Health Canada Santé Canada

GOOD MANUFACTURING PRACTICES GUIDANCE DOCUMENT

Natural Health Products Directorate

August 2006
Version 2.0

Canada

“Our mission is to help the people of Canada maintain and improve their health, while respecting individual choices and circumstances.”

Health Canada

“Our role is to ensure that Canadians have ready access to natural health products that are safe, effective and of high quality while respecting freedom of choice and philosophical and cultural diversity.”

Natural Health Products Directorate

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ABOUT THIS GUIDANCE DOCUMENT

This guidance document is intended for manufacturers, packagers and labellers of natural health products (NHPs) in Canada and elsewhere, including Canadian importers and distributors of these products. It is meant to help them meet the good manufacturing practice (GMP) requirements of the *Natural Health Products Regulations* (the Regulations). In addition, the guidance document is a tool for the Quality Assurance Person (QAP) to implement and maintain GMP and to fulfill their role in assuring the quality of a NHP before it is made available for sale. It is the responsibility of the manufacturer, packager, labeller or importer to ensure that the QAP has the relevant training, experience and technical knowledge and the QAP is capable of carrying out all the necessary quality-related functions.

GMPs are ongoing measures designed to ensure an effective overall approach to product quality control and risk management. They do so by setting appropriate standards and practices for product testing, manufacturing, storage, handling and distribution.

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

Manufacturers, packagers, labellers and importers must demonstrate that they adhere to these practices before the NHPD will issue them a site licence. Distributors must follow the relevant GMPs, but are not required to hold a site licence.

Chapter 1 of the guidance document covers all of Part 3 (sections 43 to 62) of the Regulations, dividing GMP into the following categories:

- Places (premises and equipment);
- People (personnel and quality assurance);
- Processes (sanitation program and operations); and
- Products (specifications, stability, samples, records, recall reporting and sterile products).

Each section under places, people, processes and products begins with a brief explanation of what the Regulations say, followed by a box with the actual Regulations. Following that is the section **To Meet the Requirements**, which explains in more detail how to comply with the Regulations.

Chapter 2 provides the supplementary GMP requirements for homeopathic medicines.

The definitions of terms used in this guidance document are provided in the **Glossary**.

A complete version of the Regulations is available on the Internet at http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/acts-lois/prodnatur/regs_cg2_e.htm.

The first draft of this guidance document was developed in the spring of 2002 with input from the NHP industry, academics, researchers, consumers, health practitioners and representatives from other government programs. The experts represented four areas of specialty: herbal medicines and botanicals, homeopathic medicines, traditional herbal medicines, and vitamins and minerals. Shortly afterwards, NHPD held workshops for the public and industry about the GMP requirements of the Regulations. These helped provide additional information and guidance for preparing the final *Good Manufacturing Practices Guidance Document*. NHPD's GMPs working group compiled, analyzed and incorporated the information received at these workshops to produce the final document.

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1.0 GOOD MANUFACTURING PRACTICES

Part 3 (sections 43 to 62) of the *Natural Health Products Regulations* (the Regulations) sets out the good manufacturing practices (GMPs) that manufacturers, packagers, labellers and importers must meet before the Natural Health Products Directorate (NHPD) will issue a site licence for each location they intend to manufacture, package, label or import natural health products (NHPs) for sale in Canada. Distributors must follow the GMPs, as defined in the Regulations, however they are not required to hold a site licence. Distributors' responsibilities are identified in the guidance 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*.

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 manufacturer, packager, labeler or importer in Canada and their corresponding site licence numbers. They are also responsible to provide evidence that imported NHPs will be manufactured, packaged, labeled, imported, distributed and stored according to GMPs as set out in part 3 of the Regulations or their equivalent. For more information on product licences, see the *Product Licensing Guidance Document.*

The site licence holder is responsible to carry out each activity in which they are authorized to conduct in accordance with the GMPs. In addition, the site licence holder must ensure that all activities or services contracted out are conducted in accordance with Part 3 of the Regulations.

Part 3 begins with section 43, which states that any NHP sold must be manufactured, packaged, labelled, imported, distributed and stored according to the requirements of this part of the Regulations. NHPs that are imported into Canada must also be manufactured, packaged, labelled, imported, distributed and stored in accordance with requirements set out in Part 3 or its equivalent. It is the importer's responsibility to ensure that imported NHPs come from sites that meet the Canadian GMPs. For information related to evidence required from importers with respect to the foreign sites, refer to the *Site Licensing Guidance Document*.

PART 3: GOOD MANUFACTURING PRACTICES
Prohibition
Section 43

(1) Subject to subsection (2), no person shall sell a natural health product unless it is manufactured, packaged, labelled, imported, distributed and stored, as the case may be, in accordance with this Part.

(2) A person may sell a natural health product that is manufactured, packaged, labelled, imported, distributed and stored, as the case may be, in accordance with requirements that are equivalent to those set out in this Part if the natural health product is imported.

Each section under Places, People, Processes and Products, below, begins with a brief explanation of what the Regulations say, followed by a box with the text of the relevant Regulations. Following that is the section To Meet the Requirements, which explains in more detail how to comply with the Regulations. Readers are recommended to follow GMPs described

in this document to get a complete understanding of their responsibilities. However, NHPD will consider alternative means of complying with the Regulations, when additional rationale is provided.

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.

1.1 Places

1.1.1 Premises

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

PART 3: GOOD MANUFACTURING PRACTICES
Premises
Section 45

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

(a) permits the premises to be kept clean and orderly;

(b) permits the effective cleaning of all surfaces in the premises;

(c) permits the natural health product to be stored or processed appropriately;

(d) prevents the contamination of the natural health product; and

(e) prevents the addition of an extraneous substance to the natural health product.

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

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.

- 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;
  - provide 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 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 prevent pests from entering the premises.
- provide explosion proof bulbs and fixtures to avoid glass contamination

- 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.
- 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.
- Ensure supply water is of potable quality for processing and cleaning and shall meet the Guidelines for Canadian Drinking Water Quality [see http://www.hc-sc.gc.ca/ewh-semt/water-eau/drink-potab/guide/index_e.html], 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*.
- Ensure that floor drains are screened and trapped.
- Maintain the grounds around the manufacturing buildings to protect against the contamination of products.
- Install refuse receptacles and follow waste disposal practices that protect against contamination or harborage of pests.
- 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).
- Clearly mark physical quarantine areas when used.

1.1.2 Equipment

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

PART 3: GOOD MANUFACTURING PRACTICES
Equipment
Section 46

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

(a) permits the effective cleaning of its surfaces;

(b) permits it to function in accordance with its intended use;

(c) prevents it from contaminating the NHP; and

(d) prevents it from adding an extraneous substance to the NHP.

To Meet the Requirements

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

- 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.
- Protect analytical instruments and associated control systems from vibration, electrical interference and contact with excessive moisture or other external factors.
- Ensure that 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.
- Avoid the possibility of lubricants 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).
- Control and monitor temperature-sensitive compartments, and keep records.
- Properly maintain instruments and controls, including laboratory equipment, to ensure that they remain accurate, and retain records.
- Develop a calibration program for critical manufacturing, packaging and testing equipment, and maintain records.
- Maintain records of equipment and facility cleaning.
- Maintain equipment usage logs.

1.2 People

1.2.1 Personnel

Section 47 covers the education, training and/or experience requirements of personnel involved in manufacturing, packaging, labelling and storing NHPs.

> PART 3 GOOD MANUFACTURING PRACTICES
> Personnel
> Section 47
>
> Every natural health product shall be manufactured, packaged, labelled and stored by personnel who are qualified by education, training or experience to perform their respective tasks.

To Meet the Requirements

Manufacturers, packagers, labellers, importers and distributors must ensure the following:

- ensure that individuals in charge of manufacturing and quality assurance have adequate education, training and/or practical experience to control and supervise the activities; and
- ensure that all personnel have appropriate education (including ongoing GMPs or other continuing training) and/or have the practical experience necessary to perform their assigned duties. Maintain records of education and training and update when needed.

1.2.2 Quality Assurance

Section 51 sets out the requirements and responsibilities of the quality assurance person.

> PART 3: GOOD MANUFACTURING PRACTICES
> Quality Assurance
> Section 51
>
> (1) Every manufacturer, packager, labeller, importer and distributor shall
>
> (a) have a quality assurance person who
>
> (i) is responsible for assuring the quality of the natural health product before it is made available for sale, and
>
> (ii) has the training, experience and technical knowledge relating to the activity conducted and the requirements of this Part; and
>
> (b) investigate and record every complaint received in respect of the quality of the natural health product and, if necessary, take corrective action.
>
> (2) Every natural health product shall be manufactured, packaged and labelled using only material that, prior to its use in the activity, has been approved for that use by a quality assurance person.
>
> (3) Every natural health product shall be manufactured, packaged, labelled and stored using methods and procedures that, prior to their implementation, have been approved by a quality assurance person.
>
> (4) Every lot or batch of a natural health product shall be approved by a quality assurance person before it is made available for sale.
>
> (5) Every natural health product that is sold and subsequently returned to its manufacturer, packager, labeller, importer or distributor, as the case may be, shall be approved by a quality assurance person before that natural health product may be made available for resale.

To Meet the Requirements

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

- Establish and follow written procedures to ensure that products conform to specifications and regulatory requirements.
- Establish and follow written procedures for sampling, inspecting and testing raw and/or packaging materials, in-process and finished products.
- 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.
- 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.
- Review and maintain completed batch records.
- Approve or reject the product for distribution against the completed batch record.
- Approve or reject product quality deviations and product reprocessing in the manufacture of a product. Written procedure shall be established and implemented.
- 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.
- 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.
- Ensure that laboratories (in-house and contract) are capable of performing all of the tasks and responsibilities assigned to them.
- Maintain laboratory records of tests and investigations.
- Set up and follow written procedures for handling product complaints. These procedures must include determining whether further investigation and corrective action are required.
- 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.

Note: It is good practice for manufacturers, packagers, labellers, importers and distributors to provide a written job description to their quality assurance person to help protect him or her from a conflict of interest that may arise when duties conflict with those outlined in section 51.

1.3 Processes

1.3.1 Sanitation Program

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

> PART 3: GOOD MANUFACTURING PRACTICES
> Sanitation Program
> Section 48
>
> Every natural health product shall be manufactured, packaged, labelled and stored in accordance with a sanitation program that sets out
>
> (a) procedures for effectively cleaning the premises in which the activity is conducted;
>
> (b) procedures for effectively cleaning the equipment used in the activity;
>
> (c) procedures for handling any substance used in the activity; and
>
> (d) all requirements, in respect of the health, the hygienic behaviour and the clothing of the personnel who are involved in the activity, that are necessary to ensure that the activity is conducted in sanitary conditions.

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

- Develop a written sanitation program that includes the following elements:
  - cleaning procedures for facilities and processing equipment;
  - a list of cleaning /sanitizing agents and pesticide chemicals that shall be identified, used and stored in such a manner to prevent the contamination of raw materials and packaging and process equipment;
  - identification, use and storage of pesticide chemicals in such a manner to prevent the contamination of raw and 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; and
  - procedures for the destruction and disposal of waste materials and debris.
- Contain or ventilate dusty operations to prevent contamination of other areas.
- Develop a written pest control program outlining effective measures for preventing pest infestations of the building.

Health and Hygiene Program

- Ensure that 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 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.

1.3.2 Operations

Sections 49 and 50 set out the requirements for standard operating procedures for the manufacturing, packaging, labelling and storing of NHPs and a system for product recall.

PART 3: GOOD MANUFACTURING PRACTICES
Operations
Section 49

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

PART 3: GOOD MANUFACTURING PRACTICES
Operations
Section 50

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

To Meet the Requirements

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

Material Control

- Set up and follow written procedures for the transportation, receipt, identification, examination, handling, sampling, testing and approval or rejection of raw and/or packaging materials. Update the procedures as required.
- Identify each lot of raw and/or packaging materials with a distinctive lot number.
- Inspect containers of raw and/or packaging materials upon receipt for closure and physical integrity.
- Assess each lot of raw and/or packaging materials against specifications, such as plant identity, detectable foreign matter and the integrity (appropriate characteristics) and quality of plant material or extracts.
- Retest raw and/or packaging materials after any exposure to conditions likely to adversely affect their purity, quality or composition.
- Identify and control each lot of raw and/or packaging materials according to its quality status (e.g. quarantined, approved or rejected).
- Store raw materials, in-process materials and reprocessed materials in appropriate conditions, including temperature and humidity, to protect against quality deterioration and contamination.
- 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 First In First Out system, FIFO.)
- Ensure that the quality assurance person approves and releases materials prior to their use.
- Establish appropriate systems and controls to ensure water used to fabrication products is of potable quality and meets the Guidelines for Canadian Drinking Water Quality [see http://www.hc-sc.gc.ca/ewh-semt/water-eau/drink-potab/guide/index_e.html], WHO guidelines for Drinking Water Quality or other standards specified by the regulatory agency governing the manufacturer.
- Destroy outdated or obsolete printed packaging materials and record the disposal.

Process Control

- Formulate the product to ensure that it adheres to regulatory requirements and claims stated on the label.
- Prepare a master production document for the manufacture of each product, and have the quality assurance person review and approve the document.
- 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.
- Allocate and track each batch of manufactured product by an individual control number.
- 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 quality assurance person.
- 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.
- Identify all materials, products, samples, containers, processing lines and major equipment at all times to indicate their contents and/or status.
- Ensure procedures are in place to prevent extraneous materials from being included in the products and finished package.
- Ensure procedures are in place to identify, store and dispose of rejected or contaminated/adulterated products.
- Establish written procedures for reprocessing batches that do not conform to finished product specifications.
- Securely store labels to prevent mix-ups (e.g. stored and withdrawn against a packaging order). Specifically, this means the following:
    - preventing mix-ups by not returning samples taken away 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 mix-ups or mislabelling occurs); and
    - investigating and accounting for, before release, any significant or unusual discrepancies observed during reconciliation of the amount of bulk product, printed packaging materials and/or labels.
- Prevent cross-contamination and mislabeling by establishing procedures for removing all raw and/or packaging materials and finished products from previous runs (i.e. written line clearance procedures).
- Set up and follow written procedures to ensure the correct labels and packaging materials are issued and used.
- Identify each package with a lot number and expiry date that permits determination of the history of the manufacture and control of the lot.
- Restrict access to production premises to authorized personnel.

Inspection Program for Contractors

- Manufacturers, packagers, labellers or importers must ensure that activities contracted out to other sites meet the GMPs requirements, which can be demonstrated by an inspection and/or an evaluation of the contractor. This inspection program allows quality assurance of the portions of production that are contracted out (e.g. when a manufacturer contracts out labelling) and ensures compliance to NHP GMPs 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 (manufacturing, packaging, labeling and importing). See the records section for information related to contractors and required documentation.

Recall

- Establish written procedures that define controls to ensure the effective recall of a product, including notification of Health Canada. Specifically, this means the following:
  - identifying any individuals be responsible for initiating and coordinating recall activities;
  - ensuring the recall procedure can be put into operation at any time, during and outside normal working hours;
  - ensuring the recall procedure outlines the steps for implementing a recall (e.g. determining extent of the recall, and means of notifying affected parties);
  - maintaining distribution records so each lot can be traced;
  - 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 issuing a final report, including a final reconciliation; and
  - notifying all Canadian and foreign sites involved in the manufacture, distribution and import of the recalled product

1.4 Products

1.4.1 Specifications

Section 44 sets out the specifications that NHPs must meet.

PART 3: GOOD MANUFACTURING PRACTICES
Specifications
Section 44

(1) Every natural health product available for sale shall comply with the specifications submitted in respect of that natural health product under paragraph 5(i) and with every change to those specifications made by the product licence holder.

(2) The specifications shall contain the following information:

(a) detailed information respecting the purity of the natural health product, including statements indicating its purity tolerances;

(b) for each medicinal ingredient of the natural health product, detailed information respecting its quantity per dosage unit and its identity, including statements indicating its quantity and identity tolerances;

(c) if a representation relating to the potency of a medicinal ingredient is to be shown on a label of the natural health product, detailed information respecting the potency of the medicinal ingredient, including statements indicating its potency tolerances; and

(d) a description of the methods used for testing or examining the natural health product.

(3) The specifications and every change to those specifications shall be approved by a quality assurance person.

To Meet the Requirements

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

Finished Products

- Develop and implement written specifications for all finished products.

  Note: Product specifications are assessed by NHPD as part of the product's licence application and verified at the site licence submission review. For guidance related to finished product specifications pertaining to identity, purity, quantity, potency and tolerances, see the *Evidence for Quality of Finished Natural Health Products Guidance Document*.
- Ensure specifications are maintained and every change is approved by the quality assurance person prior to use.

  Note: Changes to specifications as per section 11(i) of the *Natural Health Products Regulations* requires an amendment to the product licence.
- 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.

- Confirm that all test methods provide accurate and consistent results.
- Assess each lot for compliance with specifications prior to release.

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

  - Fully test against specifications, the first lot of product received for *each product* and *each supplier*;
  - Each subsequent lot received thereafter must:
    - undergo a review of the Certificate of Analysis 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 the imported product is shipped;
    - take precautions to ensure that transportation and storage conditions do not adversely affect product potency, purity or physical characteristics;
  - Conduct complete confirmatory testing against specifications on at least one lot per dosage form per supplier per year.

1.4.2 Stability

Section 52 sets out the requirements for product stability.

PART 3: GOOD MANUFACTURING PRACTICES
Stability
Section 52

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

(a) it is stored under its recommended storage conditions; or

(b) if it does not have recommended storage conditions, it is stored at room temperature.

To Meet the Requirements

Manufacturers and importers must ensure the following:

- Use data from accelerated or real-time stability studies or from similar product formulations to make an initial determination of the expiry date.
- Provide data and rationale to reasonably ensure that each finished product meets its label claims at the expiry date.
- 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.

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

1.4.3 Samples

Section 61 explains that the NHPD may ask a manufacturer, importer or distributor to submit samples of a lot or batch of a product if NHPD has concerns about the safety of that product.

PART 3: GOOD MANUFACTURING PRACTICES
Lot or Batch Samples
Section 61

(1) Subject to subsection (3), if the Minister has reasonable grounds to believe that a lot or batch of a natural health product made available for sale may result in injury to the health of a purchaser or consumer, the Minister may require the manufacturer, importer or distributor to provide a sample of that lot or batch.

(2) The sample shall be of sufficient quantity to enable a determination of whether the lot or batch of the natural health product complies with the specifications for that natural health product.

(3) The Minister shall not require a sample of a lot or batch referred to in subsection (1) to be provided if more than one year has elapsed since the expiry date of that natural health product.

To Meet the Requirements

Manufacturers, importers and distributors must ensure the following:

- 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;
- retain samples in their final trade packages or in containers of the same material and construction;
- store samples in the environmental conditions listed on the label;
- ensure that samples are of sufficient size to permit complete testing according to specifications; and
- maintain samples for at least one year after the expiry date. Shorter retention times may be approved by applying in writing to NHPD.

Note: Importers are responsible to notify NHPD when making alternate arrangements for retaining samples. The applicant must commit to retaining the samples in the same containers as those marketed in Canada and conform to the conditions set out in the Application for Alternate Sample Retention form.

1.4.4 Records

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

PART 3: GOOD MANUFACTURING PRACTICES
Records (Manufacturers)
Section 53

Every manufacturer who sells a natural health product shall maintain the following records at the site at which the natural health product is manufactured:

(a) the master production document for the natural health product;

(b) a list of all ingredients contained in each lot or batch of the natural health product;

(c) records of any testing conducted in respect of a lot or batch of raw material used in the manufacture of the natural health product;

(d) records of any testing conducted in respect of a lot or batch of the natural health product;

(e) a copy of the specifications for each natural health product that is being manufactured at the site;

(f) records demonstrating that each lot or batch of the natural health product was manufactured in accordance with the requirements of this Part;

(g) a record of each determination made by the manufacturer in accordance with section 52 and the information that supports that determination;

(h) records containing sufficient information to enable the recall of every lot or batch of the natural health product that has been made available for sale;

(i) a list of all natural health products that are being manufactured at the site; and

(j) a copy of the sanitation program in use at the site.

PART 3: GOOD MANUFACTURING PRACTICES
Records (Packagers)
Section 54

Every packager who sells a natural health product shall maintain the following records at the site at which the natural health product is packaged:

(a) records of any testing conducted in respect of the material used to package the natural health product;

(b) records demonstrating that each lot or batch of the natural health product was packaged in accordance with the requirements of this Part;

(c) records containing sufficient information to enable the recall of every lot or batch of the natural health product that has been made available for sale;

(d) a list of all natural health products that are being packaged at the site; and

(e) a copy of the sanitation program in use at the site.

PART 3: GOOD MANUFACTURING PRACTICES
Records (Labellers)
Section 55

Every labeller who sells a natural health product shall maintain the following records at the site at which the natural health product is labelled:

(a) records demonstrating that each lot or batch of the natural health product was labelled in accordance with the requirements of this Part;

(b) records containing sufficient information to enable the recall of every lot or batch of the natural health product that has been made available for sale;

(c) a list of all natural health products that are being labelled at the site; and

(d) a copy of the sanitation program in use at the site.

PART 3 GOOD MANUFACTURING PRACTICES
Records (Importers)
Section 56

Every importer who sells a natural health product shall maintain the following records:

(a) the master production document for the natural health product;

(b) a list of all ingredients contained in each lot or batch of the natural health product;

(c) records of any testing conducted in respect of a lot or batch of the natural health product;

(d) a copy of the specifications for the natural health product;

(e) a record of each determination made by the importer in accordance with section 52 and the information that supports that determination;

(f) records containing sufficient information to enable the recall of every lot or batch of the natural health product that has been made available for sale; and

(g) a copy of the sanitation program in use by the importer.

PART 3: GOOD MANUFACTURING PRACTICES
Records (Distributors)
Section 57

Every distributor shall maintain the following records at the site at which the natural health product is stored:

(a) records containing sufficient information to enable the recall of every lot or batch of the natural health product that has been made available for sale;

(b) a list of all natural health products that are being stored at the site; and

(c) a copy of the sanitation program in use at the site.

PART 3: GOOD MANUFACTURING PRACTICES
Record Maintenance
Section 58

Every person required under this Part to maintain a record that relates to a lot or batch of a natural health product shall maintain that record for a period of one year following the expiry date of the natural health product to which that record relates.

To Meet the Requirements

- Manufacturers, packagers, labellers, importers and distributors shall meet the minimum record-keeping requirements set out in **Appendix 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.

  Note: 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 has been deleted.
- Records must demonstrate that each lot has been manufactured, packaged, labelled and imported according to the requirements of Part 3 of the Regulations:
  - 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; and
    - document and maintain records of all tasks carried out by the contractor;
    - 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 in 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.
  - When the product is manufactured, packaged and/or labelled outside of Canada, importers must ensure that records can be accessed in a timely manner.
- Manufacturers and importers must maintain evidence establishing the expiry date of each product.
- 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.
- Packagers must maintain evidence or records of packaging material testing conducted with

respect to the material used to package the NHP.

- Maintain evidence showing compliance of each finished product with specifications.
- 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 ensure 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. 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.
  - 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.
  - 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 (**chapter 1.4.5**) for further information.
  - Manufacturing, testing and distribution records must be retained for at least one year after the lot expiry date.

1.4.5 Recall Reporting

Section 62 explains what information manufacturers, importers and distributors must send to Health Canada when they recall a product.

PART 3: GOOD MANUFACTURING PRACTICES
Recall Reporting
Section 62

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

(a) the proper name and the common name of each medicinal ingredient that it contains;

(b) each brand name under which it is sold;

(c) its product number;

(d) the number of each lot or batch recalled;

(e) the name and address of each manufacturer, importer and distributor of the natural health product;

(f) the reasons for commencing the recall;

(g) the quantity manufactured or imported into Canada;

(h) the quantity that was distributed in Canada;

(i) the quantity remaining in the possession of each manufacturer, importer and distributor of the natural health product; and

(j) a description of any other action that the manufacturer, importer or distributor, as the case may be, is taking in respect of the recall.

To Meet the Requirements

- Manufacturers, importers and distributors who recall a NHP must submit product recall information to their Regional Operational Centre within three days of initiating the recall. For more information regarding recall requirements and responsibilities see the Health Products and Food Branch Inspectorate Recall Policy (POL-0016), available on the Compliance and Enforcement section of Health Canada's Web site at the following address: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/docs/index_e.html
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1.4.6 Sterile Products

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

PART 3: GOOD MANUFACTURING PRACTICES
Sterile Natural Health Products
Section 59

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

(a) in a separate and enclosed area;

(b) under the supervision of a person trained in microbiology; and

(c) using a method scientifically proven to ensure its sterility.

PART 3: GOOD MANUFACTURING PRACTICES
Ophthalmic Use
Section 60

(1) Section C.01.064 of the Food and Drug Regulations applies in respect of natural health products except that it shall be read without reference to the words "or parenteral".

(2) Section C.01.065 of the Food and Drug Regulations applies in respect of natural health products except that it shall be read without reference to

(a) the words "or parenteral"; and

(b) the words "or to its common name if there is no proper name".

To Meet the Requirements

- Manufacturers, packagers, labellers, importers and distributors must treat all sterile NHPs in the same manner as any other sterile health product. Follow the guidance for sterile products provided in the Health Canada's Health Products and Food Branch Inspectorate's *Good Manufacturing Practices Guidelines*, 2002 Edition, Version 2. The current version of this document is available at http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/guide-ld-2002/index_e.html. The guidelines for sterile products apply in addition to the other requirements outlined in this document.

2.0 SUPPLEMENTARY GOOD MANUFACTURING PRACTICES FOR HOMEOPATHIC MEDICINES

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 derived from pathological tissues, excretions or secretions. Due to these factors, manufacturers must ensure the critical steps to process raw materials are carried out under controlled conditions.

Manufacturers, packagers and labellers of NHPs used in homeopathy, 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.

Also note, in this chapter, potency refers to the degree of dilution of a homeopathic medicine.

2.1 Places

2.1.1 Premises

To Meet the Requirements

- Manufacturers, packagers and labellers must design their premises to accommodate hazardous raw material storage and homeopathic processing requirements. These requirements include, but are not limited to, the following:
  - isolating toxic raw materials from other materials;
  - handling raw materials of biological origin in segregated areas with appropriate environmental controls suitable for each material;
  - restricting the entry of unnecessary personnel in processing areas designated for attenuation and trituration;
  - performing successive attenuations in a laminar airflow workstation; and
  - designating an area separate from the processing and storage areas to quarantine and dispose unused intermediate homeopathic potencies.
- Supporting documentation would include a floor plan showing the location of segregated areas, ventilation and flow of materials through the site.

2.2 People

2.2.1 Personnel

To Meet the Requirements

- Manufacturers, packagers and 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. Attire, appropriate to designated working areas, must be provided for personnel.

2.3 Processes

2.3.1 Sanitation

To Meet the Requirements

- Manufacturers, packagers and labellers must ensure that the sanitation program contains standard operating procedures (SOPs) appropriate for the production of homeopathic medicines. The SOPs must specify the following:
  - cleaning requirements for raw material storage areas, including toxic and biological materials;
  - cleaning, microbial and environmental monitoring requirements for all processing areas, with emphasis on areas designated for attenuation and trituration;
  - methods that ensure cleaning products do not contaminate product; and
  - cleaning production equipment and utensils using heat methods (e.g. autoclave), if applicable.

2.3.2 Operations

To Meet the Requirements

Manufacturers, packagers and labellers must do the following:

- Maintain written procedures for the following:
  - handling raw materials that are potentially toxic or pathogenic;
  - preparing samples of raw materials, in-process materials and finished products to retain, including the conditions for their storage and the duration of such storage;
  - retaining samples of raw materials of vegetable origin until testing of the mother tincture is completed (Note: Vegetable matter refers to plants, algae, and fungi);
  - storing mother tincture and potencies; and
  - disposing collections of unused intermediate homeopathic potencies.

Critical Production Processes

- Control critical production processes for vegetable matter by recording the duration and efficiency of maceration and/or percolation. For trituration record the duration and intensity for each type and size of apparatus, through particle size analysis of the raw materials in the triturate matrix, when these procedures are available. Include the following information:
  - efficiency of impregnation, through the use of distribution monitors such as dyes; and

- adequacy of the parameters established for the heat processing of the first attenuation in the preparation of nosodes, through checks for sterility.

- Label raw materials with their human safety status (e.g. allergenic, toxic) or Material Safety Data Sheet equivalent.
- On completion of each stage of processing, label the equipment and containers used during critical in-process stages.
  - For in-process attenuations or triturations, the information on the labels and/or manufacturing documentation must include the following:
    - a reference number unique to a particular series, different from the batch number assigned to the product (for combination preparations in which ingredients are potentised separately, each series is assigned a unique reference number);
    - 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;
    - the storage conditions, when applicable;
    - the precautions to be adopted during handling, when applicable; and
    - the date of preparation and identification of the person(s) responsible for its compounding.
  - For bulk preparations, the labels and/or manufacturing documentation must include at least the following:
    - the name, batch number and batch size of the preparation;
    - its composition or reference to the master formula;
    - the reference number(s) of attenuation or trituration series with which the dosage form is impregnated, or if the mother tincture(s) is impregnated, its internal code and analytical control number;
    - the date(s) of impregnation; and
    - the storage conditions, when applicable.
- Include the following information in the master formula:
  - the system for the particular attenuation series (e.g. Hahnemannian, Korsakovian);
  - the standard operating procedures, or reference to procedures, for the cleaning of vessels and containers employed in successive attenuations or triturations; and
  - Standard Operating Procedures (SOPs), or reference to SOPs, to be followed at each processing stage including the following, when applicable:
    - comminution and/or size separation of raw materials, when applicable;
    - maceration and/or percolation, when applicable;
    - quarantine and/or packaging of mother tincture, when applicable;

    - › number of succussions during each attenuation;
    - › duration of trituration;
    - › disposal of unused intermediate homeopathic potencies;
    - › quarantine of target homeopathic potencies;
    - › technique for impregnation;
    - › manufacture and quarantine of the dosage form; and
    - › in-process controls with specifications.
  - the SOPs, or reference to SOPs, for washing, drying and, when applicable, sterilizing packaging materials; and
  - special precautions that may be relevant to the particular classification of preparation (e.g. nosode).
- Process fresh raw materials from vegetable origin promptly.
  - When processing cannot be initiated within a few hours, do not harvest in damp weather conditions. Take adequate precautions to ensure that plants are not wet or are covered in dew when gathered.
  - When processing cannot be initiated prior to eight hours after harvesting, store raw materials under conditions that are appropriate for the conservation of the medicinal plant. Ideally refrigerate and use raw materials within 48 hours.
- Schedule manufacturing to ensure continuity within the attenuation or trituration series. Avoid prolonged storage of intermediate homeopathic potencies.
- Transport target homeopathic potencies from the processing area in hermetically sealed containers with appropriate environmental controls (e.g. for temperature and humidity).
- Transport the first attenuation in the preparation of nosodes from the processing area in a container that can be sterilized directly.
- Dispose unused intermediate homeopathic potencies according to instructions outlined in the standard operating procedures for the attenuation or trituration series.
- Record in the manufacturing order the volume or weight of tailings of destroyed finished product.

2.4 Products

2.4.1 Specifications

To Meet the Requirements

Specifications must be of pharmacopoeial (e.g. *The Homeopathic Pharmacopoeia of the United States*, the *Pharmacopée Française*, *the Homöopathische Arzneimittel* or the *European Pharmacopoeia*) or equivalent status.

Raw Materials

Manufacturers include the following in specifications for raw materials:

- Raw materials of vegetable origin:
    - identity (as Latin binomial), including genus, specific epithet and authority (e.g. Linnaeus);
    - test method to verify identity, absence of foreign materials and adulterants;
    - geographical source;
    - cultivation and collection techniques;
    - time of harvest; and
    - growth stage (e.g. of bark).
- Raw materials of animal origin:
    - identity (as Latin binomial), genus and specific epithet;
    - test method to verify identity, absence of foreign materials and adulterants;
    - part and/or constituent of the animal;
    - location and hygienic conditions of the animal's housing prior to slaughter;
    - slaughter or removal time;
    - pre-treatment, processing (e.g. freeze drying) and storage, when applicable; and
    - potentially toxic contaminants
- Include genus, specific epithet and strain, if any, in specifications for raw material of bacterial origin.
- Include identity and purity tests in specifications for raw materials of mineral origin. Identity and purity testing for homeopathic medicines is outlined in the *Evidence for Homeopathic Medicines Guidance Document* and the *Evidence for Quality of Finished Natural Health Products Guidance Document*.
- Include appropriate specifications and tests used in the manufacturing of potencies of biological origin.
- Verify the identity and potency of the raw materials. A Certificate of Identity or voucher specimen from the supplier can be used and documented.

Finished Products

Manufacturers must do the following:

- 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*.
- 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, viscosity or rheology).

2.4.2 Stability

To Meet the Requirements

- Manufacturers should:
  - develop and maintain standard operating procedures that ensure the stability of the homeopathic medicines; and
  - maintain records of ongoing purity testing as outlined in the *Evidence for Homeopathic Medicines Guidance Document*.
    Note: Because of the unique quality of homeopathic medicines, the evidence of stability would focus on the non-medicinal ingredients.
- Additional evidence to support stability includes, but is not limited to, the following:
  - confirmation that the expiry date of an attenuation does not exceed that of the raw materials from which it is prepared.
  - dosage form testing demonstrating that the homeopathic medicine continues to meet specifications (e.g. concentration of alcohol remains consistent, granules/tablets hardness and disintegration are consistent);
  - packaging materials testing, such as bottles and caps, demonstrating that they do not contaminate product; and
  - confirmation that the labels do not fade or come away from the packaging.

REFERENCES

Australian Department of Health and Ageing, *Australian Code of Good Manufacturing Practice for Medicinal Products*, http://www.health.gov.au/tga/docs/html/gmpcodau.htm (December 11, 2002)

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.

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United States Food and Drug Administration, *Good Manufacturing Practices (GMP)/Quality System (QS) Regulation*, June 2002, http://www.fda.gov/cdrh/devadvice/32.html (December 11, 2002).

United States Food and Drug Administration, *Quality System Audits*, http://www.fda.gov/cdrh/qsr/17audit.html (December 11, 2002).

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 digits and/or letters that specifically identifies a batch, and appears on documents such as the batch record or certificate of analysis.

Batch record: A 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 NHP 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.

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 NHP to another person for the purpose of further sale by that other person.

Dosage form: The final physical form of the NHP 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. Also 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.

Formulate: To prepare components and combine raw materials into a bulk NHP.

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), the *European Pharmacopoeia* or the *Encyclopedia of Homeopathic Pharmacopoeia*, as amended from time to time, and that are prepared in accordance with these pharmacopoeias.

Importer: A person who imports a NHP into Canada for the purpose of sale. This includes bulk NHPs.

In-process control: Checks performed during production to monitor and, if necessary, adjust the process to ensure that the finished product conforms to its specifications. The control of the

production environment or equipment can 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. The 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, NHP, device or package.

Label (v)**:** To affix the inner or outer label of the NHP.

Lot: A quantity of any NHP 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, digits or both, by which any NHP 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 ingredients from a raw material.

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

Manufacturer: A person who fabricates or processes a NHP 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 NHP 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 NHP in dosage form.

Marketing authorization: A legal document issued by the NHPD authorizing the sale of a NHP 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 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.

Menstruum: A combination of water and alcohol used in the extraction of herbal constituents.

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

Natural health product (NHP) : 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:

- diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state or its symptoms in humans;
- restoring or correcting organic functions in humans; or
- modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

However, a NHP 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: These can be:

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

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

Package (n)**:** Includes any material 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 the *Supplementary Good Manufacturing Practices for Homeopathic Medicines*, potency refers to the degree of dilution of a homeopathic medicine.

Potentization: The process of preparing a homeopathic medicine by repeated dilution and succussion to reach a prescribed homeopathic potency.

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: Requirement to be 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 NHP before it is made available for sale. This person should be qualified by education, training and/or experience relating to the specific activity (i.e. manufacturing, packaging, labelling and importing).

Quality Assurance Report (QAR): A report prepared by either a quality assurance person or a 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 Canadian or foreign educational facility (e.g. a university, college or professional or post-secondary institute), generally government-approved or having a secure reputation and is 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(s) 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 and have in possession for sale and distribute, regardless of whether the distribution is made for consideration.

Standard operating procedures: 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.

Succussions: The act of vigorously shaking an attenuation, usually performed by striking against an elastic body. The combination of dilution and succussion are used to reach a prescribed potency.

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 independent of the company he or she is auditing and who is qualified by education, training, and experience to conduct a NHP good manufacturing practices site audit.

Training: To make proficient with specialized instruction and practice.

Trituration: The process of preparing a homeopathic medicine when the starting material is insoluble. This technique consists of grinding the starting material together with a powdered inactive ingredient such as lactose. This prepares the substance for potentisation.

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

APPENDIX 1: SCHEDULES 1 AND 2 OF THE *NATURAL HEALTH PRODUCTS REGULATIONS*

Schedule 1 - Included NHP Substances	
Item	**Substances**
1.	A plant or a plant material, an alga, a bacterium, a fungus or a non-human animal material
2.	An extract or isolate of a substance described in item 1, the primary molecular structure of which is identical to that which it had prior to its extraction or isolation
3.	Any of the following vitamins: • biotin • folate • niacin • pantothenic acid • riboflavin • thiamine • vitamin A • vitamin B_6 • vitamin B_{12} • vitamin C • vitamin D • vitamin E
4.	An amino acid
5.	An essential fatty acid
6.	A synthetic duplicate of a substance described in any of items 2 to 5
7.	A mineral
8.	A probiotic

Schedule 2 - Excluded NHP Substances	
Item	**Substances**
1.	A substance set out in Schedule C of the *Food and Drugs Act*
2.	A substance set out in Schedule D of the Act, except for the following: a drug that is prepared from any of the following micro-organisms, namely, an alga, a bacterium or a fungus; and any substance set out in Schedule D when it is prepared in accordance with the practices of homeopathic pharmacy
3.	A substance regulated under the *Tobacco Act*
4.	A substance set out in any of Schedules I to V of the *Controlled Drugs and Substances Act*
5.	A substance that is administered by puncturing the dermis
6.	An antibiotic prepared from an alga, a bacterium or a fungus or a synthetic duplicate of that antibiotic

APPENDIX 2: RECORDS

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	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