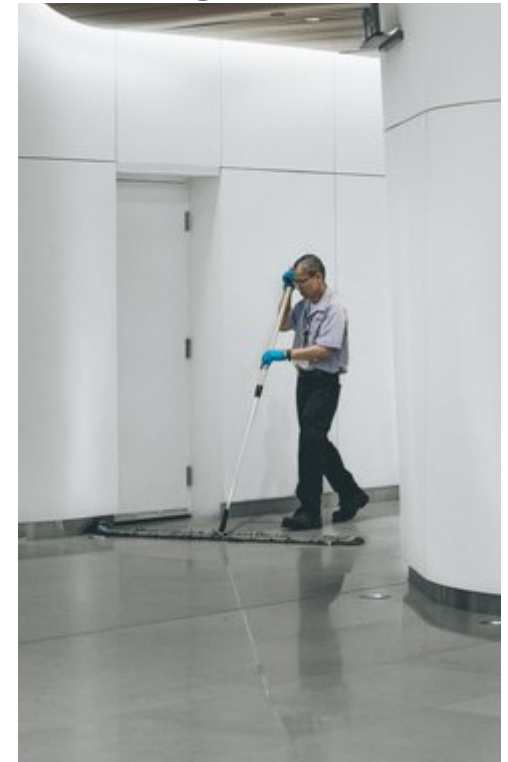
- (a) procedures for effectively cleaning the premises in which the activity is conducted;*
- (b) procedures for effectively cleaning the equipment used in the activity;*
- (c) procedures for handling any substance used in the activity; and*
- (d) all requirements, in respect of the health, the hygienic behaviour and the clothing of the personnel who are involved in the activity, that are necessary to ensure that the activity is conducted in sanitary conditions.*

Sanitation Program

GOAL: To ensure areas that are free from environmental contamination and free from contamination by another product.

There are 2 important aspects to the sanitation program:

- Facility sanitation program:
 - Includes these elements & information:
 - cleaning procedures for facilities and processing equipment;
 - list of cleaning/sanitizing agents, used and stored in such a manner to prevent cross-contamination;
 - cleaning frequencies and cleaning lines between the production of different products;
 - provisions for storing cleaned equipment to avoid recontamination;
 - clear identification of dirty/clean equipment and utensils; and
 - procedures for the destruction and disposal of waste materials and debris.



Sanitation Program



- Health and hygiene program:
 - Personnel having direct contact with materials and unpackaged products or who use processing equipment
 - May include these elements (when applicable):
 - report to supervisors any health conditions of personnel that could adversely affect products and respect quarantine times imposed by public health authorities;
 - remove from the facility any person who has, or appears to have, an illness that could be a source of product contamination, until the disease or condition is no longer a risk for possible product contamination
 - wear outer garments, including shoe coverings, to prevent contamination of products and equipment;
 - Remove unsecured jewellery (covering hand jewellery that cannot be removed); wear hairnets, caps, beard covers or other effective hair restraints;
 - wash hands thoroughly before starting work and at any other time when hands may have become soiled or contaminated; using intact, clean and sanitary gloves;
 - store clothing or other personal effects outside of processing areas;
 - refrain from consuming food and drink, as well as chewing products or smoking, in production areas;

GMP Evidence for Sanitation

- Evidence may include but is not limited to:
 - Facility cleaning schedule and cleaning completion logs.
 - Microbiological surface test results.
 - Personnel hygiene training log.
 - Relevant SOPs and associated blank record templates related to sanitation.

NHPR Sections 49-50

Operations

49 *Every natural health product shall be manufactured, packaged, labelled and stored in accordance with standard operating procedures that are designed to ensure that the activity is conducted in accordance with the requirements of this Part.*

50 *Every manufacturer, packager, labeller, importer and distributor shall establish and maintain a system of control that permits the rapid and complete recall of every lot or batch of the natural health product that has been made available for sale.*

Operations

GOAL: to set practices and procedures in place that maintain the integrity of NHPs throughout production

Standard Operating Procedure (SOP):

- Specific to a task, process or procedure in your operation
- Describes the steps necessary to complete a task in accordance with regulations, GMPs and/or your own standards.
- Provides adequate information to keep results consistent from person to person
- Used to train employees

Operations – How to Create an SOP

1. Header contains the SOP title, number and version
2. Footer contains author name, page number, dates of creation and approval
3. Details of Approval appears at the beginning or end of the SOP (name of author, reviewer and approval by QAP)

 Health Canada Santé Canada				STANDARD OPERATING PROCEDURE	
Title: Name of the SOP					
Division:		SMD		Document #	SOP-SLAU-XXX-RXX
Unit:		SLAU		Supersedes:	New
Prepared by:	AO name	Date:	Month <u>dd</u> , <u>yyyy</u>	Issuance Date:	Month <u>dd</u> , <u>yyyy</u>
Verified by:	AO name	Date:	Month <u>dd</u> , <u>yyyy</u>	Review Date:	N/A (enter date if it is a revision)
Approved by:	UH name	Date:	Month <u>dd</u> , <u>yyyy</u>		

Operations – How to Create an SOP

4. Divided into sections:

- A. **Scope:** gives the purpose of the activity and to which department it applies
- B. **Responsibilities:** mentions all job positions that should follow the SOP
- C. **Materials:** lists equipment, devices necessary for this activity
- D. **Safety:** when applicable, outlines safety measures for the activity
- E. **Procedure:** step by step instructions to perform the activity
- F. **Records:** states where to annotate and keep related records
- G. **Attachments:** annexes, forms to be completed with the activity
- H. **History:** tracks dates of revision and all changes made

5. Additional sections can be added for clarity

6. Pictures may be used to enhance understanding

Operations – Good Documentation Practices

1. Document completion:

- Completed at the same time as the documented event
- Checked for errors and accuracy

2. Approval:

- Approved, signed and dated by authorized personnel (e.g. Quality assurance person)

3. Handwritten entries:

- Written in indelible ink
- Checked by second person verification
- Unused spaces are crossed out or “N/A”
- Ditto marks not acceptable
- Stamps may not replace signatures



Operations – Good Documentation Practices

4. Copies:

- Must be clear and legible
- Does not introduce new errors

5. Document maintenance:

- Systems are regularly reviewed and validated to be kept up to date
- Documents retained for appropriate duration
- Records are backed up

6. Document modification:

- Handwritten modifications are signed and dated (no backdating)
- Original text still visible (e.g. no White-out)
- Reason for alteration noted
- Controls prevent inadvertent use of old versions
- A history (audit trail) of changes and deletions is necessary: **CoAs**

Operations – Tracking Documents

- Prepare a **master production document** for the manufacture of each product
 - QAP must review and approve the document
- Prepare and follow **batch records** for each batch of product
 - Must be an accurate representation of the master production document and include documentation that each significant step in the manufacturing process was completed
 - Each batch of manufactured product must be tracked by an individual **batch number**
- Identify each package with a **lot number** and expiry date
 - Tracks the manufacturing history and control of the lot

Operations – Tracking Documents

- Record deviations from manufacturing processes, standards and test methods
 - Assess whether the deviation has an impact on the product
 - If OOS product, institute investigation and/or CAPA
 - Final approval by the QAP
- Establish and document the roles and responsibilities of each party involved in contracted operations
 - Can be demonstrated by an inspection and/or an evaluation of the contractor



GMP Evidence for Operations

- Evidence may include but is not limited to:
 - Master production documents
 - Batch records
 - Certificates of analysis for finished products and/or raw materials
 - Finished Product specification change control logs
 - Records for Out of specification (OOS) results and ensuing investigation report
 - Product complaint logs, resulting action and investigation report
 - List and copies of SOPs in use for the production run
- All records related to a product have to be kept at least one year following the expiry date of the NHP to which that record relates (stated in s. 58 of the Regulations).

Records – Specified under s.53 to 58 of the NHPR

Record keeping requirements by activities						
Record	Activity	Manufacturer	Packager	Labeller	Importer	Distributor
Master production document		Maintain	None	None	Maintain	None
Batch record		Maintain	Maintain	Maintain	Access	None
Test results: raw material		Maintain	None	None	Maintain	None
Test results: packaging material		None	Maintain	None	Access	None
Test results: finished product		Maintain	None	None	Maintain	None
Specifications: raw material		Maintain	None	None	Access	None
Specifications: packaging material		None	Maintain	None	Access	None
Specifications: finished product		Maintain	None	None	Maintain	None
Stability		Maintain	None	None	Maintain	None
Ingredients list		Maintain	None	None	Maintain	None
Products list		Maintain	Maintain	Maintain	Maintain	Maintain
Complaints		Maintain	Maintain	Maintain	Maintain	Maintain
Recall		Maintain	Maintain	Maintain	Maintain	Maintain
Sanitation program		Maintain	Maintain	Maintain	Maintain	Maintain

Maintain: Indicates that records must be retained and readily available by that party

Access: Refers only to the need to make sure that records are available in timely manner.

None: Records that are not required to be kept under the Regulation.

NHPR Sections 62

Recall Reporting

Every manufacturer, importer or distributor who commences a recall of a natural health product shall provide the Minister with the following information in respect of that natural health product within three days after the day on which the recall is commenced:

- (a) the proper name and the common name of each medicinal ingredient that it contains;*
- (b) each brand name under which it is sold;*
- (c) its product number;*
- (d) the number of each lot or batch recalled;*
- (e) the name and address of each manufacturer, importer and distributor of the natural health product;*
- (f) the reasons for commencing the recall;*
- (g) the quantity manufactured or imported into Canada;*
- (h) the quantity that was distributed in Canada;*
- (i) the quantity remaining in the possession of each manufacturer, importer and distributor of the natural health product; and*
- (j) a description of any other action that the manufacturer, importer or distributor, as the case may be, is taking in respect of the recall.*

Recall Reporting

GOAL: ensuring that all the pertinent information is available and all products on the market are given the correct disposition.

Establish written procedures that define controls to ensure the effective recall of a product, including:

- identifying individual(s) responsible for initiating and coordinating recall;
- ensuring that the recall procedure can be put into operation at any time, during and outside normal working hours;
- ensuring that the recall procedure outlines the steps for implementing a recall;
- maintaining distribution records to enable tracing of each lot;
- identifying and storing recalled products separately in a secure area until further action is determined;
- assessing at intervals and recording in writing, the progress and efficacy of the recall, and issue a final report, including a final reconciliation; and
- notifying all Canadian and foreign sites involved in the manufacture, import, or distribution of the recalled products.

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NHPR Section 44

Specifications

- (1) Every natural health product available for sale shall comply with the specifications submitted in respect of that natural health product under paragraph 5(i) and with every change to those specifications made by the product licence holder.*
- (2) The specifications shall contain the following information:*
 - (a) detailed information respecting the purity of the natural health product, including statements indicating its purity tolerances;*
 - (b) for each medicinal ingredient of the natural health product, detailed information respecting its quantity per dosage unit and its identity, including statements indicating its quantity and identity tolerances;*
 - (c) if a representation relating to the potency of a medicinal ingredient is to be shown on a label of the natural health product, detailed information respecting the potency of the medicinal ingredient, including statements indicating its potency tolerances; and*
 - (d) a description of the methods used for testing or examining the natural health product.*
- (3) The specifications and every change to those specifications shall be approved by a quality assurance person.*

Specifications

GOAL: to ensure products consistently meet their specifications as outlined in the Quality of Natural Health Products Guide

- Both manufacturers and importers need to have specifications on-site
- Compare test results / certificates of analyses (CoA's) to specifications before release for sale
- Document this comparison against the specifications through a formal "QA Release" record
- Transfer released products to the correct storage area



Specifications – Medicinal Ingredients

- Must be identified, quantified and tolerance limits clearly stated
- Quantity must conform to the label claims and the specifications in the product licence (NPN)
- Tolerance must conform to the relevant pharmacopoeial standard and/or must be within the established tolerance limits, i.e. 80-120%* or relevant pharmacopoeial standard.



* Exceptions apply for various products

Specifications – Medicinal Ingredients

Table 2: NNHPD required physical and medicinal ingredient tests

Test Parameter	Tolerance Limits
<i>Physical Description</i>	Color, shape, other tolerance limits as appropriate
<i>Identity of each Medicinal ingredient (raw material or finished product stage)</i>	As appropriate (examples below)

Identification Technique Examples

- **Botanical products/extracts:** combination of microscopic and chemical techniques to confirm species identity
- **Isolates and synthetic duplicates:** physical description and chemical identification tests (e.g. IR spectroscopy)
- **Enzymes:** details of source organism, gel electrophoresis, substrate specificity, isoelectric point, specific activity
- **Probiotics:** qualitative description of culture (e.g. Latin name), strain identity verified by phenotypic and genotypic methods

Specifications – Exemptions

Medicinal Ingredient exemptions (all of the following are required):

- Acceptable justification for quantification by input*
- Certificates of Analysis for raw materials quantified by input
- Batch record with target quantities and range of variation indicated
- Weight variation on finished dosage form



* Quantification by assay must be demonstrated to be too complex

Specifications – Microbial Contaminants

- Testing done according to pharmacopoeia, WHO or other recognized methods
- Tolerance limits must comply with relevant pharmacopoeia

Table 3: NNHPD required microbial contaminant tests

Requirements:
Total viable aerobic plate count
Contaminating fungi (yeast and mould)
<i>Salmonella</i> spp.
<i>Escherichia coli</i>
<i>Staphylococcus aureus</i>
<i>Pseudomonas aeruginosa</i>
Other as required by pharmacopoeias



Specifications – Exemptions

- Exemptions are accepted with scientific rationales that include valid test methods, on multiple batches, throughout the product's life-cycle.



Examples of microbiological exemptions*:

- Low water activity (such as per USP <1112>)**
- Antimicrobial properties**
- Historical testing shows low microbial load**
- Proposed testing frequency on subsequent batches**

*Rationales for reduced testing, not a complete exemption

**Must be supported by data and scientific evidence

Specifications – Chemical Contaminants

Table 4: NNHPD chemical contaminant limits (Quality of Natural Health Product Guide, Appendix 3)

Test Parameter		Tolerance Limits
<i>Heavy Metals</i>	Arsenic <i>Inorganic:</i> <i>Organic:</i>	Oral: <0.14 µg/kg b.w./day <0.03 µg/ kg b.w./day <20 µg/ kg b.w./day Topical: 3 ppm
	Cadmium	Oral: < 0.09 µg/ kg b.w./day Topical: 3 ppm
	Lead	Oral: < 0.14 µg/ kg b.w./day Topical: 10 ppm
	Mercury <i>Methylmercury:</i>	Oral: < 0.29 µg/ kg b.w./day < 0.029 µg/ kg b.w./day Topical: 1 ppm
	Chromium IV	Oral: < 0.29 µg/ kg b.w./day Topical: 5 ppm
<i>Solvent Residues</i>		ICH or USP limits
<i>Pesticides</i>		USP limits

Specifications – Examples of exemptions

Pesticide exemptions:

- Ingredients are organic and organic certification is provided
- OR
- Ingredients are synthetic or individually tested for pesticides

Heavy Metal exemptions:

- Raw materials are synthetic, pharmacopoeial grade or individually tested
- Companies can also consult, for more information, the ICH Q3D – Guideline for elemental impurities:
https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf

GMP Evidence for Specifications

- Examples of evidence may include but are not limited to:
 - Product specifications for all products to be manufactured, packaged, labeled or imported to the site
 - Records of approval of finished product specifications by the Quality Assurance Person (QAP)
 - Record of approval from the QAP regarding any changes to the finished product specifications (and amend the product licence as per section 11 (1) of the Regulation)
 - SOPs/templates for finished product testing
 - CoA for each lot of finished product
- Additional Evidence for Importers:
 - Quality Technical Agreements should be provided clearly stating who is responsible for finished product testing
 - An independent confirmatory testing program is encouraged for products tested by the supplier

NHPR Section 52

Stability

Every manufacturer and every importer shall determine the period of time during which, after being packaged for sale, the natural health product will maintain its purity and physical characteristics and its medicinal ingredients will maintain their quantity per dosage unit and their potency when

- (a) it is stored under its recommended storage conditions; or*
- (b) if it does not have recommended storage conditions, it is stored at room temperature.*

Stability Period

GOAL: to set an expiry date by determining how long products can remain within specifications under storage conditions

SL Holders must demonstrate:

- Physical description at expiry
- Microbiological contaminant testing at expiry (or demonstration of exemption)
- Medicinal ingredients quantities at expiry
- Testing for heavy metals, pesticides and solvent not required at expiry
- **Importers** must have this information available even if tested off-site
- **Contract manufacturers** must have this information available as well



Stability Period – Methods

Suggested process (based on ICH Q1)

Real-Time Study:

- Must be performed until expiry
- Used to confirm and/or adjust the expiry date

Accelerated Study:

- Starting point to make initial expiry determination
- Should be performed in tandem with real-time studies
- Can be used increase the stability period by up to 12 months (refer to ICH Q1E, appendix A)
- Minimum test time points: 0, 3, 6 months

Stability Period – Storage Conditions

Table 5: Suggested general case storage conditions (from ICH Q1A 2.1.7.1.)

Study	Storage Condition	Minimum Time
Long Term* (Real Time)	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH [†]	Until expiry
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2° C/60% RH ± 5% RH or 30° C ± 2° C/65% RH ± 5% RH.

[†]Please note that the World Health Organisation (WHO) stability guideline lists Canada as 30° C ± 2° C/65% RH ± 5% RH for stability studies.

GMP Evidence for Stability

- Evidence may include but is not limited to:
 - CoA and summary reports demonstrating that every product meets specifications at expiry
 - Stability testing protocol, stability failure investigations and recalls, and details for establishing a longer shelf life
 - Testing results as indicated in the stability testing protocol (i.e. T=0, T=6 months, T=1 year, etc.)
 - Relevant SOPs and associated blank record templates
- Additional Evidence for Importers:
 - Quality Technical Agreements should be provided clearly stating who is responsible for stability testing
 - An independent confirmatory testing program is encouraged for products tested by the supplier

NHPR Section 61

Samples

- (1) Subject to subsection (3), if the Minister has reasonable grounds to believe that a lot or batch of a natural health product made available for sale may result in injury to the health of a purchaser or consumer, the Minister may require the manufacturer, importer or distributor to provide a sample of that lot or batch.*
- (2) The sample shall be of sufficient quantity to enable a determination of whether the lot or batch of the natural health product complies with the specifications for that natural health product.*
- (3) The Minister shall not require a sample of a lot or batch referred to in subsection (1) to be provided if more than one year has elapsed since the expiry date of that natural health product.*

Samples

GOAL: maintain evidence of product quality should an investigation ensue (e.g. customer complaint, product recall)

- Retain an **adequate number and of sufficient size** each lot of a finished product (tip: consult with your QA to know how much samples are needed for testing).
- In their final trade packages or in containers of the same material and construction.
- Stored in the environmental conditions listed on the label.
- Maintained at least one year after the product's expiry date.
- **Importers** may have the manufacturer or a designated third party keep samples for them, provided the samples are readily available.
- **Contract manufacturers** must keep samples as well.

GMP Evidence for Samples

- Evidence may include but is not limited to:
 - List of all samples being held, including product name and lot number.
 - Description, SOP, or record confirming that the samples are held and maintained for at least one year past the product expiration date.
 - Approved (by Quality Assurance) sampling protocol.
 - Samples made available within a reasonable timeline upon request



NHPR Section 59

Sterile NHPs

59 Every natural health product that is intended to be sterile shall be manufactured and packaged

- (a) in a separate and enclosed area;*
- (b) under the supervision of a person trained in microbiology; and*
- (c) using a method scientifically proven to ensure its sterility.*

Sterile NHPs

GOAL: ensure the product meets the definition of a sterile product, whether through manufacturing or terminal sterilization.

- Manufacturers, packagers and importers shall treat all sterile NHPs in the same manner as any other sterile health product.
- Refer to the [annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs \(GUI-0119\)](#) from Health Canada (available online)



For more information about GMP:

Refer to the **Good Manufacturing Practices Guidance Document:**

<https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/good-manufacturing-practices.html>

44 - Specifications

Finished Product Specification Form User Guide (Appendix 2):

<https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/finished-product-specifications-form-user-guide.html>

Quality of Natural Health Product Guide:

<https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/quality-guide.html>

Compendium of Monographs:

<http://webprod.hc-sc.gc.ca/nhp/bdpsn/monosReq.do?lang=eng>

49 & 50 – Operations

GMP Guidance Document, appendixes 3 and 4:

Appendix 3 discusses Good Documentation Practices and appendix 4 describes Standard Operating Procedures

51 – Quality Assurance

GMP Guidance Document appendix 5:

Appendix 5 has a list of GMP observations and their risk ratings; the QAP should ensure the observations listed are not present within the company

52 – Stability Period

ICH Q1 (especially Q1A and Q1E):

<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>

59 & 60 – Sterile NHPs

Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119):

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-annex-1-manufacture-sterile-drugs-0119/document.html>

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