Good Manufacturing Practices

Webinar

September 2018

Overview

- GMP Summary
- Premises (NHPR S.45)
- Specifications (NHPR S.44)
- Operations (NHPR S.49-50)
- Quality Assurance (NHPR S.51)
- Stability (NHPR S.52)

Good Manufacturing Practices: A Responsibility set in the Regulations

- As stated in 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. The product meets its specifications before being released for sale.

2017 Compliance Monitoring Project: Most Common Deficiencies Observed

Relevant NHPR section	Examples of observations
44 – Specifications	• Specifications unavailable or incomplete
45 – Premises	• No storage or quarantine area • No separation of production and non-production area
49 & 50 – Operations	• Deficient Standard Operating Procedures (SOP) • Incomplete/insufficient batch records • Lack of Quality technical agreements between contractors, Product licence and/or Site Licence holders

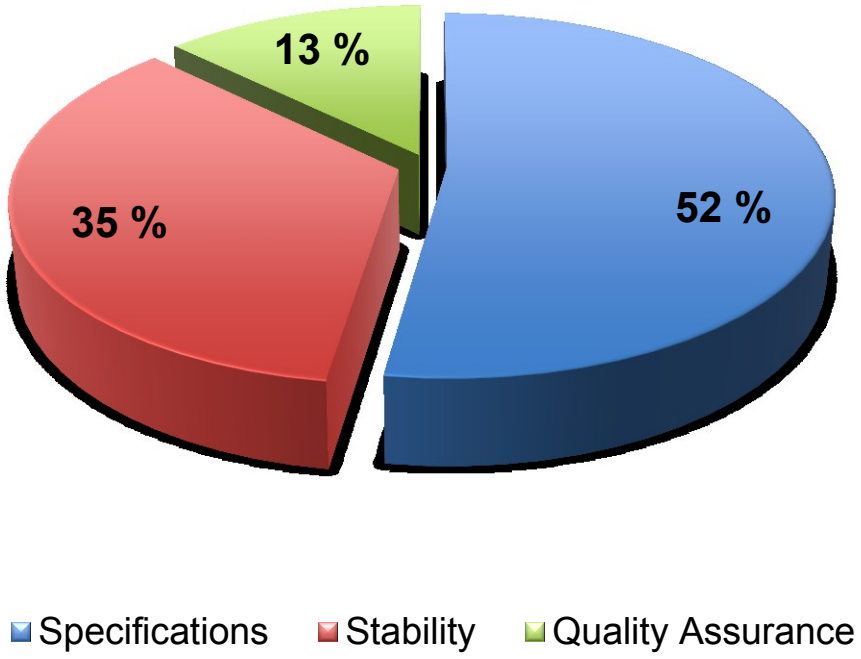
51 – Quality Assurance	• Products not properly assessed against their specifications
	  • Partial or no testing
	  • Not assessed by importer

52 – Stability Period	• No data, scientific rationale or program available to establish a product's shelf life.

Common Site Licence Submission Deficiencies

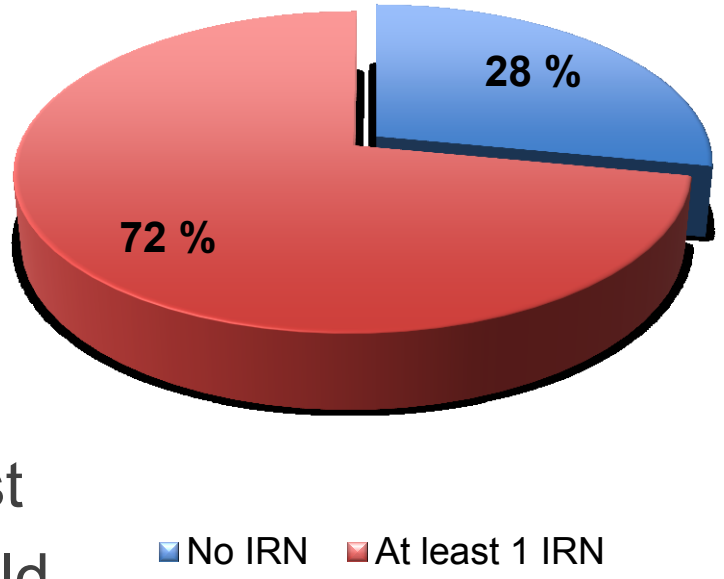
- The observations from the Compliance Monitoring Project correlate with the deficiencies observed during Site Licensing.

- Most common observation
  1. Specifications (S.44)
  2. Stability (S. 52)
  3. Quality Assurance (S. 51)



Common Site Licence Submission Deficiencies

- The observations from the Compliance Monitoring Project correlate with the deficiencies observed during Site Licensing.
- 72% of all submissions to NNHPD require at least 1 Information Request Notice
- Addressing the deficiencies most commonly observed will also yield benefits during Site Licensing.



Good Manufacturing Practices: Tips and tricks to meet GMP compliance

Relevant NHPR section	Guidance available
44 – Specifications	• Finished Product Specification Form User Guide, appendix 2 • Quality of Natural Health Product Guide • Good Manufacturing Practices Guidance Document, sections 2.4.1 and appendix 5 • NNHPD's Compendium of Monographs (on Health Canada's website)
45 – Premises	• Good Manufacturing Practices Guidance Document, sections 2.1.1 and appendix 5
49 & 50 – Operations	• Good Manufacturing Practices Guidance Document, sections 2.3.2 and appendixes 3, 4 & 5
51 – Quality Assurance	• Good Manufacturing Practices Guidance Document, sections 2.2.2 and appendix 5
52 – Stability Period	• Good Manufacturing Practices Guidance Document, sections 2.4.2 and appendix 5 • ICH Q1 (especially Q1A and Q1E)

NHPR Section 45

Premises

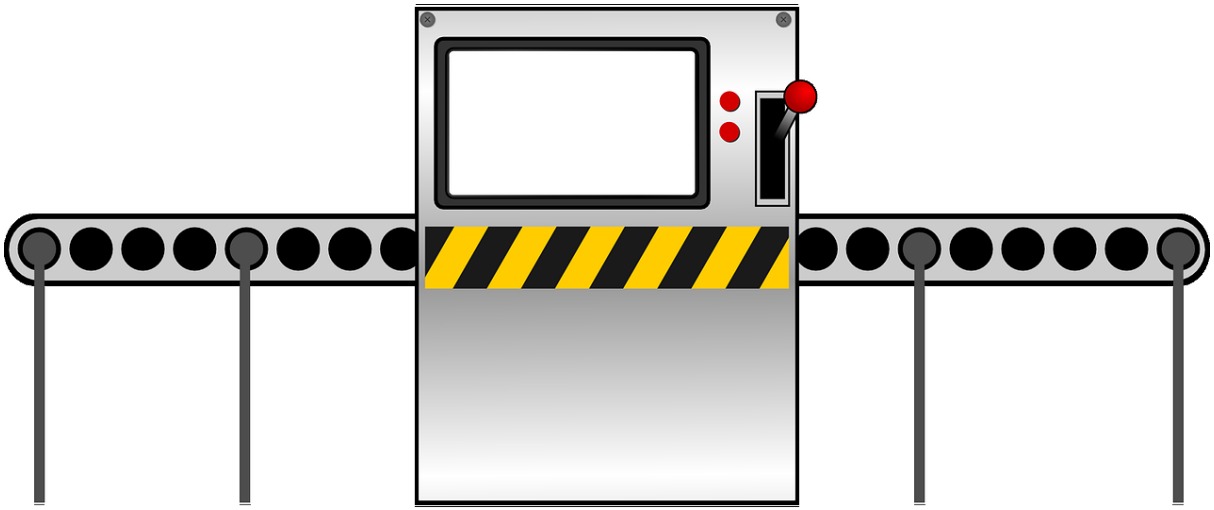
Part 3: Good Manufacturing Practices
Premises
Section 45

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

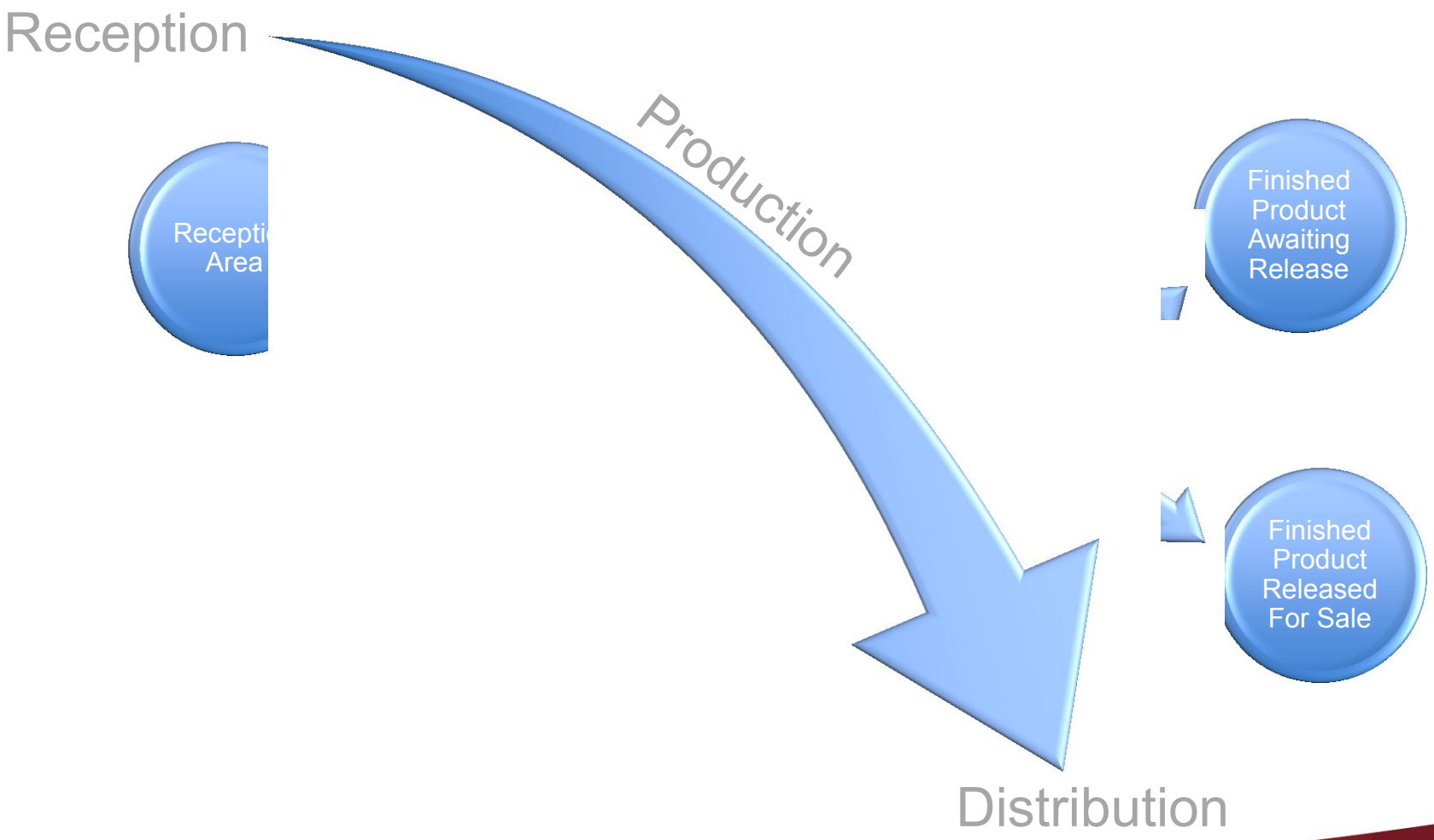
- Protect materials in storage from chemical and/or microbial contamination, and deterioration
- Physical **quarantine** areas should be clearly marked

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)

* Further segregation may be required within each area

Figure 1: Example of storage areas within a manufacturing facility

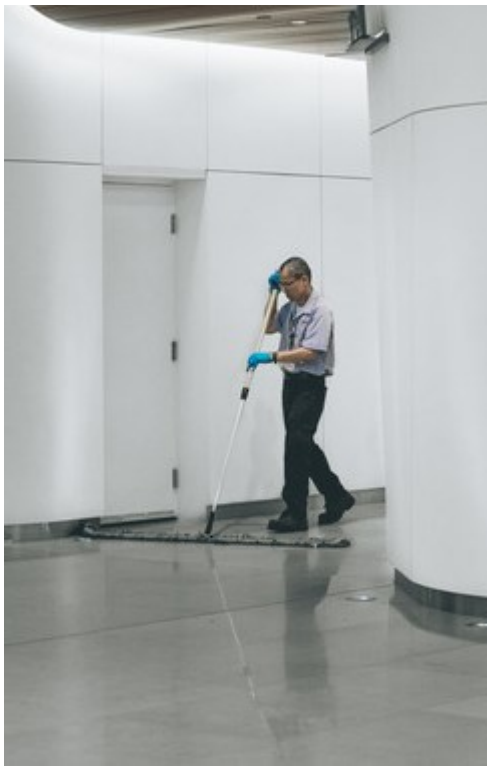


Premises – Non-Production Areas

- Non-Production Areas
  - Permit good sanitary practices
  - Separate toilets, wash stations, change rooms and break areas from the production areas
  - Maintain grounds around the building
  - 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

- When completing the QAR, a self-inspection should be carried out to assure adequate 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
  - Daily pest control logs or inspection reports
  - Janitorial duty schedule, cleaning records
  - Relevant standard operating procedures (SOPs)



NHPR Section 44

Specifications

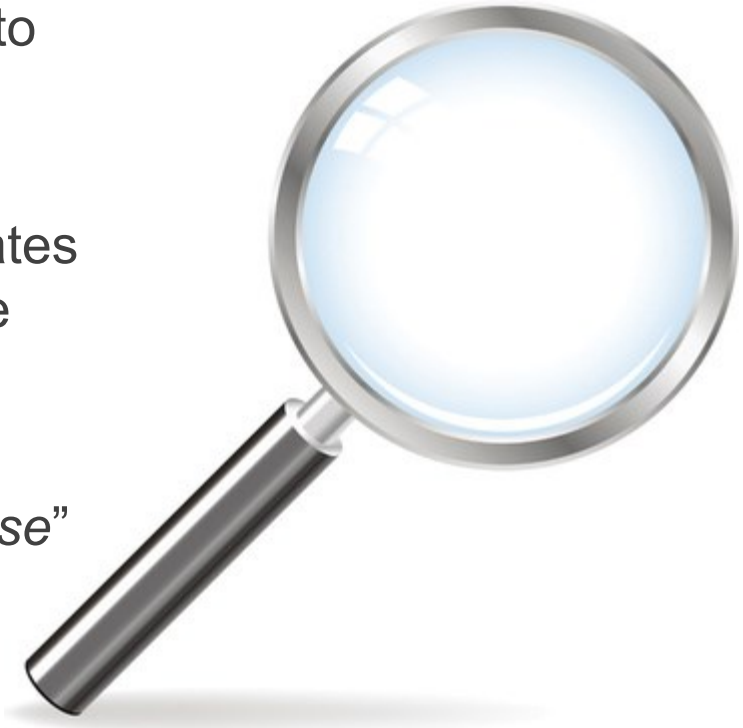
Part 3: Good Manufacturing Practices
Specifications
Section 44

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 specifications to results/ certificates of analyses (CoA's) 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 AND quantified
- 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
Physical Description	Color, shape, other tolerance limits as appropriate
Identity of each Medicinal ingredient (raw material or finished product stage)	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

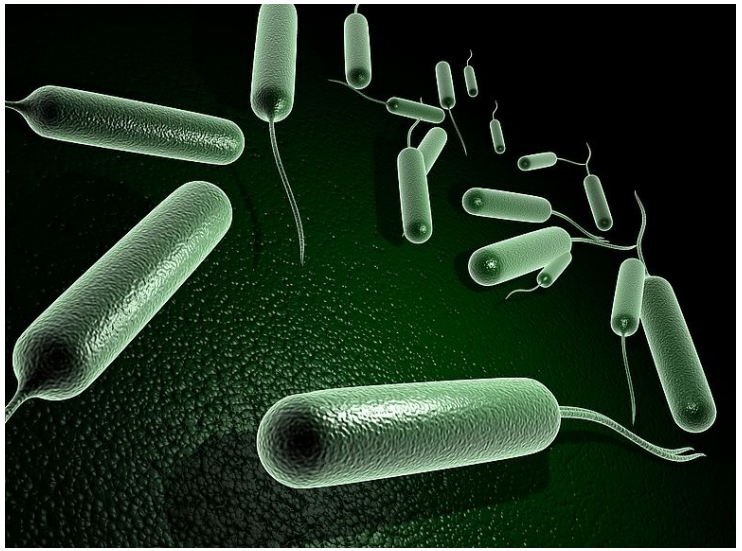
* Quantification by assay must be demonstrated to be too complex

Specifications – Microbial Contaminants

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

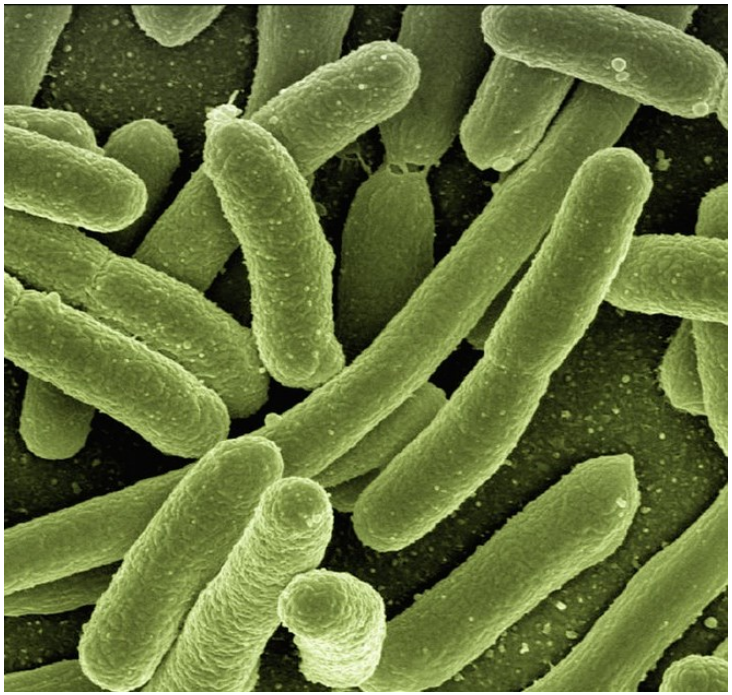
Table 3: NNHPD required microbial contaminant tests

Requirements:
Total viable aerobic plate count
Contaminating fungi (yeast and mould)
Salmonella spp.
Escherichia coli
Staphylococcus aureus
Pseudomonas aeruginosa
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 shelf life



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

Specifications – Chemical Contaminants

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

Test Parameter		Tolerance Limits
Heavy Metals	***Arsenic*** • *Inorganic:* • *Organic:*	**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 • *Methylmercury:*	**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
Solvent Residues		ICH or USP limits
Pesticides		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

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
  - 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 Sections 49-50

Operations

Part 3: Good Manufacturing Practices
Operations
Section 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.

Part 3: Good Manufacturing Practices
Operations
Section 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 dd, yyyy*	*Issuance Date:*	*Month dd, yyyy*
Verified by:	*AO name*	*Date:*	*Month dd, yyyy*	*Review Date:*	*N/A (enter date if it is a revision)*
Approved by:	*UH name*	*Date:*	*Month dd, yyyy*		

Operations – How to Create an SOP

3. 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

4. Additional sections can be added for clarity
5. 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
   - 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

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

NHPR Section 51

Quality Assurance

Part 3: Good Manufacturing Practices
Quality Assurance
Section 51

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 the 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
- 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:
  - Job Descriptions
  - QAP resume, C.V., educational degrees
  - Approved finished product specification
  - 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, including investigations into route causes
  - SOPs/templates related to quality assurance
  - Organization structure which clearly demonstrates independence of function (e.g. from activities such as manufacturing)

NHPR Section 52

Stability

Part 3: Good Manufacturing Practices
Stability
Section 52

Every manufacturer and every importer shall determine the period of time that, after being packaged for sale, the natural health product will continue to comply with its specifications 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

Stability Period – Methods

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: 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 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

For more information about GMP:

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

GMP Guidance Document, sections 2.4.1 and appendix 5:
https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/good-manufacturing-practices.html#a2d1

Compendium of Monographs:
http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq.do?lang=eng

45 – Premises

GMP Guidance Document, sections 2.1.1 and appendix 5:
https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/good-manufacturing-practices.html#a2a1

49 & 50 – Operations

GMP Guidance Document, sections 2.3.2 and appendixes 3, 4 & 5:
https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/good-manufacturing-practices.html#a2c2

51 – Quality Assurance

GMP Guidance Document, sections 2.2.2 and appendix 5:
https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/good-manufacturing-practices.html#a2b2

52 – Stability Period

GMP Guidance Document, sections 2.4.2 and appendix 5:
https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/good-manufacturing-practices.html#a2d2

ICH Q1 (especially Q1A and Q1E):
http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

References

- Health Canada. (2010, February 24). Finished Product Specifications Form User Guide. Retrieved from 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
- Health Canada. (2015, May 1). Quality of Natural Health Products Guide. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/quality-guide.html
- Health Canada. (2015, December 01). Good Manufacturing Practices Guidance Document. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/good-manufacturing-practices.html#a2d1
- Health Canada. (2018, July 06). Listing of Monographs. Retrieved from http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq.do?lang=eng
- ICH. (2003, February). Q1A(R2) Stability Testing of New Drug Substances and Products. Retrieved from http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html
- ICH. (2003, February). Q1E Evaluation of Stability Data. Retrieved from http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html