



Health
Canada Santé
Canada

*Your health and
safety... our priority.*

*Votre santé et votre
sécurité... notre priorité.*

Good Manufacturing Practices Guidance Document

Natural Health Products Directorate

June 11, 2014
Version 3.0



Canada 



Table of Contents

Foreword.....	3
1.0 General overview	4
1.1 Purpose of the good manufacturing practices guidance document	4
1.2 Purpose of good manufacturing practices	4
1.3 Roles and responsibilities.....	4
Natural health products GMP regulations applicable to various activities.....	5
2.0 Good manufacturing practices	6
2.1 Places	6
2.1.1 Premises.....	6
2.1.2 Equipment	8
2.2 People.....	9
2.2.1 Personnel.....	9
2.2.2 Quality assurance.....	9
2.3 Processes	11
2.3.1 Sanitation program	11
2.3.2 Operations	13
2.4 Products.....	15
2.4.1 Specifications	15
2.4.2 Stability	17
2.4.3 Samples.....	18
2.4.4 Records	19
2.4.5 Recall and recall reporting.....	21
2.4.6 Sterile products.....	22
References.....	23
Glossary	24
Appendix 1: Records.....	30
Record keeping requirements for various activities.....	30
Appendix 2: Good documentation practices	31
Appendix 3: Standard operating procedure	33
Appendix 4: Supplementary good manufacturing practices for homeopathic medicines	35
Places	35
Premises	35
People.....	36
Personnel.....	36
Processes.....	36
Sanitation	36
Operations	36
Products.....	37
Specifications.....	37
Stability	37
Appendix 5: Quality technical agreements.....	39
What is a quality technical agreement?.....	39
The quality technical agreement instruction	39



Foreword

Good Manufacturing Practices (GMP) standards are necessary for the production of high quality health products. Regulatory bodies, such as the Therapeutic Goods Administration (Australia TGA) and United States Food and Drug Administration (US FDA) have similar sets of GMP standards that must be met for products that are sold within their jurisdictions. There are also some voluntary standards, such as Ecocert, Organic and Kosher that some companies choose to meet to ensure production of high quality products that meet specific requirements.

The NHPD recognizes that companies meeting other types of GMP standards are already meeting parts of the NHP GMP standard and therefore will only have to make adjustments to existing processes to come into compliance with the NHP GMP standard.

For example, Hazard Analysis Critical Control Point (HACCP) is an approach to food safety that is systematic and preventive. It is recommended by the Codex Alimentarius Commission, the United Nations international standards organization for food safety. HACCP is used by most countries around the world and it goes beyond inspecting finished food products. It helps to find, correct, and prevent hazards throughout the production process, including physical, chemical, and biological hazards. Prerequisite GMPs required for HACCP program development include (but are not limited to) documented procedures to control: Personnel Practices, Materials Shipping, Receiving, Handling & Storage, Sanitation, Preventative Maintenance & Calibration, Pest Control, Recall, Water Treatment Training, Water Safety Monitoring Training, Equipment and Specialized Process Training. As such, the NHPD may accept an inspection conducted against HACCP standards, with evidence of finished product and stability testing, in lieu of the Quality Assurance Report as evidence of GMP compliance.

Similarly, inspections by the US FDA to their current GMPs for dietary supplements or by Australia's TGA to their GMP standard would be accepted by the NHPD as evidence of compliance to the NHP GMP standard. Note that for US FDA cGMP, additional finished product testing, especially for heavy metals, may be required.

This guidance document outlines section by section the process required to come into compliance with various parts of the NHP GMP standard.

1.0 General overview

1.1 Purpose of the good manufacturing practices guidance document

This guidance document pertains to Part 3 of the *Natural Health Product Regulations* (the Regulations) and is intended for manufacturers, packagers, labellers, importers, and distributors of natural health products (NHPs) for sale in Canada. It is meant to facilitate compliance the good manufacturing practices (GMPs) requirements outlined in part 3 of the Regulations. In addition, the guidance document is a tool for the Quality Assurance Person (QAP) to implement and maintain GMPs and to fulfill their role in assuring the quality of a NHP before it is made available for sale.

The Natural Health Products Directorate (NHPD) recognizes that there are various ways of meeting the GMPs and producing safe and effective NHPs. For example, specific methods to achieve GMPs compliance in sanitation may vary with the particular operation. Therefore, this guidance document sets out GMPs requirements, which are not regarded as the only interpretation of the Regulations. Alternative means of complying with the Regulations will be considered by the NHPD given that the appropriate rationale or justification is provided.

1.2 Purpose of good manufacturing practices

The GMP requirements are ongoing measures designed to ensure an effective overall approach to product quality control and risk management. They do this by setting appropriate standards and practices for the manufacturing, packaging, labeling, storing, and importing of NHPs intended for sale in Canada.

An NHP may pass all of the specification tests, but may have microbial, physical or chemical contamination if manufactured or packaged in poor GMP conditions. Therefore, complying with GMPs is a mandatory aspect in the Regulations as it assures a higher level of quality and confidence in the product.

Part 3 (sections 43 to 62) of the Regulations sets out the GMPs that manufacturers, packagers, labellers, and importers must meet before the NHPD will issue a site licence for each location where they intend to manufacture, package, label, or import NHPs for sale in Canada. Distributors and storage sites must follow the GMPs, as defined in the Regulations; however they are not required to hold a site licence. The responsibilities of the distributor are identified in this document with respect to the GMPs related to storage, distribution and transportation. For more information on site licensing, refer to the [Site Licensing Guidance Document](#).

Each section under **Places, People, Processes** and **Products**, below, begins with a brief explanation of what is outlined by the Regulations. The next section “To Meet the Requirements,” explains in more detail how to comply with the Regulations. It is recommended that applicants follow GMPs described in this document; however the NHPD will consider alternative means of complying with the Regulations, when acceptable rationale is provided. To conclude this portion, the section “Examples of Evidence to Demonstrate GMP...” which provides examples of documentation and records that are acceptable as GMP evidence to support a licence application. Note that all records should be signed/initialed and dated. In addition, the examples may or may not apply, depending on the activities being performed. The examples provided are not an exhaustive list.

1.3 Roles and responsibilities

Prior to the sale of a NHP in Canada, the product licence holder is responsible to provide the NHPD with information, as defined in section 22 of the Regulations, concerning the relevant names, addresses and contact details of each manufacturer, packager, labeller, importer and distributor with their corresponding site licence numbers. For more information on product licensing, see the [Product Licensing Guidance Document](#).

Adherence to GMPs is the responsibility of everyone involved in the life cycle of a NHP, from the harvesting or manufacturing to its availability for sale to consumers. The site licence holder is responsible to carry out each activity, in which they are authorized to conduct, in accordance with GMPs, which includes ensuring that the quality assurance person (QAP) has the relevant training, experience and technical knowledge to ensure they are capable of carrying out all the necessary quality-related functions. The site licence holder must also ensure that all activities or services contracted out are conducted in accordance with Part 3 of the Regulations.

Part 3 of the Regulations begins with section 43, which states that any NHP sold must be manufactured, packaged, labelled, imported, distributed, and stored according to the requirements outlined therein. It is the importer's responsibility to ensure that imported NHPs are manufactured, packaged, and labelled at sites that meet the Regulations. For information related to evidence required from importers with respect to the foreign sites, refer to the [Site Licensing Guidance Document](#).

The following table outlines which activities are applicable to each section of the Regulations. A checkmark indicates that the section of the Regulations is applicable to the activity specified. Note that a site license is not required for the activity of distribution.

Natural health products GMP regulations applicable to various activities

Section of the Regulations	Manufacturing	Packaging	Labelling	Importing	Distributing
1. Prohibition (43)	✓	✓	✓	✓	✓
2. Specifications (44)	✓	✓*		✓	✓*
3. Premises (45)	✓	✓	✓	✓	✓
4. Equipment (46)	✓	✓	✓	✓*	
5. Personnel (47)	✓	✓	✓	✓	✓
6. Sanitation program (48)	✓	✓	✓	✓	✓
7. Operations					
i) SOP (49)	✓	✓	✓	✓*	✓*
ii) Recall (50)	✓	✓	✓	✓	✓
8. Quality assurance (51)	✓	✓	✓	✓	✓
9. Stability (52)	✓			✓	
10. Records					
i) Manufacturers (53)	✓				
ii) Packagers (54)		✓			
iii) Labellers (55)			✓		
iv) Importers (56)				✓	
v) Distributors (57)					✓
vi) Records maintenance (58)	✓	✓	✓	✓	✓



Section of the Regulations	Manufacturing	Packaging	Labelling	Importing	Distributing
11. Sterile NHP's (59/60)	✓	✓			
12. Lot or Batch samples (61)	✓			✓	✓
13. Recall reporting (62)	✓			✓	✓

* = if applicable

2.0 Good manufacturing practices

Please note in the text that follows that the GMPs are divided into four categories (**Places, People, Processes and Products**). As a result, the sections of the Regulations do not run in numerical order.

2.1 Places

2.1.1 Premises

Section 45 of the Regulations sets out the requirements for the physical premises in which NHPs are manufactured, packaged, labeled, and stored.

Intent

The building should be designed and constructed in a manner that permits cleanliness and orderliness while preventing contamination. Regular maintenance is required to prevent deterioration of the premises. The objective is to ensure products do not become contaminated through unsanitary conditions.

To meet the requirements

Manufacturers, packagers, labellers, importers, and distributors should ensure the following, where applicable. Alternatively, justification with rationale for the exemption of the requirements should be provided.

1. Ensure that the buildings are of adequate size and are designed and built to facilitate maintenance, cleaning and sanitary operations, prevent entry of insects and other animals, facilitate waste treatment and disposal, and prevent mix-ups and cross-contamination of raw, packaging and product materials. Every site shall:
 - ensure that effective controls are in place to minimize the potential for mix-ups or the adulteration of raw, packaging and in-process materials;
 - designate separate production and non-production areas, as necessary, to prevent cross-contamination. When required, clearly identify and segregate individual manufacturing, packaging, and testing areas;
 - restrict, during production, the use of doors giving direct access from manufacturing and packaging areas to the outdoors (these doors must be adequately sealed to prevent unauthorised persons and pests from entering);
 - ensure that doors, windows, walls, ceilings and floors contain no holes or gaps, except those that are part of the design;
 - ensure that floors, walls and ceilings permit cleaning, and that all surfaces are made of materials that do not shed particles;
 - seal surfaces and joints to prevent contamination from extraneous materials and to permit effective cleaning;
 - provide adequate ventilation, filtration and lighting;
 - control humidity and temperature, where required, to protect materials and products;



- take appropriate measures to controlling, removing and preventing pests from entering the premises; and
 - provide explosion proof bulbs and fixtures to avoid glass contamination
2. Separate the rest, change, wash-up and toilet facilities from production areas, and ensure that they are sufficiently spacious and well ventilated, and permit good sanitary practices.
 3. Provide plumbing of an appropriate scale and design to avoid adulteration of products or contamination of water supplies or equipment, and identify outlets for liquids and gases used in production.
 4. Ensure water supply is of potable quality for processing and cleaning and shall meet the [Guidelines for Canadian Drinking Water Quality](#), World Health Organization (WHO) guidelines for Drinking Water Quality or other standards specified by the regulatory agency governing the manufacturer. When purified water is required, water purification, storage and distribution equipment must be operated to ensure a reliable source of water of appropriate chemical and biological purity as defined in any standard listed in [Schedule B](#) to the *Food and Drugs Act*.
 5. Ensure that floor drains are screened and trapped.
 6. Maintain the grounds around the manufacturing buildings to protect against the contamination of products.
 7. Install refuse receptacles and follow waste disposal practices that protect against contamination or harborage of pests.
 8. Protect raw materials, packaging materials, in-process, and finished products against physical, chemical and microbial contamination, as well as deterioration of the products and the container during storage and temporary storage while in transit (e.g. between the importer and the distributor, or between the manufacturer and the labeller).
 9. Clearly mark physical quarantine areas when used.

Examples of evidence to demonstrate GMP compliance for premises (see appendix 3 for good documentation practices):

1. A detailed floor plan showing production, non-production, quarantine, packaging and/or labeling areas, etc.
2. Ventilation filter change record.
3. Water quality test records (for manufacturers).
4. Daily temperature, relative humidity, and light (as required) control records.
5. Facility maintenance records (wall, floor or ceiling repair, new drain grates etc.).
6. Pest control inspection report (internal program or contractor visit) with trap replacement information, daily pest control logs.
7. Janitorial duty schedule and cleaning completion records (must be for areas related to activities; i.e. manufacturing, packaging, labeling, and/or storage).
8. Relevant standard operating procedures (SOPs) and associated blank record templates, related to maintenance of premises.



2.1.2 Equipment

Section 46 of the Regulations sets out the requirements for the equipment used to manufacture, package, label, and store NHPs, during operation.

Intent

The purpose of these requirements is to prevent the contamination of NHPs by other products, by dust, cleaning agents and by foreign materials such as rust, lubricant and particles coming from the equipment. Contamination problems may arise from inadequate cleaning practices, poor maintenance, the misuse of equipment, exceeding the capacity of the equipment and the use of worn-out equipment. Equipment arranged in an orderly manner permits effective cleaning and does not interfere with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials.

To meet the requirements

Manufacturers, packagers, labellers, importers and distributors should ensure the following, where applicable. Alternatively, justifications with rationale for the exemption of the requirements should be provided.

1. Production equipment is designed, constructed, installed, and maintained to facilitate cleaning, sanitizing (where appropriate), and inspection of the equipment 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.
2. Each piece of production equipment is operated according to its SOP.
3. Protect analytical instruments and associated control systems from vibration, electrical interference and contact with excessive moisture or other external factors.
4. Production equipment and utensils having direct contact with materials and products are constructed of smooth, non-reactive and non-toxic materials, and are designed to withstand repeated cleaning.
5. Avoid the possibility of lubricant or other maintenance materials contaminating the products by ensuring proper equipment design (e.g. tanks, chain drives and transmission gears must be enclosed or properly covered).
6. Control and monitor temperature-sensitive compartments, and keep records.
7. Properly maintain instruments and controls, including laboratory equipment, to ensure that they remain accurate, and retain records.
8. Develop a calibration program for critical manufacturing, packaging, and testing equipment, and maintain records.
9. Maintain records of equipment cleaning.
10. Maintain equipment usage logs.

Examples of evidence to demonstrate GMPs compliance for equipment:

1. Preventative maintenance schedule for equipment.



2. Equipment cleaning and maintenance logs.
3. Equipment usage logs.
4. Calibration records for essential equipment.
5. Relevant SOPs and associated blank record templates.

2.2 People

2.2.1 Personnel

Section 47 of the Regulations requires NHPs to be manufactured, packaged, labelled, and stored by personnel who are qualified by education, training or experience to perform their respective tasks.

Intent

People are the most important element in performing any authorized activity. The appropriate personnel with sufficient training are necessary to manufacture, package, label, import, or store NHPs of high quality.

It is essential that qualified personnel be employed to supervise the manufacturing, packaging, labeling, importing and storage of NHPs. The operations involved in the handling of NHPs require constant monitoring, attention to details and a high degree of competence on the part of employees. Inadequate qualification or training of personnel may lead to the failure of an NHP to meet its specifications and its quality requirements.

To meet the requirements

Manufacturers, packagers, labellers, importers, and distributors must ensure that:

1. Individuals in charge of manufacturing and quality assurance have adequate education, training, and/or practical experience to control and/or supervise the activities.
2. 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.

Examples of evidence to demonstrate GMP compliance of personnel:

1. Job description.
2. Resume, C.V., or copy of educational degrees (shows the person meets their job description).
3. Employee training schedule and/or attendance records (demonstrating on-going training).
4. Certificates of completion (i.e. GMP).
5. Relevant SOPs and associated blank record templates related to personnel.

2.2.2 Quality assurance

Section 51 of the Regulations sets out the requirements and responsibilities of the QAP.

Intent



Quality assurance is the area of GMP concerned with sampling, specifications, testing; including documentation, and release procedures. The QAP bears the responsibility of assuring each product is suitable for sale. This regulation ensures that the necessary and relevant tests are carried out and that products are not released for sale, until their quality has been determined to be satisfactory by confirming that products specifications are met.

To meet the requirements

Manufacturers, packagers, labellers, importers, and distributors must have a QAP who is responsible to do the following:

1. Establish and follow written procedures to ensure that products conform to specifications and regulatory requirements.
2. Establish and follow written procedures for sampling, inspecting and testing raw and/or packaging materials, in-process and finished products.
3. Approve or reject all formulations, procedures, specifications, test methods, controls and results that affect the purity, quality and composition of each ingredient and product. Written procedures shall be established and implemented.
4. Approve or reject all raw materials, packaging materials and finished products, including products manufactured by contractors, based upon conformance/nonconformance to respective specifications. Written procedures shall be established and implemented.
5. Review and maintain completed batch records.
6. Approve or reject the product for distribution against the completed batch record.
7. Approve or reject product quality deviations and product reprocessing in the manufacture of a product. Written procedures shall be established and implemented.
8. Destroy returned products unless he or she determines, by assessment or other investigation, that they may be released for resale. Written procedure shall be established and implemented.
9. Maintain records with respect to returned, reprocessed and redistributed products and include the name and description of the product, lot number, reason for return, quantity returned and date and means of final disposition.
10. Ensure that laboratories (in-house and contract) are capable of performing all of the tasks and responsibilities assigned to them.
11. Maintain laboratory records of tests and investigations.
12. Set up and follow written procedures for handling product complaints. These procedures must include determining whether further investigation and corrective action are required.
13. Document all complaints with the following information: the name and description of the product, the lot number, the source and nature of the complaint, and any response. When an investigation is conducted, include in the written record the findings and any follow-up action taken.

It is good practice for manufacturers, packagers, labellers, importers, and distributors to provide a written job description to the QAP to avoid a conflict of interest with duties versus the requirements outlined in Section 51 of the Regulations.

Examples of evidence to demonstrate GMP compliance for quality assurance:

1. Job Description.



2. QAP resume, C.V., or educational degrees (to demonstrate the person meets their job description).
3. Approved product specification for products handled at the site.
4. Master production document and batch record.
5. Product specification change control log.
6. Certificates of analysis for all raw materials (medicinal and non-medicinal ingredients).
7. Raw material release records.
8. Complete finished product testing against approved specification.
9. Out of Specification (OOS) investigation.
10. Finished product release record.
11. Product complaint log, investigation report and corrective/preventative action.
12. Product disposition logs.
13. Product distribution log.
14. Returned products log.
15. Product disposal logs.
16. Relevant SOPs and associated blank record templates related to quality assurance.

2.3 Processes

2.3.1 Sanitation program

Section 48 of the Regulations sets out the sanitation requirements for the premises and the health and hygiene of personnel.

Intent

Sanitation of a building, as well as employee hygiene, influences the quality of NHPs. The GMPs requirements indicate that activities be performed in areas that are free from environmental contamination and free from contamination by another product.

A written sanitation program informs employees of the expectation as well as the necessary steps to ensure sanitation is maintained. It also provides some assurance that levels of cleanliness in the plant are maintained.

To meet the requirements

Manufacturers, packagers and labellers shall have a facility sanitation program and a health and hygiene program in place, as detailed below. Importers and distributors shall meet the appropriate requirements with respect to storage.

Facility Sanitation Program

1. Develop a sanitation program adequate to prevent contamination of product.



2. Develop a written sanitation program that includes the following elements:
 - cleaning procedures for facilities and processing equipment;
 - a list of cleaning /sanitizing agents, pesticide chemicals shall be identified, used and stored in such a manner to prevent the contamination of raw, packaging materials and process equipment;
 - procedures for 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.
3. Contain or ventilate dusty operations to prevent contamination of other areas.

Health and Hygiene Program

All personnel having direct contact with raw and/or packaging materials, in-process materials and any unpackaged products, as well as personnel, who use processing equipment, must follow appropriate practices to protect products against contamination. This health and hygiene program must be in writing and should include the following requirements:

- wearing outer garments, including shoe coverings, that protect against contamination of products and equipment, when applicable;
- removing all unsecured jewellery and hand jewellery, or covering hand jewellery that cannot be removed, when applicable;
- using intact, clean and sanitary gloves;
- wearing hairnets, caps, beard covers or other effective hair restraints;
- maintaining personal cleanliness;
- washing hands thoroughly before starting work and at any other time when hands may have become soiled or contaminated;
- storing clothing or other personal effects outside of processing areas;
- refraining from consuming food and drink, as well as chewing products or smoking, in manufacturing, packaging, storage, and testing areas;
- periodically conducting eye examinations of personnel responsible for visual inspection;
- reporting to supervisors any health conditions of personnel that could adversely affect products;
- respecting quarantine times imposed by public health authorities; and
- removing from the manufacturing facility any person who has, or appears to have, an illness that could be a possible source of product contamination, until the disease or hygienic condition is no longer a risk for possible product contamination.

Examples of evidence to demonstrate GMP compliance for a sanitation program:

1. Facility cleaning schedule and cleaning completion logs.
2. Microbiological surface swab test results.
3. Personnel hygiene training log.
4. Visitor entrance log.
5. Relevant SOPs and associated blank record templates related to sanitation.



2.3.2 Operations

Section 49 of the Regulations requires every NHP to be manufactured, packaged, labelled, and stored in accordance with SOPs designed to ensure that the activity is conducted in accordance with the Regulations.

Intent

This Regulation requires that measures be taken to maintain the integrity of an NHP from when raw materials enter the plant to the time the finished dosage form is released for sale and distributed.

To meet the requirements

Manufacturers, packagers, labellers, importers, and distributors shall ensure that practices and procedures are in place for material control, process control, the inspection program for contractors, and product recall, where applicable. Alternatively justifications with rationale for the exemption of the requirements should be provided.

Material control

1. Set up and follow written procedures for the transportation, receipt, identification, examination, handling, sampling, testing and approval, rejection and disposal of raw and/or packaging materials. Updating the procedures as required.
2. Identify each lot of raw and/or packaging materials with a distinctive lot number for traceability.
3. Inspect containers of raw and/or packaging materials upon receipt for closure and physical integrity.
4. Assess each lot of raw and/or packaging materials against specifications, such as species identity, detectable foreign matter and the integrity (appropriate characteristics) and quality of species material or extracts.
5. Retest raw and/or packaging materials after any exposure to conditions likely to adversely affect their purity, quality or composition.
6. Identify and control each lot of raw and/or packaging materials according to its quality status (e.g. quarantined, approved or rejected).
7. Store raw materials, in-process materials and reprocessed materials in appropriate conditions, including temperature and humidity, to protect against quality deterioration and contamination.
8. Set a time limit beyond which raw materials that are subject to deterioration may not be used in production without additional testing. When appropriate, use the oldest approved stock of raw and/or packaging materials first (follow the first in first out system).
9. Ensure that the QAP approves and releases materials prior to their use.
10. Establish appropriate systems and controls to ensure that water used in the production of products is of potable quality and shall meet the guidelines and standards specified by the regulatory agency governing the manufacturer.
11. Destroy outdated or obsolete printed packaging materials and record the disposal.

Process control

12. Formulate the product to ensure that it adheres to regulatory requirements and claims stated on the label.
13. Prepare a master production document for the manufacture of each product, and have the QAP review and approve the document.



14. Prepare and follow batch records for each batch of product. These records must be an accurate representation of the master production document and include documentation that each significant step in the manufacturing process was completed.
15. Allocate and track each batch of manufactured product by an individual control number.
16. Record and evaluate any deviations from written and approved manufacturing processes, standards and test methods, with final approval by the person in charge of production as well as the QAP.
17. Conduct manufacturing, packaging, and storage operations according to written procedures and appropriate sanitation principles, in a manner that protects against adulteration and in conditions that minimize the potential for contamination.
18. Identify all materials, products, samples, containers, processing lines, and major equipment at all times to indicate their contents and/or status.
19. Ensure adequate procedures are in place to prevent extraneous materials from being included in the products and finished package.
20. Ensure adequate procedures are in place to identify, store and dispose of rejected or contaminated/adulterated products.
21. Establish written procedures for reprocessing batches that do not conform to finished product specifications.
22. Securely store labels to prevent mix-ups (e.g. stored and withdrawn against a labelling order and reconciled at the end of every run). Specifically, this means the following:
 - not returning sample labels taken from the processing areas;
 - labelling the product as quickly as possible after filling and sealing (when labelling is delayed, follow procedures to ensure that no mislabelling occurs); and
 - before release, investigating and accounting for any significant or unusual discrepancies observed during reconciliation of the product, or labels.
23. Prevent cross-contamination and mislabelling by establishing procedures for removing all raw and/or packaging materials and finished products from previous runs (i.e. written line clearance procedures and appropriate area to record completion).
24. Set up and follow written procedures to ensure that the correct labels and packaging materials are issued and used.
25. Identify each package with a lot number and expiry date that permits determination of the history of the manufacture and control of the lot.
26. Restrict the access to production areas to authorized personnel.

Inspection program for contractors

27. Manufacturers, packagers, labellers, and importers must ensure that activities contracted out to other sites meet the GMP requirements, which can be demonstrated by an inspection and/or an evaluation of the contractor. This inspection program of contracted activities verifies that Part 3 of the regulations is met by all parties at all times. It is essential to clearly establish and document the roles and responsibilities of each party involved in the contracted operations. See the records section for information related to contractors and required documentation.



Examples of evidence to demonstrate GMP compliance for operations:

1. Approved product specification for products handled at the site.
2. Master production document and batch record.
3. Product specification change control log.
4. Certificates of analysis for all raw materials (medicinal and non-medicinal ingredients).
5. Raw material release records.
6. Complete finished product testing against approved specification.
7. Out of specification (OOS) investigation.
8. Finished product release record.
9. Product complaint log and resulting action.
10. Product disposition logs.
11. Product distribution log.
13. Product disposal records.
14. List of all SOPs in use for the production run/importation.
15. Record indicating samples from the product run/importation have been secured.
16. A completed checklist/questionnaire for approved contractors.
17. Product distribution record.
18. Relevant SOPs and associated blank record templates related to operations.

2.4 Products

2.4.1 Specifications

Section 44 of the Regulations describes the requirements related to product specifications.

Intent

Ensuring that a product meets its specifications has two aspects. The first is that product specifications are established and the second is that the manufacturer has a quality system in place that ensures the product consistently meets the established specifications. Finished product tests complement the controls employed during the manufacturing and importing process. It is the responsibility of each manufacturer and importer to have accurate specifications, adequate quality systems in place, and appropriate test methods that will help ensure that each NHP sold meets the product specifications.

To meet the requirements

The manufacturer, importer and, if applicable, packager, and distributor must ensure the following, where applicable. Alternatively, justifications with rationale for the exemption of the requirements should be provided.

Develop and implement written specifications for all finished products pertaining to identity, purity, quantity, potency and tolerances as per the [Quality of Natural Health Products Guide](#).

1. Develop and implement written specifications for all finished products pertaining to identity, purity, quantity, potency, and tolerances as per the [Quality of Natural Health Products Guide](#).
2. Ensure specifications are maintained and every change is approved by the QAP prior to use. Changes to specifications as per section 11(i) of the Regulations requires an amendment to the product licence.
3. Set up and follow written procedures that describe tests to be conducted to ensure the identity, purity, and quantity of finished products. When applicable, these procedures should include potency testing.
4. Verify that all test methods provide accurate and consistent results.
5. Assess each lot for compliance with specifications prior to release.

Importers may apply a reduced testing program that relies on test results from their manufacturer (supplier) provided that a certificate of analysis (CoA) is submitted with each lot received. The following outlines the parameters of a reduced testing program:

- a. fully test against specifications, the first lot of product received from each supplier for **each product**;
- b. each subsequent lot received thereafter must:
 - undergo a review of the CoA showing actual test results;
 - positively identify and verify upon receipt each lot or ensure its identification and verification by qualified personnel at another site to which imported product is shipped; and
 - take precautions to ensure that transportation and storage conditions do not adversely affect product potency, purity or physical characteristics;
- c. conduct complete confirmatory testing against specifications on at least one lot per dosage form per supplier per year.

Examples of evidence to demonstrate GMP compliance for specifications:

1. Product specifications for all products to be manufactured, packaged, labeled or imported to the site.
2. Approval of product specifications by the QAP.
3. Record of approval from the QAP regarding any changes to the product specification.
4. Relevant SOPs related to finished product testing and associated blank record templates related to specification.
5. The CoA for each lot of finished product demonstrating the product meets its specifications according to the requirements outlined in the [Quality of Natural Health Products Guide](#).

Skip lot testing may be accepted on a case by case basis and should include the following:

- scientific justification including supporting references (e.g. USP and ICH);
- historical data, challenge studies, or other detailed investigation;
- identity tests: CoA for each ingredient (medicinal and non-medicinal) and the full batch record; and



- appropriate GMP procedures to be followed if a batch fails testing or for changes in raw material suppliers. Procedures should include retesting of previous lots, re-evaluating raw material suppliers, investigation of batch failures, corrective actions and preventative actions.

An exemption to microbiological contaminants testing would be acceptable if the manufacturer is able to demonstrate **all** of the following, (using valid test methods, on multiple batches and throughout shelf-life):

- i. low water activity;
- ii. antimicrobial properties ;
- iii. historical testing showing low microbial load;
- iv. procedures and/or testing for control of microbial bio burden of the raw material; and
- v. proposed frequency of microbial testing to be performed on subsequent batches (e.g. every 10th batch to be tested to a minimum of 1 batch per annum).

An exemption to the various chemical contaminants testing would be acceptable if the manufacturer is able to demonstrate the following:

- i. pesticide testing if all ingredients are organic and evidence of organic certification is provided;
- ii. solvent testing if solvents are not used in the manufacturing process (and the raw materials have been tested for or are not manufactured with solvents); and/or
- iii. heavy metal testing if raw materials (medicinal and non-medical ingredients) are tested and the raw material suppliers test results are verified.

An exemption to identity testing in the finished would be acceptable if the manufacturer is able to demonstrate all of the following:

- i. justification for using quantification by input rather than assaying the final product using an appropriate method;
- ii. certificates of analysis for raw material for all the medicinal ingredients to be quantified by input; and
- iii. a batch record as objective evidence that these medicinal ingredients were added to the final product. The manufacturing documents should indicate the target quantity for the medicinal ingredient (i.e. 100% of the label claim) and an acceptable range of variation for addition of the ingredient during manufacturing (based on current industry standards for weight variation).

2.4.2 Stability

Section 52 of the Regulations sets out the requirements for product stability.

Intent

The purpose of a stability program is to determine how long the NHP can be expected to remain within approved specifications under recommended storage conditions.

To meet the requirements

Manufacturers and importers must ensure the following:

1. Use data from accelerated or real-time stability studies or from similar product formulations to make an initial determination of the expiry date.
2. Provide data and rationale to reasonably ensure that each finished product meets its label claims at the expiry date.
3. Confirm and adjust the expiry date, when required, on the basis of real-time studies on product

stored in the conditions noted on the label, for the period of time indicated by the expiry date.

4. Display the lot expiry date on the label of each finished product.
5. Ensure that all packaging and labelling requirements are met, and that the product will remain free from contamination until the expiry date (e.g. deterioration of packaging material and labelling).
6. Establish the shelf life from the date of original fabrication.
7. Re-evaluate the product shelf life when significant changes are made to the formulation, process or package that may affect the product's stability.
8. Carry out testing appropriate to each product.

Examples of evidence to demonstrate GMP compliance for stability:

1. The CoA demonstrating that every product meets specifications at expiry. Please note that chemical contaminants do not need to be tested to support stability (i.e. heavy metals, pesticides, solvent residues etc.).
2. Stability testing protocol for a product manufactured or imported to the site, including actions to be taken when a product fails stability, stability failure investigations and recalls, and details for establishing a longer shelf life.
3. The corresponding testing results as indicated in the stability testing protocol (i.e. T=0, T=6 months, T=1 year etc.).
4. Relevant SOPs and associated blank record templates related to stability data.

2.4.3 Samples

Section 61 of the Regulations indicates that the NHPD may ask a manufacturer, importer, or distributor to submit samples of a lot or batch of a product if a concern arises regarding the safety of that product.

Intent

Samples are maintained as evidence of product quality should an investigation ensue from a customer complaint, product recall, etc. Samples are to be maintained in an environment that would mimic regular storage requirements to ensure the sample is equivalent to products available for sale.

To meet the requirements

Manufacturers, importers and distributors must ensure the following:

1. Retain an adequate number of samples of each lot of a finished product. Importers and distributors may have the manufacturer or a designated third party keep samples for them, provided the samples are readily available upon request.
2. Retain samples in their final trade packages or in containers of the same material and construction.
3. Store samples in the environmental conditions listed on the label.
4. Ensure that samples are of sufficient size to permit complete testing according to specifications.
5. Maintain samples for at least one year after the expiry date.

Importers are responsible to notify NHPD when making alternative arrangements for retaining samples. The alternate site must commit to retaining the samples in the same containers as those marketed in

Canada.

Examples of evidence to demonstrate GMP compliance for sampling:

1. List of all samples being held, including product name and lot number.
2. Description, SOP, or record confirming that the samples are held and maintained for at least one year past the product expiration date.

2.4.4 Records

Sections 53 to 58 of the Regulations set out the record-keeping requirements for manufacturers, packagers, labellers, importers, and distributors.

Intent

Records are maintained as evidence of product production and quality should an investigation ensue from a customer complaint, product recall, etc.

To meet the requirements

1. Manufacturers, packagers, labellers, importers and distributors shall meet the minimum record-keeping requirements set out in Appendix 2.
2. Records must demonstrate that each batch has been manufactured, packaged and labelled according to the procedures described in the master production document. For importers, a certificate of manufacture is an acceptable alternative to lot or batch documents. However, complete batch documentation must be made available upon request.

When the manufacturer is located outside Canada, specific parts of the master production document considered to be a trade secret or confidential may be held on behalf of the importer by an independent party in Canada; however, the importer or independent party must ensure that the NHPD can access the data in a timely manner. The master production document must describe in general terms what, if anything, has been deleted.

3. Records must demonstrate that each lot of product has been manufactured, packaged, labelled, and imported according to the requirements of Part 3 of the Regulations.
 - a. when a product is manufactured, packaged, labelled and/or imported by a contractor in Canada, it is recommended that the site licence holder:
 - maintain a copy of the contractor's site licence, when applicable;
 - document and maintain records of all tasks carried out by the contractor; and
 - establish and maintain a written document or technical agreement covering the arranged manufacturing, packaging, labelling, importing, storage, or distribution in accordance with Part 3 of the Regulations. All arrangements for contracting including any proposed changes to technical arrangements should be in accordance with the GMPs as well as the marketing authorization for the product concerned.

Note: The technical agreement or relevant parts thereof should be made available to the NHPD upon request in the event that further assessment and clarification is needed.

- b. when the product is manufactured, packaged and/or labelled outside of Canada, importers must ensure that records can be accessed in a timely manner.
4. Manufacturers and importers must maintain evidence establishing the expiry date of each product.
 5. Manufacturers must maintain evidence or records of raw material testing conducted with



- respect to a lot or batch of raw material used in the manufacture of the NHP.
6. Packagers must maintain evidence or records of packaging material testing conducted with respect to the material used to package the NHP.
 7. Maintain evidence showing compliance of each finished product with specifications.
 8. Other record-keeping practices may include the following.
 - retain authorized written procedures for all sections of these requirements for reference and inspection. Review written procedures regularly and have authorized employees keep them up to date. Document the reasons for revising the procedures, and establish a system to ensure that only current procedures are in use;
 - have authorized employees approve, sign and date all relevant documents related to GMPs, such as records of actions taken or conclusions reached, and procedures. Ensure that any alteration of a document is signed and dated and that the alteration permits reading of the original information. Do not alter documents without authorization;
 - records may be maintained by authorized person(s) in electronic format provided that there is adequate back-up. Such electronic data must be printable and all alteration must be tracked. Manufacturers, packagers, labellers, importers and distributors must be able to access their electronic records and documents at least one year after the product's expiry date; and
 - electronic signatures are acceptable as an alternative to handwritten signatures. The electronic signature identification system must be tested and evaluated for security, validity and reliability. The electronic signature identification system must be secured from abuse, and include electronic protection against willful or accidental damage. All stages of development of electronic signature identification systems must be documented.
 9. Manufacturers, packagers, labellers, importers, and distributors must maintain at their premises in Canada distribution records that contain sufficient information to enable the recall of every lot that has been made available for sale. Please refer to the recall reporting section of this guidance document for further information.
 10. Manufacturing, testing, and distribution records must be retained for at least one year after the lot expiry date.

Examples of evidence to demonstrate GMP compliance for record maintenance:

1. Master Production Document and/or batch record.
2. A list of all contract manufacturers, packagers and labellers used.
3. For each contract manufacturers, packagers and labeller used, a signed Quality Technical Agreement clearly demonstrating who is responsible for each section of Part 3 of the Regulations.
4. Stability data and testing records for each product.
5. Records of all raw material testing for each product.
6. Relevant SOPs.
7. List of all NHPs that are at the site.

2.4.5 Recall and recall reporting

Section 50 of the Regulations requires that every manufacturer, packager, labeller, and distributor must establish and maintain a system for recall. Section 62 of the Regulations outlines what information manufacturers, importers, and distributors must provide to Health Canada when a product recall is initiated.

Intent

The requirements for recall system and recall reporting are to ensure that the manufacturer, packager, labeller, and/or importer may execute a product recall successfully ensuring that all the pertinent information is available and all product on the market is given the correct disposition.

To meet the requirements

1. Establish written procedures that define controls to ensure the effective recall of a product, including notification of [Health Canada Regional Operational Centres](#). Specifically, this means the following:
 - identifying individual(s) to be responsible for initiating and coordinating recall activities;
 - 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 (e.g. determining extent of recall, and means of notifying affected parties);
 - 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 and recording at intervals the progress and efficacy of the recall, and issue a final report, including a final reconciliation; and
 - notify all Canadian and foreign sites involved in the manufacture, import, and distribution of the recalled products.
2. Manufacturers, importers, and/or distributors who recall a NHP must submit product recall information to the appropriate Health Products and Food Branch Inspectorate (HPFBI) Regional Operational Centre within three days of initiating the recall. The following information is required to be provided:
 - 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 NHP;
 - 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 NHP; and
 - j) description of any other action that the manufacturer, importer, and distributor, as the case may be, is taking in respect of the recall.

Examples of acceptable evidence to demonstrate GMP compliance for recall reporting:

1. Recall record or recall report from within the last 12 months.
2. Product distribution records.
3. Mock recall.



4. Should a recall have occurred, all recall information and product disposition.
5. SOPs related to recall information required to be provided (indicated above) to Health Canada in the event of a recall as well as the contact information for the appropriate HPFBI Regional Operational Centre.

2.4.6 Sterile products

Sections 59 and 60 of the Regulations set out the requirements for manufacturing and packaging of sterile products.

Intent

This regulation requires that proper GMPs are implemented to ensure the product meets the definition of a sterile product, whether through manufacturing or terminal sterilization.

To meet the requirements

1. Manufacturers, packagers, labellers, importers and distributors must treat all sterile (ophthalmic) NHPs in the same manner as any other sterile health product. Follow the guidance for sterile products provided in the Health Products and Food Branch Inspectorate's [Good Manufacturing Practices Guidelines](#) as it is amended time to time. The guidelines for sterile products apply in addition to the non-sterile requirements outlined in this document.

Examples of evidence to demonstrate GMP compliance for sterile manufacturing:

1. Batch records.
2. In-process and finished product testing.
3. Validation and monitoring records.
4. QAP and product support staff qualifications.
5. Records related to specialized training in microbiology.
6. SOP related to clean room maintenance.
7. SOP related to laminar flow maintenance.
8. SOP related to product sterilization methods.



References

Australian Department of Health and Ageing, *Australian Code of Good Manufacturing Practice for Medicinal Products*, <http://www.tga.gov.au/archive/manuf-medicines-cgmp-020816.htm> (August 16, 2002)

Good Manufacturing Practices for Pharmaceutical Products: Main Principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4.

HACCP for Excellence: <http://www.haccpforexcellence.com/> (December 11, 2002)

Health Canada, *Proposed Good Manufacturing Practices for Natural Health Products Workbook*, used at information workshops in June—July 2002, 2002.

Health Canada, *Food and Drugs Act and Regulations*:
http://laws.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html

Health Canada, *Good Manufacturing Practices Guidelines 2002 Edition, Version 2*, <http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/gmp-bpf-eng.php>

Health Canada, Natural Health Products Directorate Evidence for Quality of Finished Natural Health Products Guidance Document 2007 Edition, Version 2.0: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/eq-paq_e.html

Health Canada, Natural Health Products Directorate, Site Licence Guidance Document, Version 3.0, <http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/slqd-drle-eng.php>

Health Canada, *Natural Health Products Regulations of June 18, 2003*.

Health Canada, *Statement of Qualifications: Compliance Officer*, Ontario Operations Centre, October 1, 2002.

Natural Nutritional Foods Association, *NNFA GMP Certification Program Overview*, 2001.
http://www.supplementquality.com/testing/NNFA_GMP_5yr.html (December 11, 2002).

NSF International Strategic Registrations, Ltd., *Glossary*, <http://www.nsf.org/services/by-company/nsf-isr/> (December 11, 2002).

NSF International, *Dietary Supplements and Functional Foods & Beverages Auditor Position Description*, November 15, 2002.

Official Journal of the European Union. European Commission Directive 2003/94/EC of 8 October 2003.

WHO Guidelines on Good Manufacturing Practices (GMP) for Herbal Medicines. Geneva, World Health Organization, 2007.



Glossary

The definitions given below apply to the terms used in this guidance document. Certain terms may have different meanings in other contexts.

Assess. Steps taken by the site licence holder to ensure that the requirements in the *Food and Drugs Act*, the *Natural Health Products Regulations* and in-house standards are met. The steps could include, among others, monitoring and testing of raw and/or packaging materials, tracking of production, maintenance of records and testing of finished products.

Attenuation. Attenuations are prepared by dissolving one part of the soluble basic substance in a sufficient quantity of purified water or other appropriate menstruum, specified in the recognized monograph, to produce (x) parts by volume of liquid attenuation (e.g. 1X, 1CH).

Batch. A quantity of product in the processing stage, homogeneous within specified limits, produced according to a single manufacturing order and as attested by the signatories to the order. In the case of continuous manufacture, the batch corresponds to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number. A distinctive combination of numbers and/or letters that specifically identifies a product batch, and appears on documents such as the batch record, certificate of analysis.

Batch record. Production document that captures the quantity and lot number of all materials used, as well as production steps in the manufacturing of a single batch of a natural health product in dosage form.

Bulk natural health product. Unpackaged dosage form, usually in quantities larger than the largest commercially available package size.

Bulk preparation. Unpackaged homeopathic preparation, usually in quantities larger than the largest commercially available package size.

Certificate. A legally authenticated written declaration issued by a recognized institution to a person completing a course of study.

Certificate of Analysis. A document signed by a qualified analyst that includes the product name, ingredient listing, lot number of the product, test conducted, test method and results, conclusion of the test (satisfactory or unsatisfactory), name and position of the analyst, and date of issuance.

Certificate of Manufacture. A document issued by a vendor to a distributor or importer that attests that a specific lot of product has been produced according to its master production document. Such certificates include a summary of the current batch documentation, with reference to respective dates of revision, manufacture and packaging, and are signed and dated by the vendor's authorized quality assurance person.

Comminution. The act of reducing to a fine powder or to small particles.

Contract Manufacturer. A firm (business) that manufactures, packages, and/or labels a natural health



product, or performs any other activity or operation in respect of a natural health product, under the terms of an agreement with another party. Additional terms of reference may include: contract manufacturing organization, contractor, contract acceptor.

Critical process. A process that may cause significant variation in the quality of the finished product.

Diploma. A document issued by an educational institution, such as a university, college, or technical institute, vouching that the recipient has earned a degree or successfully completed a particular course of study.

Distributor. A person who sells a natural health product to another person for the purpose of further sale by that other person.

Dosage form. The final physical form of the natural health product which may be used by the consumer without requiring any further manufacturing.

Education. The act or process of imparting or acquiring knowledge or skills; the learning of information by instruction, training, or study can be testified to by a degree, certificate or diploma.

Experience: Active participation in events or activities leading to the acquisition of knowledge or skills; the knowledge or skills retained from personally observing, encountering, or undergoing something.

Filling. Transferring and enclosing a bulk product into its final container.

Finished product. A product that has undergone all stages of production, including packaging in its final container and labelling.

Food and Drugs Act. A federal statute regulating the health and safety of food, drugs, natural health products, cosmetics, and medical devices. The Minister of Health is responsible for the administration of the Act.

Formulate. To prepare components and combine raw materials into a bulk natural health product.

Hazard Analysis and Critical Control Points (HACCP). An internationally recognized system of food safety methods. It is a systematic approach to the identification, evaluation, and control of food safety hazards.

Homeopathic Medicines. Medicines that are manufactured from or contain as medicinal ingredients only those substances or sources referenced in *The Homeopathic Pharmacopoeia of the United States* (HPUS), the *Homöopathische Arzneibuch* (HAB), the *Pharmacopée Française* (PhF) or the *European Pharmacopoeia*, as amended from time to time, and that are prepared in accordance with these pharmacopoeias.

Import. To bring into Canada a natural health product for the purpose of sale.

Importer. A person who imports a natural health product into Canada, for the purpose of sale. This would include bulk natural health products.

In-process control. Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as a part of in-process control.

In-process product. Any materials or mixture of materials that must, to become a product in dosage form, undergo further processing.



In-process testing. The examination or testing of any materials or mixture of materials during the manufacturing process.

ISO (International Organization for Standardization). A worldwide organization of national standards bodies; ISO is a non-governmental organization that maintains a group of global standards.

Label (n). Includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package. Natural health products are included.

Label (v). To affix the inner or outer label of the natural health product.

Lot. A quantity of any natural health product in dosage form, a raw material or a packaging material, homogeneous within specified limits, constituting all or part of a single batch and identified by a distinctive lot number which appears on the label of the finished product.

Lot number. Any combination of letters, figures or both, by which any natural health product can be traced in manufacture and identified in distribution.

Maceration. Processing method using unheated solvent (cold or room temperature water, alcohol, or other organic solvent) to extract medicinal properties from a raw material.

Manufacture. To fabricate or process a product for the purpose of sale.

Manufacturer. A person who fabricates or processes a natural health product for the purpose of sale, but does not include a pharmacist or other health care practitioner who, at the request of the patient, compounds a natural health product for the purpose of sale to that patient.

Manufacturing order. Instructions that outline in detail the materials and procedures required to manufacture, prepare and preserve a single batch of a natural health product in dosage form.

Marketing authorization. A legal document issued by the Natural Health Products Directorate authorizing the sale of a natural health product in Canada.

Master formula. A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product.

Master production document. A document that includes specifications (raw material, packaging material, packaged dosage form), master formula, sampling procedures and critical processing related standard operating procedures, whether or not these procedures are specifically referenced in the master formula. It also includes a complete list of raw materials used in the manufacture of the product, designated by names or codes; the amount of each raw material required for the theoretical product formulation; manufacturing and process control instructions and in-process testing requirements (e.g. checks on materials, pre-treatments, sequence of adding materials, mixing time and temperatures); a statement of the principal equipment to be used; a statement of the theoretical weight or measure of the manufactured product and the acceptable limits beyond which an investigation is required; a description of the finished product containers, closures and packaging labels; any special precautions to be observed; and dates and times (if applicable) of commencement and completion of significant intermediate stages, such as blending or heating, and of completion of production.

Mother tincture. A relatively concentrated aqueous alcoholic extract from which subsequent attenuations are prepared. Synonyms: mother liquor, stock solution, starting solution.

Natural health product. A substance set out in Schedule 1 of the *Natural Health Products Regulations* or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine that is manufactured, sold or represented for use in



- a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- b) restoring or correcting organic functions in humans; or
- c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

However, a natural health product does not include a substance set out in Schedule 2 of the *Natural Health Products Regulations* or any combination of substances that includes a substance set out in Schedule 2. See Appendix 1 for Schedules 1 and 2.

Nosodes. Attenuations of pathological organs or tissues; causative agents such as bacteria, fungi, ova, parasites, virus particles, and yeast; disease products; excretions or secretions.

Observation. A deviation or deficiency of good manufacturing practice noted by an inspector or assessor.

Package (n). Includes immediate container in which any food, drug, cosmetic or device is wholly or partly contained, placed or packed.

Package (v). To put a product in its immediate container.

Packaging material. Labels, printed packaging materials and those components in direct contact with the dosage form.

Packaging order. Instructions that outline in detail the materials and special procedures required to package and label a single lot of a product in dosage form.

Percolation. A method used for the extraction of dried substances that have been reduced to the proper degree of fineness.

Potency. The amount per dosage unit of the standardized component(s) which further characterizes the quantity of the ingredient. It is required only when a claim on the potency is to be on the label, or it is required for a specific product (i.e. when literature supports the product with that standardized component). In Supplementary Good Manufacturing Practices for Homeopathic Medicines, potency refers to the degree of dilution of a homeopathic medicine.

Production. All operations involved in the preparation of a finished product, from receipt of materials, through processing and packaging, to completion of the finished product, including storage.

Purity. The extent to which a raw material or a product in dosage form is free from undesirable or adulterating chemical, biological or physical entities as defined by specification.

Qualification. To make competent or eligible for an office, position, or task by having the proper or necessary skills, knowledge, credentials, accomplishments or qualities.

Quality assurance. All the planned and systematic activities applied within the quality system to provide adequate confidence that the predetermined standards for quality and safety will be met.

Quality assurance person. The person who is responsible for assuring the quality of the natural health product before it is made available for sale. This person has the training, experience and technical knowledge relating to the specific activity conducted (i.e. manufacturing, packaging, labelling, and importing) and the requirements of Part 3 of the *Natural Health Products Regulations*.

Quality Assurance Report. A report prepared by either a quality assurance person or a Natural Health Products Directorate recognized third party auditor who meets the requirements with respect to



education, training, and experience according to section 51(a) (ii) of the *Natural Health Products Regulations*. This report is based on the assessment against the good manufacturing practices regulations and requirements set out in the good manufacturing practices guidance document. It is considered a self-assessment document and evidence of good manufacturing practices compliance.

Quantity. The amount of medicinal ingredient(s) per dosage unit. It is always required for a product, as it is the amount of medicinal ingredient in the product.

Quarantine. Effective restriction of the availability of material or product for use (physically or by system), until released by the quality assurance person.

Raw material. Any substance, other than in-process product or packaging material, intended to be used in the manufacture of products, including those that appear in the master formula but that do not appear in the product such as solvents and processing aids.

Recognized institution. A post-secondary educational facility (e.g. a university, college or professional institute) generally approved for having a secure reputation; credible, reputable, and authoritative.

Reconciliation. A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

Reprocessing. Subjecting all or part of a batch or lot of an in-process product or finished product to a previous step or alternate manufacturing process due to failure to meet predetermined specifications.

Returned product. Bulk or finished product sent back to the manufacturer, distributor, or importer.

Sampling. Collection of a number of units that comprises representative sample from a designated lot or batch of product.

Sell (section 2 of the *Food and Drugs Act*). “Sell” includes offer for sale, expose for sale, have in possession for sale and distribute, regardless of whether the distribution is made for consideration.

Site. A place of or for an activity specified under the *Natural Health Product Regulations*.

Standard operating procedure. An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning, cleaning of premises and environmental control, sampling and inspection). Certain standard operating procedures may be used to supplement product-specific master production documents.

Sterile dosage form. A dosage form that is free from microbial contamination.

Storage. A site, also called a warehouse, whose main purpose is to hold natural health products.

Technical agreement. A formal written document between two or more parties outlining the technical portions of a contract and the specific duties of each party involved with respect to Part 3 of the *Natural Health Products Regulations*. A technical agreement is mutually understood and signed by each party.

Third-party auditor. An auditor who is qualified by education, training and experience and who is recognized by the Natural Health Products Directorate for the purpose of conducting an on-site audit based on the requirements outlined in part 3, Good Manufacturing Practices of the *Natural Health Products Regulations*.

Training. To make proficient with specialized instruction and practice.

Trituration. Attenuations of solid substances are prepared by trituration of the crude substance with lactose.



Voucher Specimen. A representative specimen preserved to permit independent verification of identity and to allow further examination (e.g. pressed plants, non-human animal material in preserving fluids).



Appendix 1: Records

Sections 53 to 58 of the Regulations set out the record-keeping requirements for manufacturers, packagers, labellers, importers, and distributors.

In this chart, *site* indicates that records must be retained on the premises, while *access* means that records need not be kept on the premises, but rather must be readily available.

Record keeping requirements for various activities

Record	Manufacturer	Packager	Labeller	Importer	Distributor
Master production document	site			access	
Manufacturing order	site			access	
Packaging order	site	site		access	
Labelling order	site		site	access	
Test results: raw material	site			access	
Test results: packaging material	site	site		access	
Test results: finished product	site			access	
Specifications: raw material	site			access	
Specifications: packaging material	site	site		access	
Specifications: finished product	site			access	
Stability summary	site			access	
Ingredients list	site			access	
Products list	site	site	site	access	site
Distribution list	site	site	site	access	site
Complaints	site	site	site	site	site
Sanitation program	site	site	site	site	site



Appendix 2: Good documentation practices

Below are the generally recognized elements that define Good Documentation Practices (GDP).

- 1) Documentation creation:
 - Completed at the same time as the event they describe;
 - not handwritten (except for handwritten entries thereon);
 - when electronically produced, the documentation must be checked for accuracy;
 - free from errors; and
 - in a format that permits trend evaluation, when applicable.
- 2) Document approval:
 - approved, signed, and dated by appropriate authorized personnel .
- 3) Handwritten entries:
 - adequate space is provided for expected handwritten entries;
 - handwritten entries are in indelible ink;
 - critical entries must be independently checked (SPV, or second person verified);
 - no spaces for handwritten entries are left blank - if unused, they are crossed out or "N/A" (or similar text) entered;
 - ditto marks or continuation lines are not acceptable; and
 - a stamp in lieu of a handwritten signature is not acceptable.
- 4) Copies of documents:
 - clear, legible; and
 - errors are not introduced.
- 5) Document maintenance:
 - regularly reviewed and kept current;
 - retained and available for appropriate duration;
 - electronic document management systems are validated; and
 - electronic records are backed up.
- 6) Document modification:
 - handwritten modifications are signed and dated;
 - altered text is not obscured (e.g., no Wite-Out);
 - where appropriate, the reason for alteration must be noted ("E.E." is a common abbreviated reason, indicating "Entry Error");
 - controls exist to prevent the inadvertent use of superseded documents;
 - electronic versions can only be modified by authorized personnel;
 - access to electronic versions must be controlled by password or other means; and
 - a history (audit trail) must be maintained of changes and deletions to electronic versions.

Regarding the GDP interpretation from the guidance above, additional expectations or allowances can be inferred by extension. Among these are:

- a) prohibition against removing pages - the removal of a page would obscure the data that were present, so this is not permissible;
- b) page numbering - the addition of page numbers, particularly in "Page x of y" format, allows a reviewer to ensure that there are no missing pages;
- c) stamped signatures in Asia - the culture of certain Asian countries, and the controls they employ, are such that their use of a stamp in lieu of handwritten signatures has been accepted;
- d) date and time formats - dates may be written in a variety of formats that can be confusing if read



by personnel with a different cultural background. In the context where different cultures interact, a date such as "07-05-10" can have numerous different meanings and therefore, by GDP standards above, violates the requirement for being clear;

- e) transcription - a transcription of data, where the original document is not retained, effectively obscures the original data and would be prohibited. Transcription may be helpful where the original is of poor quality writing or is physically damaged, but it should be clearly marked as a transcription and the original retained nevertheless;
- f) scrap paper, post-it notes - intentionally recording raw data on non-official records is a set-up for transcription and is therefore prohibited; and
- g) avoiding asterisks as part of the notation of a hand-change - Where insufficient white space permits a fully notated hand change, a common practice is to use an asterisk (or other mark) near the correction, and elsewhere record the same mark and the notation. The risk is that additional changes are made by another person who uses the same mark, and now the notation can be interpreted to apply to all changes with the mark. Some will therefore advise against the use of the asterisk. Others will accept it, if the notation clearly includes the number of changes that it applies to, such as, "* Three entries changed above due to entry errors. KAM 13-Jan-2011".



Appendix 3: Standard operating procedure

Intent

Standard operating procedures (SOPs) aim to systemize your processes and document them; they play a major role in the quality assurance system of a company. When followed, SOPs create efficiency, consistency and reliability in activities performed; they help generate fewer errors and a healthy and safe environment.

What is a SOP?

A SOP is a procedure specific to your operation that describes the steps necessary to complete tasks in accordance with regulations and/ or your own standards. Their format, structure and level of detail should provide adequate information to keep performance consistent from one person to another. They are also used to train employees and should be available to all. SOPs are of limited value, if written incorrectly. It is recommended that each SOP is specific to a given task, activity or process.

To meet the requirements

All SOPs must contain the following:

1. Header section with the SOP's title, number, and version. Footer section with SOP's author name, page number, creation, and approval dates.
2. Scope: describe the purpose and to what activity the SOP is related, as well as to whom or which department it applies.
3. Responsibilities: mention all job position that should follow this SOP as part of their task.
4. Material: list all materials, equipment or devices that will be needed to perform this activity.
5. Safety: this section could be added when it applies, to raise awareness on any safety issues regarding a specific task (e.g.: wearing a mask).
6. Procedure: describe step by step how to perform the activity in a consistent and repeatable fashion.
7. Records: states where to annotate and keep records related to the activity.
8. List of attachments: a SOP can have attachments or annexes that are forms to be completed when an activity is executed (e.g.: cleaning of equipment log, that will be used to track the dates at which a certain equipment was cleaned, the person who performed the task, the signature and any other comments if necessary).
9. History: track the dates of revision and the change that were made to the SOP.
10. Approval: this last section should show the name of the author, reviewer and approval of the Quality Assurance Person (QAP).

Additional sections can be added to a SOP if needed, especially if it improves the quality of the document. It is recommended to maintain style and consistency across documents to assist in their readability.

Illustrations or pictures can be used to ease understanding and cross references to other SOPs can be made.

Control of SOPs

A SOP should be:

- a) reviewed by one or more individuals. The final version should be approved and dated by the



Quality Assurance Person;

- b) updated and re-approved whenever procedures are changed;
- c) systematically reviewed on a periodic basis to ensure that procedures remain current and appropriate; and
- d) a controlled document with a numbering system to systematically identify and label them. Each page of a SOP should have control documentation notation. The revision number and date are very useful in identifying the SOP in use when reviewing historical data and is critical when the need for evidentiary records is involved and when the activity is being reviewed. When the number of pages is indicated, the user can quickly check if the SOP is complete.

A list of all SOPs should be maintained and updated. Codes can be used when assigning them a number and can be related to the department that owns the SOP. For example, the SOP for the warehouse cleaning can be identified as WA-01-V0: Warehouse Cleaning, where:

- a) WA will be the code for all procedures related to the warehouse;
- b) 01 will be for procedure # 1;
- c) V0 will be for Version 0, (if changes are made to this procedure, the updated SOP will be WA-01-V1); and
- d) The code is followed by the title of the SOP.



Appendix 4: Supplementary good manufacturing practices for homeopathic medicines

To be considered a homeopathic medicine, a product must meet two criteria. It must be:

1. Manufactured from, or contain as medicinal ingredients, only substances referenced in a homeopathic monograph in one of the following homeopathic pharmacopoeias, as they are amended from time to time:
 - Homeopathic Pharmacopeia of the United States (HPUS).
 - Homöopathisches ArzneiBuch (HAB) or German Homeopathic Pharmacopoeia (GHP).
 - Pharmacopée française or French Pharmacopoeia (PhF).
 - European Pharmacopoeia (Ph.Eur.).
 - Encyclopedia of Homeopathic Pharmacopoeia (EHP).
2. Prepared in accordance with the methods outlined in one of the homeopathic pharmacopoeias listed above, as they are amended from time to time.

Homeopathic medicines are made from a wide range of materials such as plants, animals, chemicals and minerals many of which are highly toxic in the raw material form. Nosodes are another type of homeopathic medicines, which are preparations of pathological tissues, excretions or secretions. Due to these factors, manufacturers must ensure the critical processes (i.e. raw material identification, raw material handling, attenuations, etc.) are carried out under controlled conditions.

Manufacturers, packagers, labellers of homeopathic medicines, in addition to meeting the requirements in Chapter 1, must meet the supplementary requirements of this chapter. The sections in Chapter 1 on equipment, quality assurance, samples, records, recall reporting and sterile products fully address the requirements for homeopathic medicines, and therefore are not repeated here.

The [Evidence for Homeopathic Medicines](#) guidance document outlines product requirements. Also note, in this chapter, potency refers to the degree of dilution of a homeopathic medicine

Places

Premises

To meet the requirements

Due to the infinitesimal dose of active ingredients, homeopathic medicines must be prepared in a manner that eliminates the possibility of cross-contamination and/or outside contamination, within reason.

1. Manufacturers, packagers, labellers must design their premises so that the homeopathic attenuations are prepared in rooms or workstations that have appropriate environmental controls (e.g. a room with filtered air under positive pressure or in a laminar airflow workstation) and must be distinctly separate from products which are volatile or have permeating odours.
2. Manufacturers, packagers, labellers must design their premises to accommodate hazardous raw material storage and processing requirements. These requirements include, but are not limited to, the following:
 - Isolating toxic or infectious raw materials from other materials; and
 - Handling raw materials in segregated areas with appropriate environmental controls suitable for each material.

Note: A list of raw materials that should be “Stored with care” and “Stored with great care” are listed in the German Homeopathic Pharmacopoeia (GHP).

3. Equipment and utensils used must be exclusive to homeopathic preparations. In addition:



- Must be made of materials that do not shed particles;
- The cleaning and maintenance products used (e.g. lubricants) must not lead to contamination; and
- Standard operating procedures include the cleaning of vessels and containers employed in successive attenuations or trituration's.

People

Personnel

To meet the requirements

1. Manufacturers, packagers, labellers must provide training specific to the attenuation and/or trituration of homeopathic medicines. Supporting documents would provide details of training content and completion dates.
2. Restricting the entry of untrained or unnecessary personnel in processing areas designated for attenuation and trituration.

Processes

Sanitation

To meet the requirements

1. Manufacturers, packagers, labellers must ensure that the sanitation program does not contaminate the homeopathic product with chemical or particulate matter:
 - cleaning, microbial and environmental monitoring requirements for all processing areas, with emphasis on areas designated for attenuation and trituration;
 - methods ensure cleaning products do not contaminate product; and
 - methods are adequate to ensure there is no cross contamination of product.

Operations

To meet the requirements

Manufacturers, packagers, labellers shall maintain separate written procedures for homeopathic products and do the following:

Critical Production Processes

Homeopathic medicines must be made according to the preparation methods in one of the 5 accepted homeopathic pharmacopoeias.

1. Raw materials are harvested or produced as per the pharmacopoeias. The identity of all raw materials must be verified and recorded. Raw materials that are toxic or potentially infections must be labelled as to their safety status (e.g. allergen, toxic) or MSDS equivalent.
2. Mother tincture batch records must contain sufficient information, such as: the duration of maceration and/or percolation, trituration duration and intensity for each type and size of apparatus, particle size of the raw materials in the triturate matrix, quality specifications and QA release, ensuring sterility of nosodes, such as heat processing of the first attenuation in the preparation, etc.
3. In-process attenuations or triturations are the most critical steps in the production of homeopathic medicines and every effort must be made to ensure the process is consistent, reliable and contaminant-free. Include the following information in the master formula and batch record:
 - the system for the particular attenuation series (e.g. Hahnemannian, Korsakovian);



- SOPs, or reference to SOPs, to be followed at each processing stage;
 - number of succussions during each attenuation;
 - duration of trituration, where applicable;
 - disposal of unused intermediate homeopathic potencies;
 - technique for impregnation, where final dosage forms are manufactured;
 - in-process controls with specifications;
 - a reference number unique to a particular series, different from the batch number assigned to the product;
 - the attenuation or trituration number at the particular stage of preparation (e.g. this could be designated by potency);
 - the name, dosage form, batch number and batch size of the preparation for which it is intended;
 - the composition or reference to the master formula;
 - the internal code and analytical control number of each raw material or mother tincture used;
 - precautions to be adopted during handling, when applicable; and
 - Schedule manufacturing to ensure continuity within the attenuation or trituration series and avoid prolonged storage of intermediate homeopathic potencies.
4. For the manufacturing of impregnated pellets from medicating potencies made by a separate company, the following is required:
- Raw material identity testing and the batch record demonstrating that the raw material was added during the manufacturing process;
 - Studies demonstrating that impregnation procedure is adequate;
 - the SOPs, or reference to SOPs, for washing, drying and, when applicable, sterilizing packaging materials; and
 - Stability studies or challenge studies from your site demonstrating that the procedures and materials used adequately ensure there is no microbiological contamination until expiry.

Products

Specifications

To meet the requirements

Manufacturers, packagers and labellers shall maintain written specifications that describe the homeopathic medicine and the required test methods. For specifications pertaining to identity, purity, quantity, potency and tolerances, see the Evidence for Homeopathic Medicines Guidance Document. Specifications must be of pharmacopoeial (e.g. The Homeopathic Pharmacopoeia of the United States, the Pharmacopée Française, the Homöopathische Arzneimittel or the European Pharmacopoeia)

Manufacturers must also follow conventional testing protocols for the dosage form (e.g. for tablets, uniformity of weight, hardness and disintegration; for liquid, alcohol type and percentage; for ointments/syrups, viscosity or rheology; etc.).

Stability

To meet the requirements

Manufacturers, packagers and labelers shall establish a period of time that the product meets its specifications:

- develop and maintain standard operating procedures that ensure the stability of the homeopathic medicines;
- maintain records of ongoing purity testing as outlined in the Evidence for Homeopathic Medicines Guidance Document. Note: Due to the unique quality of homeopathic medicines, the evidence of



stability would focus on microbiological contamination (ie. in products of <50% alcohol) and the non-medicinal ingredients (e.g. concentration of alcohol remains consistent, granules/tablets hardness and disintegration are consistent); and

- packaging materials testing, such as bottles and caps, demonstrating that they do not contaminate product; and demonstrating that the labels do not fade or come away from the packaging.



Appendix 5: Quality technical agreements

What is a quality technical agreement?

A quality technical agreement can be defined as a formal written document between two or more parties that relates to the manufacturing, packaging, labelling, importing, storage and/or release for sale of products that are regulated by the NHPD. It refers to the quality-related technical portions of a contract and defines the specific duties, responsibilities and expectations of each party. It is a clear, quality plan that is discussed, written, understood and signed by all parties.

The NHPD encourages the development of written agreements between parties to include every activity or operation that is carried out in respect of a NHP when more than one party is involved. Written agreements, or contracts, may differ between organizations depending on the activities or operations being contracted out and the specific needs of the parties.

Clearly documented roles and responsibilities should occur by means of a written document that covers the manufacturing, packaging, labelling, importing, distribution, and storage arranged under agreement.

The quality technical agreement instruction

Technical aspects of a business arrangement that are not clearly spelled out in a written agreement may lead to misunderstandings and potentially to the manufacturing of a NHP that does not meet quality, safety and efficacy requirements. While one site alone may not meet all the regulations, 2 or more sites can demonstrate that the quality systems in place collectively are able to satisfy all of Part 3 of the NHPR. The quality technical agreement provides firms with the flexibility to contract out activities or operations, while demonstrating compliance with regulatory requirements.

The following points represent key areas of consideration when drafting a quality technical agreement. They do not represent an exhaustive list of requirements for an agreement; rather, they highlight areas that may require special consideration when planning and negotiating a quality technical agreement with your contract manufacturing, packaging, labelling, importing, and/or storage partner.

- Specifications: the agreement should summarize the NHP specifications that are mutually agreed upon and include tolerance limits and test methods for each test;
- Operations: the agreement should specify that the SOPs relating to NHPs be specifically designed and maintained for the control of NHPs and in accordance with Part 3 of the Regulations. The procedures must be independent of procedures in use for the work and control of other products (e.g., foods, cosmetics, etc.) by the contracted party;
- Recall: the quality technical agreement should clearly define the parties who are responsible for the coordination and the execution of a recall, in the event one become necessary;
- Quality Assurance: the agreement should state the way in which the authorized quality assurance person releasing each batch of product for sale or issuing the certificate of analysis exercises his or her full responsibility. The quality technical agreement should clearly define which party is responsible for sampling, testing and/or approving and releasing materials, including packaging materials, bulk, raw, intermediate and finished.
- Complaints: the agreement should describe how the contracted party will handle, record and investigate, any complaints received in respect of the quality, safety and/or efficacy of a NHP;
- Stability: define which party is responsible for product stability (including program, monitoring, and analysis);



- Records and Record Maintenance: the agreement should specify which records related to manufacturing, packaging, labelling, importing, storage, distribution, testing/analysis of NHPs, or any other required records, should be maintained by the contracted party;
- Lots or Batch Samples: the agreement should define which party is responsible for retaining lot or batch samples; and
- General: the sponsor and contract manufacturer should agree on the period of validity of the quality technical agreement as well as the timelines for review and the process for amendments to the agreement.

Both firms have engaged in a partnership; however, prior to entering into a formal contract, it is necessary to establish and define clear roles and responsibilities to ensure that the NHPs produced under the partnership are consistently safe, of high quality, and effective. Product license holders are ultimately responsible for ensuring the quality of the NHPs. Activities and/or responsibilities not specifically detailed within a quality technical agreement will by default, be the responsibility of the product license holder. The following simplified diagram depicts a common contract manufacturing scenario.