Good manufacturing practices guide for natural health products (GUI-0158)

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The following legend shows the alerts used in this document and the way they are intended to be used.

Key or cautionary information.

Supplementary information like quotes and legal references.

Helpful ideas, information, suggestions, or examples.

1. Purpose

This guide will help you understand and comply with Part 3 on good manufacturing practices (GMP) of the Natural Health Products Regulations (regulations). This guide is for people, including organizations and companies, conducting activities or performing roles that involve natural health products (NHPs). This includes:

- manufacturing
- packaging
- labelling
- importing
- distributing
- storing
- testing
- holding the product licence

Distributing and storing are not licensable activities under Part 2 of the regulations. However, NHPs must be distributed and stored according to the requirements set out in Part 3 of the regulations. This guide identifies the responsibilities of the distributor for the GMP related to storage (including storage during transportation) and distribution. Warehouses or other storage facilities used by the following people must also comply with the GMP requirements:

- importers
- those who store for retailers
- those who store to sell directly to individual consumers
    - such as solely through an e-commerce platform

The GMP requirements of the regulations do not apply to storage activities at retail establishments that sell directly to consumers. However, this exemption does not apply to a retail establishment that manufactures or imports NHPs.

Finished product testing complements the GMP controls employed during the manufacturing, packaging and importing processes. As an integral part of product release, testing provides the results that are used to demonstrate whether an NHP meets its specifications. Activities and records related to testing must comply with GMP.

Refer to the glossary and acronyms used in this guide, as well as the references.

2. Scope

This guide applies to all types of NHPs, including:

- non-sterile NHPs, such as:
  - enzymes
  - probiotics
  - amino acids
  - herbal remedies
  - essential fatty acids
  - traditional medicines
  - vitamins and minerals
  - other products, such as certain toothpastes, antiperspirants, shampoos, facial products and mouthwashes
- sterile NHPs, such as:
  - ophthalmic products
  - sterile water for irrigation
- homeopathic medicines

For additional guidance on related topics, consult:

- Site licensing guidance document on the requirements to get a site licence
- Natural health products management of applications policy on the requirements to get a product licence
- Quality of natural health products guide on the quality requirements for NHPs
- Finished product specifications form and Finished product specifications form user guide for the form to be submitted as part of your product license application

3. Introduction

This guide interprets the requirements for GMP of Part 3 of the regulations. Health Canada engaged stakeholders throughout the various stages of developing this version of the guide.

Poor GMP conditions are likely to lead to the manufacturing and importing of NHPs that mislead consumers on the product's quality. Although an NHP may pass all its finished product specification tests, it may become contaminated or adulterated if manufactured or handled in poor GMP conditions.

Therefore, complying with the GMP requirements of the regulations is mandatory.

Sections 8 and 9 of the Food and Drugs Act state that no person shall sell any NHP that is adulterated or advertised (including on its label) in a manner that is:

- false, misleading or deceptive **or**
- likely to create a wrong impression about its character, value, quantity, composition, merit or safety

For site licensing and GMP, "sale" is not only release to the market. It also captures the sale from a manufacturer to the product licence holder when the manufacturer is not the party releasing to market.

Throughout this guide, we refer to other guidance documents that apply specifically to pharmaceutical drugs (such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) quality guidelines). Although the scope of these references may not always include lower-risk health products such as NHPs, the GMP concepts and processes on which they provide guidance and other information are helpful for the NHP industry and stakeholders. Other references may be added as they become available.

We highly recommend that you follow the GMP as described in this guide. However, we will consider other means of complying with the GMP requirements if you can either:

- demonstrate that the alternative way is equal to or more stringent than what is presented in this guide **or**
- provide appropriate scientific rationale to support the alternative way

4. GMP regulations by activity

Table 1 outlines which activities apply to each section of the regulations. A checkmark indicates that the section of the regulations applies to the activity specified. Note that you do not need a site licence to distribute under Part 2 of the regulations.

Table 1: GMP regulations by activity

✓ = applicable
* = where applicable, depending on the nature of the activities. For example, when packaging a liquid product in its immediate container, it may be necessary to have specifications available for microbiological testing of the product.
X = not applicable

Section of the regulations	Manufacturing	Packaging	Labelling	Importing	Distributing
43. Prohibition	✓	✓	✓	✓	✓
44. Specifications	✓	✓*	✓*	✓	X
45. Premises	✓	✓	✓	✓	✓
46. Equipment	✓	✓	✓	✓*	X
47. Personnel	✓	✓	✓	✓	✓
48. Sanitation program	✓	✓	✓	✓	✓
49. Operations	✓	✓	✓	✓*	✓*
50. Operations	✓	✓	✓	✓	✓
51. Quality assurance	✓	✓	✓	✓	✓
52. Stability period	✓	X	X	✓	X
53. Records - manufacturers	✓	X	X	X	X
54. Records - packagers	X	✓	X	X	X
55. Records - labellers	X	X	✓	X	X
56. Records - importers	X	X	X	✓	X

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X = not applicable

Section of the regulations	Manufacturing	Packaging	Labelling	Importing	Distributing
57. Records - distributors	X	X	X	X	✓
58. Record - maintenance	✓	✓	✓	✓	✓
59. Sterile NHPs	✓	✓	X	X	X
60. Ophthalmic use	✓	✓	X	X	X
61. Lot or batch samples	✓	X	X	✓	✓
62. Recall reporting	✓	X	X	✓	✓

5. About NHP quality systems

If you hold a site licence or run an operation governed by Part 3 (GMP) of the regulations, you must comply with these requirements and with your product licence. Part 3 applies to when you manufacture, package, label, import, distribute, store or test NHPs.

Guiding principles

To meet Part 3 of the regulations, you must have a well-designed and properly implemented quality system (also known as a quality management system). It should meet or exceed the requirements for NHPs and incorporate both GMP and quality risk management.

The basic concepts of a quality system, GMP and quality risk management are inter-related. We have described them in this guide to emphasize their relationships and fundamental importance to the production and control of NHPs.

5.1 Quality system

A quality system is a framework of procedures, controls and resources that your organization should use to consistently:

- meet consumer expectations
- support continual improvement
- comply with regulatory requirements

A quality system incorporates GMP and covers all matters that individually or collectively influence the quality of an NHP. Consider the size of your operation (for example, small to medium size enterprises), the complexity of your activities, and the risk to your products and processes when developing a new quality system or modifying an existing one.

Make sure your NHP quality system is properly set up for manufacturing, packaging, labelling, importing, distributing, storing or testing NHPs.

You should:

- define and document your quality system
    - have a quality manual or equivalent documentation that describes the system and responsibilities of management
- outline management roles clearly and have senior or executive management participate actively in the quality system
    - their leadership is essential as they are ultimately responsible for making sure an effective quality system is in place
- make sure the quality system is resourced properly
    - define, communicate and implement roles, responsibilities and authorities throughout the organization
- design, plan, implement, maintain and improve your system continuously
    - this allows for the consistent delivery of products with proper quality attributes
- manage product and process knowledge throughout all lifecycle stages
    - for example, by using a process flow diagram
- design and develop NHPs in a way that considers GMP requirements
- evaluate, qualify and monitor suppliers for performance and compliance
- have processes in place to manage outsourced activities properly
- take preventive actions based on the results of product and process monitoring and deviation investigations

- make sure the quality assurance person (QAP) approves each batch of NHPs before they are sold
- implement a process for self-inspection and perform a quality audit to assess the effectiveness of your quality system regularly
    - these will help you identify ways to improve products, processes and the system

5.2 Good manufacturing practices for NHPs

GMP are a part of both production and quality assurance (QA). They ensure that NHPs are produced and controlled consistently.

To meet GMP requirements, you must have:

- a qualified QAP
- qualified and trained staff
- adequate premises
- suitable equipment and utilities
- suitable materials, containers and labels
- approved procedures and instructions
- suitable storage and transportation

You must only release raw materials, packaging materials, and NHPs for use or sale if their quality is acceptable. The QAP makes sure that:

- the necessary and relevant tests are performed and ensure the quality of an NHP **and**
- quality principles are incorporated into all activities and decisions concerning NHPs

5.3 Quality risk management

Quality risk management is a systematic process used to assess, control, communicate and review risks that could affect the quality of a product over its lifecycle. It can be applied both proactively and retrospectively.

The principles of quality risk management are that the:

- evaluation of the risk to quality is based on scientific knowledge and experience with the process
    - is linked to the protection of the consumer

- level of effort, structure and documentation of the quality risk management process is in proportion to the level of risk

Consult ICH guideline Q9: Quality risk management for examples of tools for quality risk management (such as the Hazard Analysis and Critical Control Points (HACCP)).

Although NHPs are not within the scope of ICH guidelines, such references are helpful to the NHP industry and other stakeholders. The guidelines may help you gain a better understanding of GMP concepts and processes that also apply to NHPs.

6. NHP GMP guidance

General information

For each section of the guidance, we have provided the exact text from Part 3 (GMP) of the regulations for your reference. The text is followed by the intent of the regulation and our interpretation on how to comply with it.

Certain sections may also include additional information on specific topics. At the end of each section, we have given examples of evidence to demonstrate GMP (for example, written procedures (SOPs) and records). Note that those examples are not an exhaustive list.

You will also find information on how we classify GMP observations based on risk in this guide.

6.1 Prohibition (section 43)

Section 43

(1) Subject to subsection (2), no person shall sell a natural health product unless it is manufactured, packaged, labelled, imported, distributed or 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 or 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.

Intent

Part 3 of the regulations begins with section 43 on prohibition. It states that any NHP sold in Canada must be manufactured, packaged, labelled, imported, distributed or stored according to the requirements outlined in Part 3.

Everyone involved in the lifecycle of an NHP must adhere to the GMP requirements.

The site licence holder must:

- follow the GMP requirements for each activity they are authorized to conduct
    - includes ensuring that their QAP has the training, experience and technical knowledge to perform all necessary quality-related functions
- ensure that all activities or services contracted out are conducted in accordance with GMP requirements

Importers:

- must ensure that imported NHPs are manufactured, packaged and labelled at foreign sites that meet the regulations
- are responsible for the NHPs they bring into Canada if there are any issues about their safety, efficacy or quality
- must provide evidence that the foreign sites they import from meet Canadian GMP requirements (or an equivalent)

For information on the evidence required from importers concerning foreign sites, consult:

- Site licensing guidance document

The Food and Drugs Act defines “sell” as including:

- offer for sale, expose for sale or have in possession for sale, or distribute to 1 or more persons, whether or not the distribution is made for consideration **and**
- lease, offer for lease, expose for lease or have in possession for lease

The word “consideration” in this definition can mean:

- monetary payment (that is, money is exchanged)
- promise to do something or refrain from doing something

Any person who conducts an activity or sells an NHP in contravention of the act or regulations is breaking the law. They will be subjected to compliance and enforcement actions.

For more information on compliance and enforcement activities, consult:

- Compliance and enforcement policy for health products (POL-0001)

6.2 Specifications (section 44)

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.

Intent

Ensuring that a product meets its specifications involves:

- establishing product specifications
- putting in place a quality system that ensures the product meets the product specifications each and every time

The testing of finished products complements the GMP controls used during the manufacturing and importing processes. Each manufacturer, packager (when applicable) and importer must have:

- accurate specifications
- an adequate quality system in place **and**
- suitable test methods to ensure that each NHP sold meets its established specifications

Manufacturer, importer, packager, labeller requirements

The manufacturer, importer and, when applicable, packager and labeller must make sure a product meets its specifications.

As a manufacturer or importer, you must:

- implement written specifications related to purity, quantity, identity and potency for all finished products that are manufactured, packaged (when applicable) or imported
    - in accordance with the Quality of natural health products guide
- ensure the product specifications align with the specifications submitted in the product licence application (as applicable), are maintained and revised as necessary, and the QAP has approved any changes before they are used
    - the changes to specifications defined in section 11(1)(i) of the regulations require an amendment to the product licence
        - for more information, consult the Natural health products management of applications policy
        - for reference, the changes that require an amendment are:
            - removal of a test method set out in the specifications
            - modification of a test method that widens the purity tolerances or the quantity, identity or potency tolerances of any of its medicinal ingredients
            - modification of a test method that renders it less precise, accurate, specific or sensitive
    - document QAP approval of finished product specifications, including changes
    - develop written procedures (SOPs) for finished product testing, including associated blank record templates
- follow written procedures (SOPs) that describe the tests to be conducted that will ensure the purity, quantity, identity and potency of finished products

    - include potency testing or appropriate controls in your procedures if the product licence contains any potency information for any ingredients
    - ensure the test methods are suitable and have been shown to provide accurate and consistent results
        - if you use a method that you developed specifically for your ingredient or product (often called an in-house test method), demonstration of consistency should include an acceptable analytical evaluation of parameters such as accuracy, precision and linearity for multiple tests of samples with known properties
- assess each lot for compliance with its product specifications and Health Canada's regulatory requirements before releasing the product in Canada

As an importer, you must also:

- confirm the imported products meet the specifications and Health Canada's regulatory requirements before releasing them in Canada
- review the supplier's certificate of analysis submitted with each lot received to ensure the product meets its specifications
    - all required testing has been done
    - tests not completed by the foreign site are conducted by you or a third-party laboratory
- review batch records when a medicinal ingredient of a product is quantified by input
    - processes, documents and demonstrations outlined in the quantification by input section of this guide are acceptable and maintained
    - when importing from buildings inspected by a regulatory authority under a mutual recognition agreement (MRA) or under the Pharmaceutical Inspection Co-operation Scheme (PIC/S), the batch certificate can replace the batch record and the review of the raw material certificates of analysis
- review label information or have a label control process in place to ensure that all imported products align with their product licence
    - all imported products must meet the Guidance document: Labelling of natural health products

As a packager, you must keep records of the:

- testing or evaluation conducted by you or your packaging supplier on materials used for primary packaging the product
- if microbial contamination can be introduced during packaging, microbiological testing that confirms the environmental or sanitation controls implemented during the packaging process and microbiological testing on the finished product

    - if a third-party laboratory conducts the testing for you, a certificate of analysis will suffice as a record of testing

As a packager, you must also:

- ensure that your polymer-based packaging materials, if used, are acceptable
    - consult the Lists of acceptable polymers for use in food packaging applications for a list of generally accepted polymers

When placing product into primary packaging, you must make sure the processes do not introduce the risk of microbial contamination. This is especially important when packaging liquid-based products. To properly monitor this risk, implement microbial controls throughout the packaging process and on finished products.

As a labeller, you must:

- ensure a product's label information aligns with its product licence and specifications
    - product labels must align with the master production document
    - for more information on labelling, consult:
        - Guidance document: Labelling of natural health products

For all testing methods and requirements, consult:

- Quality of natural health products guide

Confirmatory testing

A confirmatory testing program is encouraged. Although it is optional, confirmatory testing provides added assurance of a product's quality, especially if manufactured by a new supplier or one that has a history of quality-related problems.

To perform confirmatory testing, an independent laboratory conducts tests to confirm the analyses of another facility and that the results already obtained for the same lot are valid.

Your confirmatory testing program should be independent of the manufacturer's testing. This will provide added assurance of a product's quality when it's manufactured or tested by a supplier.

The following is an example of a confirmatory testing program:

- Conduct full testing of the product against its specifications for the first lot received from each supplier for each product and then for each subsequent lot received:
    - review the certificate of analysis showing actual test results and verify the product meets its specifications before releasing it
    - take precautions to ensure that transportation conditions do not adversely affect product quality
        - different products have different requirements (for example, sterile products or refrigerated products)
    - verify that storage conditions do not adversely affect product quality
    - conduct confirmatory testing on at least 1 lot per dosage form per supplier per year
- Have a different laboratory (as opposed to the original) perform the confirmatory testing
    - original laboratory may perform the test in exceptional circumstances, such as when test methods are very specialized

If you do confirmatory testing, you do not need to test for:

- sterility (if the method is validated and the laboratory is accredited)
- particulate matter

You may release a product for sale while undergoing confirmatory testing as long as the original analyses of the other facility are within specifications, and your QAP has provided their approval. However, note that there is an increased risk of having to conduct product recalls if an out-of-specification (OOS) is identified subsequently during confirmatory testing.

Investigate the extent of the non-compliance for all products received from the facility if periodic confirmatory test results do not conform to the product's specifications.

Along with the items outlined in the section on QA, you may need to:

- assess the impact of the testing failure on:
    - the batch if your QAP released it before receiving the confirmatory test results
    - the reliability and accuracy of other results from the affected facility
- reassess and retest all products from the affected facility
- re-evaluate the affected facility's GMP compliance
- conduct additional confirmatory testing

Reduced testing

Reduced testing approaches can be a reasonable way to gain efficiencies in the quality control (QC) of NHPs. However, the choice of tests to perform and the justification for choosing those tests are key elements of operating a compliant reduced testing program that is also scientifically sound.

Microbial contaminants: Reduced testing

Some products have a low risk of microbial contamination because of their method of manufacture, low water activity and dosage form. When justified, a reduced microbiological testing strategy may be appropriate. In this case, use efficient manufacturing control processes and risk management strategies. These are defined in the section on QA.

You may implement a reduced testing procedure for microbial contaminants if you, as the manufacturer or importer, maintain records showing that:

- the product is in an acceptable dosage form (such as tablets, lip balms or topical ointments)
- water activity is controlled before the product is released and throughout its shelf life, and product yields an acceptable low water activity
    - defined by a recognized pharmacopoeial standard, such as the USP <1112> Application of water activity determination to nonsterile pharmaceutical products
- the product's antimicrobial properties are monitored throughout its shelf life, if required
    - defined by a recognized pharmacopoeial standard, such as the USP <51> Antimicrobial effectiveness testing
- the effectiveness of the product's microbial contamination controls is demonstrated, including:
    - raw materials
    - water used within the facility (for cleaning and rinsing equipment, for example)
    - cleaning and manufacturing processes
    - product formulation
    - packaging system
- historical testing and stability studies show a low microbial load, demonstrated by either of the following:
    - an analysis of at least 10 lots of the product, which may include:
        - finished product lots

        - pilot lots
        - any related lot types
    - a statistical analysis of:
        - an adequate quantity of historical test data
        - the statistical confidence in the controls during the manufacturing process to monitor or control micro contaminants

If these items are met, you may use the reduced testing approaches suggested by a recognized pharmacopoeia. Re-evaluate your reduced testing approach if you change manufacturing processes or manufacturers.

Note that a reduced microbiological testing approach is not acceptable for products containing live microorganisms (probiotics). For more information, consult the Quality of natural health products guide.

Remember that you cannot use water activity measurements alone to justify the elimination of all microbial content testing for product release, as NHPs may contain non-synthetic ingredients (for example, plants). Proper controls throughout the facility are always needed as some microorganisms, such as Salmonella spp. or filamentous fungi, may persist within or on the product without proliferating.

Microbial contaminants: Composite testing

Compositing refers to the process of pooling multiple samples for testing. Refer to the glossary for a more detailed description.

Composite testing alone is not acceptable for testing finished products, unless sample compositing is required by a sampling methodology described in a recognized pharmacopoeia.

Using individual samples instead of composite (pooled) samples provides a higher level of assurance in microbiological testing results. A compositing approach is not recommended as it may:

- mask or dilute contaminants
- reduce the sensitivity of the analysis
- reduce your ability to identify the contamination source
- increase the risk of releasing products that do not meet their specifications

Chemical contaminants: Exemption to product testing before release

As the manufacturer or importer, you do not need to test certain chemical contaminants if you can meet the following requirements:

- Heavy metal contaminant testing is not necessary if:
  - raw materials are of synthetic origin or of pharmacopoeial grade
    - those that aren't of synthetic origin or of pharmacopoeial grade are tested and the results verified by the QAP
  - the total daily exposure in the finished product is calculated (using USP <2232> Elemental contaminants in dietary supplements, for example), with the calculations based on the:
    - quantity of each ingredient in the product
    - maximum potential contamination given the proposed limits for each raw material
    - daily dose of the product
- Residual solvent contaminant testing is not necessary if:
  - the ingredients have been tested for residual solvents, untested ingredients are documented to be of pharmacopoeial grade, or a written confirmation is available from the supplier stating that no solvents are used during ingredient preparation
  - solvents, other than water, are not used to manufacture the finished product and a written confirmation from the manufacturer is available
- Residual pesticide contaminant testing may not be necessary if:
  - all botanical ingredients are shown to be organic, evidence of an acceptable organic certification from 1 of the certification bodies under the Canada Organic Regime is maintained, and all ingredients not identified as organic are tested for pesticides at the raw material stage
  - the product has a certified organic content that is equal to or greater than 95%
  - all the ingredients are synthetic or meet pharmacopoeial standards that have no pesticide residue limits
  - the supplier is qualified to implement a reduced pesticide testing approach
    - Although it is optional, qualifying suppliers is encouraged as it provides added assurance of quality and permits reduced pesticide testing. To qualify a supplier, you must:
      - confirm that they have a documented process they actively follow to manage quality

- evaluate their quality systems (focus on their processes to control and monitor pesticides)
- reevaluate regularly, on a defined schedule, the supplier's quality systems
- monitor the supplier for changes in their process (for example, a new source of raw materials) that may adversely affect product quality

- once a supplier is qualified, a reduced testing approach for pesticides could be implemented by:
  - confirming that the first 3 lots are tested (by you or the supplier) for pesticides and that the results are acceptable
  - if the results are acceptable, reduce testing to every 5 lots
  - once confidence levels are high, reduce testing to every 10 lots with a minimum of 1 lot per year
- if a product fails to meet acceptable pesticide levels, you should disqualify the supplier, test all further lots for pesticides and initiate an investigation to identify the root cause
  - remember to evaluate the previous lots during your investigation, because they were not tested

You must maintain supporting documents (for example, the certificate of analysis from your supplier) that demonstrate the acceptability of not testing these contaminants prior to release.

Medicinal ingredients: Rotational testing

Based on process validation (if implemented) or in-process controls and statistical confidence, a rotational testing program (also known as skip testing) is an alternative to fully testing every lot of finished product. Even when using a rotational testing program (for example, for a product containing several medicinal ingredients, such as a multi-vitamin supplement), the medicinal ingredients not being tested must meet their acceptance criteria. At least 1 medicinal ingredient must be quantified per lot.

To implement an acceptable rotational testing program for medicinal ingredients, as a manufacturer or an importer, you must:

- establish testing levels that describe which tests on the product specifications are conducted on a lot in what order
  - remember: controls need to be maintained during manufacturing to ensure that the quantity per dosage unit meets their acceptance criteria

- ensure testing of each ingredient on the product's specifications is done at least once every 3 lots or once a year if fewer than 3 lots are manufactured or imported annually
- identify tests for key potential contaminants and conduct them for every lot if required
- ensure critical tests are conducted for every lot if required. This should include tests when ingredients:
    - are used to demonstrate batch homogeneity
    - may degrade during the manufacturing process
    - are deemed critical for the labelled health claims
    - have potency limits that are not controlled at the raw material stage

As rotational testing does not fully test for each medicinal ingredient in every lot, it must be:

- scientifically supported and justified prior to implementation
- implemented after a product licence is issued using the GMP guidelines outlined in this guide

If there is a testing failure, such as OOS results, you must:

- ensure the QAP investigation includes the previous 2 lots that were not tested for the affected ingredient
    - this process should be described in your written procedure (SOP) for OOS investigation
- evaluate the need for a recall for the previous 2 lots that were not tested for the affected ingredient
- remove the affected medicinal ingredient from the rotational schedule
    - should be tested on the next 3 lots before being re-introduced into the rotational testing program
- evaluate the need to restore regular testing of the product

Companies implementing a rotational testing program can benefit from lower testing costs. However, they must be prepared to conduct product recalls if an OOS is identified as previous lots may not meet specifications.

Importing from buildings inspected by a regulatory authority under an MRA or PIC/S

The MRA and PIC/S approaches are an effective way for Canada to enhance international regulatory cooperation. They help to:

- develop closer and stronger relationships among regulatory authorities
- maintain high standards of product safety and quality for its GMP compliance program, while helping to reduce the regulatory burden for industries

Canada participates in PIC/S and several MRAs that cover drug and medicinal products GMP compliance programs. Although MRA and PIC/S programs do not cover NHPs, regulated parties may use the GMP compliance information obtained under these programs and extend it to NHPs as long as the NHP complies with the regulations.

If you import an NHP that is manufactured, packaged and labelled in buildings that are inspected and authorized by a recognized regulatory authority under an MRA or PIC/S (including US FDA's dietary supplement inspections), you must:

- maintain a copy of the certificate of compliance for the foreign site
    - certificates are valid for a period of 3 years from the date of the inspection

For each lot or batch of the product received, you may have a batch certificate in the format agreed upon in the International harmonized requirements for batch certification. This certificate can replace having the batch record to show the product meets its finished product specifications.

Before release, you are still required to review the documentation to ensure that:

- each NHP sold meets its specifications
- the NHP sold meets Canada's regulatory requirements

For products with medicinal ingredients that are quantified by input:

- the master production document must have been reviewed and approved by your QAP
    - remain informed of and approve any changes to the master production document as manufacturing and packaging processes may change over time
- a completed batch record from a lot imported must be reviewed periodically, such as once a year, to monitor that the quantification by input process is acceptable and under control by the manufacturer at the foreign site

Also, as an importer, you must still control testing reduction and exemptions or quantification by input (if used), as outlined in this guide.

If any licensable activity such as manufacturing, packaging or labelling is performed in a building not inspected by an MRA or PIC/S regulatory authority or the certificate is

expired, the controls and testing requirements revert to those outlined in this guide once the product is received in Canada.

Quantification by input

Quantification by input means the quantity of a medicinal ingredient in the finished product is estimated from the amount that is added to a batch during manufacturing. The medicinal ingredient is not assayed (that is, it is not tested to confirm quantity) at the finished product stage.

Exemptions to testing a medicinal ingredient at the finished product stage may be acceptable if the manufacturer or importer can meet certain requirements. Refer to the Quality of natural health products guide for additional information on quantification by input.

As a manufacturer or an importer, regarding all your products with any ingredient being quantified by input, you must ensure that your QAP:

- for medicinal ingredients quantified by input:
  - has comprehensive raw material specifications to ensure adequate control of the medicinal ingredient's identity and quality before manufacturing
  - maintains and compares the certificates of analysis of raw materials to their specifications before use
- if more than 1 medicinal ingredient or if the medicinal ingredient is mixed with non-medicinal ingredients:
  - documents and describes how the batch homogeneity process is controlled

As a manufacturer or an importer, you must have batch records that include:

- objective evidence that the correct quantity of each ingredient is added to the finished product
- a description and calculation of the ingredient amounts in the finished product
- the target quantity for the medicinal ingredient (100% of the label claim)
- controls on weight variation or uniformity of the dosage units that can happen during tabletting, encapsulation or molding
  - when using average weight, a 5% variation from the target for individual dosage units (such as tablets, capsules or chewable gels) is generally acceptable

- the variation may be higher if supported by a recognized pharmacopoeia (for example, USP <2091> Weight variation of dietary supplements allows higher variation for smaller dosage units and soft or hard shell capsules)
- individual dosage weight variation or uniformity of dosage units does not apply to liquids and powders

You must also:

- document the controls in place during manufacturing to ensure the correct amount of each ingredient is added to achieve the labelled quantity per dosage unit
- ensure critical tests are conducted for every lot if required, such as for ingredients used to demonstrate batch homogeneity

GMP evidence

You must demonstrate GMP compliance for specifications with supporting evidence. The type of GMP evidence for specifications may vary. Examples of evidence include the following:

- relevant written procedures (SOPs) and associated blank record templates for finished product testing and specifications, including an assessment of the following:
  - raw materials against specifications
  - packaging or labelling materials against specifications
  - finished products against specifications, including a description of:
    - how finished product specifications are tested or controlled (for example, testing is product-specific, frequency of testing)
    - how to handle OOS results (including steps for when a product is tested on a rotational or reduced testing basis)
- written finished product specifications for all products to be manufactured, packaged, labelled or imported
  - all finished product specifications must be verified and approved by the QAP
  - changes to a finished product specification must be recorded and approved by the QAP
- certificate of analysis for each lot that demonstrates the product meets its specifications according to the requirements outlined in the Quality of natural health products guide, including:
  - certificate shows the same medicinal ingredients, including quantity and potency (when applicable), as the product licence

- documentation that products are tested according to their finished product specifications, including testing methods and acceptance criteria, where documentation (when applicable) is as outlined in these sections:
  - Microbial contaminants: Reduced testing
  - Chemical contaminants: Exemption to product testing before release
  - Medicinal ingredients: Rotational testing
  - Quantification by input
- finished product specification change control log
- evidence that testing is done at a suitable laboratory that adheres to good laboratory practices (GLP) or other comparable quality standards (the International Organization for Standardization (ISO), for example)

6.3 Premises (section 45)

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.

Intent

The premises where you manufacture, package, label and store NHPs must be designed and constructed to permit cleanliness and orderliness. Regular maintenance is required to prevent deterioration of the premises and to ensure products do not become contaminated through unsanitary conditions.

Manufacturer, packager, labeller, importer, distributor requirements

Depending on your activities, at every site, you must:

- ensure that all buildings are of adequate size and are designed and built to facilitate:
  - maintenance, cleaning and sanitary operations
  - prevention of entry of insects and other animals
  - waste treatment and disposal
- designate separate production and non-production areas, as needed, to prevent cross-contamination
- clearly identify and segregate individual manufacturing, packaging, storage and testing areas
- ensure production areas are designed in a logical order, corresponding to the sequence of operations and to the requisite cleanliness level
- ensure production areas have a process flow that will prevent the finished product from becoming contaminated with raw materials
- ensure that effective controls are in place to minimize the potential for mix-ups or the chance that raw materials, packaging materials, and in-process and finished products can be adulterated
- protect raw materials, packaging materials, and in-process and finished products against physical, chemical and microbial contamination

Contamination is when NHPs are potentially unsafe for use or ineffective because they contain foreign substances or organisms including some microbial, chemical or physical matter that should not be present according to the product's specifications.

Adulteration is to intentionally or unintentionally modify an NHP to contain substances that are not declared on the label. This includes other drug products, unexpected medicinal ingredients or harmful substances as well as spoilage that make a product unfit for usage. For more information, refer to Adulteration of natural health products.

Dried plants need to be stored properly to prevent fermentation or mould growth and prevent cross-contamination. Separate enclosed areas are recommended to quarantine incoming plants or herbals.

To prevent ingredient, product and container mix-ups (for example, transferring between the manufacturer and the labeller) and to minimize the risk to quality, you should:

- clearly mark (either physically or by using a controlled electronic system) and restrict access to authorized personnel in the following areas:
    - quarantine or hold
    - release
    - destruction
    - recall or return
- restrict, during production, the use of doors giving direct access from manufacturing and packaging areas to the outdoors and from non-production areas
- ensure that doors, windows, walls, ceilings and floors contain no holes, cracks or gaps, except those that are part of the design
- take measures to prevent contamination in all areas where raw materials, primary packaging materials, in-process products or finished products are exposed (to the extent required)
    - ensure that floors, walls and ceilings permit cleaning, that all surfaces are smooth and made of non-porous materials, and that surfaces do not shed particles and permit effective and repetitive cleaning
        - examples of porous materials are exposed wood or drywall, unsealed cement block or brick
    - seal surfaces and joints to prevent product contamination and permit effective and repetitive cleaning
    - ensure that floor drains are screened and trapped and the drains do not cause water to pool
- provide adequate ventilation and filtration to reduce dust and the potential for cross-contamination of components, in-process and finished products, and contact surfaces
- provide adequate lighting in all areas where production materials are examined, processed or held, or where contact surfaces are cleaned
- use shatter-resistant bulbs and fixtures to avoid contamination from broken glass
- control humidity and temperature, where required, to protect materials and products
    - production and storage areas that have monitors or probes ensure that environmental controls accurately represent all areas and can identify where excursions may take place (for example, near a hot air or air conditioner outlet)
    - an automated data monitoring system would alert you when environmental controls deviate

The various recognized pharmacopoeias (such as the USP) and other international standards provide definitions and descriptions of storage temperature terminology. This includes ambient temperature, room temperature and cold chain.

You should also:

- take appropriate measures to control, remove and prevent pests from entering the premises:
    - ensure doors and windows are adequately sealed
    - collect data on both crawling and flying pests found in your area
        - use appropriate pest control devices
        - perform a visual inspection of the premises
    - have a pest control professional review your pest control program to ensure that pest control devices and procedures are appropriate and adequate
    - install refuse receptacles and follow waste disposal practices that protect against contamination and don't attract pests
- dispose of sewage, refuse and waste in and out of buildings and the immediate surrounding area in a safe, timely and sanitary manner
- separate the break or rest areas, change rooms, washup and toilet facilities from production areas
    - these areas should have enough space to accommodate the activities performed, be well-ventilated and permit good hygiene practices
- ensure plumbing is appropriately designed and sized that it does not drip, leak or create condensation, and thus potentially adulterate products or contaminate water supplies or equipment
- ensure the water supply is of potable quality for processing and cleaning
    - refer to the water supply section
- identify any outlets for liquids and gases used in production
- maintain the grounds around the manufacturing buildings and keep areas in and around the buildings tidy
- limit pesticide use to non-production areas
    - take precaution to prevent contamination when rodenticides, insecticides and fumigation agents are used

Water supply

Use potable water that is supplied at a suitable temperature and, as needed, pressure. Your plumbing system must be in a good state to protect against contamination or undesirable chemical reactions.

The water supply must meet at least 1 of the following guidelines:

- Canadian drinking water guidelines
- Guidelines for drinking-water quality set by the World Health Organization (WHO)
- standard specified by the regulatory agency governing the manufacturer

When purified water is required for cleaning, use calibrated water purification, storage and distribution equipment.

Always assess if water is a component in an NHP (for example, when water contacts components, in-process and finished products or any contact surface). If it does, ensure the water quality will not negatively affect the quality of the NHP over its designated shelf life.

For water used in the manufacturing process that is treated by the manufacturer to achieve a defined quality, use appropriate criteria to qualify and monitor the treatment process.

Water from a private source that may be used in the NHP must comply with any provincial and municipal requirements, and not contaminate the product. To satisfy this requirement, you may have to perform appropriate water treatment procedures, including filtration, sedimentation and chlorination.

Municipal and public water distribution systems

Establishments often use water from locally or municipally controlled water sources. You should keep a record of the analysis results for source water from the municipality. Water that has been treated by a municipality is usually of high quality before it enters the distribution system. However, the microbial and chemical constituents of the water can vary.

Municipal and public water quality may deteriorate for many reasons. For example:

- the water is disinfected but not sterilized
- plumbing materials are not 100% inert
- cross-connections and line breaks to the piping in the distribution system or in the establishment can contaminate water
- compounds such as calcium carbonate and iron may precipitate and thus provide the conditions for organisms to grow

The quality of municipal and public water distribution systems is only guaranteed until they reach your establishment. You are responsible for the system's quality after that (this includes interior plumbing, taps).

If a municipality's water safety or quality is unacceptable, the local public health unit or other responsible authority may issue advisories. This includes boil water or water safety alert or drinking water advisories. You should have measures in place, such as a subscription to an email or phone distribution list, for receiving notifications when there is a municipal water treatment failure and water advisory.

You are responsible for making sure the municipal water supply meets requirements once it reaches the establishment. For guidance, consult:

- Canadian guidelines for food processing during adverse water events

GMP evidence

You must demonstrate GMP compliance for the premises with supporting evidence. The type of GMP evidence for premises may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for maintaining premises, such as:
    - prevention of contamination and cross-contamination of NHPs
    - storage conditions of raw materials
    - storage conditions of finished products
    - pest control
- detailed floor plan of production, non-production, quarantine, packaging, labelling areas
- daily records (includes weekends and statutory holidays) noting temperature, relative humidity and light control (as needed) for storing raw materials, packaging materials, and in-process and finished products. These records serve to:
    - allow the QAP to confirm that the results of the environmental control monitoring are within all products' storage requirements (ranges should be based on, for example, valid scientific data, monographs, pharmacopoeial sources)
    - document and investigate results that deviate from the requirements, and corrective actions taken to ensure that product quality has not been impacted

    - document the maintenance and calibration for environmental control devices, when applicable
    - allow the QAP to verify the environmental control data record
- pest control inspection report (internal or third party) that includes:
    - information on where pest control devices are located (we recommend a floor plan with a legend)
    - pest control inspection schedule giving date and time of each inspection, identifying people performing the inspection, indicating trap replacements and any investigations and outcomes when pests are identified
    - pest control record and corrective actions taken by the QAP
- janitorial duty schedule and cleaning completion records for each area (for example, manufacturing, packaging, labelling, storage areas)
    - refer to the sanitation program section
- facility inspection and maintenance records (for example, wall, floor or ceiling repair, caulking replacement, door sweep installation, new drain grates)
- ventilation maintenance records (as applicable), including inspection schedule, filter replacement and periodic monitoring of pressure differentials
- water quality test records (for manufacturers and packagers)

6.4 Equipment (section 46)

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 natural health product; and
(d) prevents it from adding an extraneous substance to the natural health product.

Intent

These requirements are meant to prevent NHPs from being contaminated by:

- lubricants
- other products
- cleaning agents
- foreign materials, such as:

- rust
- dust
- particles coming from the equipment

Contamination problems may arise from different sources, such as:

- poor maintenance
- equipment misuse
- use of worn-out equipment
- inadequate cleaning practices
- equipment capacity exceeded

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.

Manufacturer, packager, labeller, importer, distributor requirements

Depending on your role, as applicable, you must:

- ensure production equipment and utensils that have direct contact with materials and products are constructed of smooth, non-reactive and non-toxic materials
  - should be designed for the environment in which they are used and to withstand repeated cleaning or be single-use (disposable)
- ensure production equipment is designed, constructed, installed and maintained so they can be cleaned, sanitized (if applicable) and inspected (inspection includes the surrounding area):
  - establish and follow procedures for cleaning and maintaining equipment and utensils used to manufacture products
    - clean between production runs of different products (including drug or cannabis products) or different batches of the same product for any shared equipment
    - establish processes to identify, store and protect clean equipment to avoid contamination
  - repair faulty equipment in a permanent and durable way and avoid using things like tape or carboard to make temporary repairs
  - label clearly or remove defective equipment
  - have enough distance around equipment to permit proper cleaning

    - make sure equipment is accessible to be disassembled for cleaning, maintenance or inspection
- ensure production and laboratory equipment is operated, maintained and calibrated according to its written procedure (SOP)
    - must be suitable for their intended use ("fit for purpose")
- protect analytical instruments and associated control systems from vibration, electrical interference and contact with excessive moisture or other external factors
- avoid the possibility of foreign or maintenance materials contaminating the products by:
    - ensuring tanks, chain drives, transmission gears and other similar manufacturing equipment are enclosed or properly covered
    - locating or placing equipment to prevent cross-contamination or possible mix-ups
    - protecting in-process and finished products against contamination from lubricants and other external sources (for example, grease, oil, leaking gaskets)

Importers and companies with storage-only facilities may not use the same type of equipment as manufacturers, packagers and labellers. However, they still need to use, maintain, calibrate and clean any equipment that is critical to preserving the quality of a product, such as environmental controls, fridges, freezers and lifts.

Equipment suitability

The NHP industry uses equipment ranging from a utensil or simple apparatus to complex computerized systems. Equipment needs to be "fit for purpose", which means it must meet the requirements of what a user expects and what it's designed for. For example, the range, precision and accuracy of a balance should be appropriate for its use, and calibration records should be maintained.

In general, the more complex the equipment or the more critical it is to assure the quality of the product, the more important it is to ensure its "fit for purpose".

The requirements for how a piece of equipment should be used must be defined to help meet user, technical and operational needs.

Determining "fitness for purpose" can be as simple as documenting your review of the manual of a piece of equipment and making sure the equipment operates as intended.

Follow your change control (CC) process when any equipment undergoes major repairs or modifications and take steps to verify the equipment continues to operate satisfactorily. If you move equipment to another location, consider the impact of the change on the equipment and make sure it continues to operate properly.

Any repair or maintenance operations must not present any hazard that will affect the quality of the product. For example, consider the location of the repairs relative to materials and finished products.

Equipment calibration

When manufacturing, packaging, labelling or storing NHPs, use equipment as it's meant to be operated. Calibrate equipment according to written procedures (SOPs), its intended use and an established schedule. Use recognized pharmacopoeial reference standards or those traceable to certified standards, if available, when calibrating.

Even with an established calibration schedule, some equipment may require supplemental calibration. For example, a balance may need re-calibrating if it's bumped or moved during cleaning or during daily operations. An appropriate standard weight (for example, represents the weight of the materials that will be on the balance) should be used to ensure the balance is still working as expected.

Investigate deviations from approved standards of calibration on critical instruments. This will determine if there was an impact on the quality of products using this equipment since the last successful calibration. Repair or replace any equipment that cannot be adjusted to agree with the reference standard.

For guidance on equipment cleaning and sanitizing, refer to the sanitation program section for more information.

GMP evidence

You must demonstrate GMP compliance for equipment with supporting evidence. The type of GMP evidence for equipment may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for the functioning, maintenance and calibration of equipment
- calibration records for equipment that requires it according to its function, including automatic, mechanical, electronic and measuring devices
    - provide proof of the calibration standard or reference being used
- equipment usage, cleaning and maintenance logs
- preventive maintenance schedule or program for all equipment that includes:

- information on where equipment requiring maintenance and calibration is located
- instructions on how to maintain and calibrate the equipment or where to find the corresponding written procedure (SOP), including:
  - frequency of such activities
  - measures to be taken if equipment does not function as intended
  - individuals who are responsible for maintenance and calibration
  - external companies that conduct such activities, if applicable

Air ventilation and filtration systems, purified water production systems, and temperature and humidity controls are examples of equipment that must be calibrated, maintained and cleaned. However, they are often overlooked when creating processes and written procedures (SOPs).

6.5 Personnel (section 47)

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.

Intent

Whom you hire is one of the most important elements in any NHP operation. Knowledgeable and well-trained personnel are needed to manufacture, package, label and store high-quality NHPs. Employing qualified personnel to supervise these activities is also important.

Without staff that have a quality mindset and are properly trained, it's almost impossible to make or store high-quality NHPs.

Requirements for manufacturers, packagers, labellers, storers (as well as importers, distributors responsible for storage or transportation)

Your senior or executive management is responsible for providing adequate resources (materials, personnel, facilities and equipment). As a manufacturer, packager, labeller and storer (including as an importer or distributor responsible for storage or transportation), you must:

- ensure enough personnel with the required qualifications and practical experience relevant to their responsibilities on-site
- not place so many responsibilities on any 1 person such that quality is at risk
- ensure personnel conducting GMP activities understand the written procedures (SOPs) for those activities
- ensure personnel have the authority to carry out their responsibilities
- record specific duties for all responsible staff in a written work description and maintain a list of written procedures (SOPs) for each position

A training matrix that outlines the written procedures applicable to each position can help to ensure all personnel are trained on the SOPs that affect them. The matrix can also be a quick reference to identify who needs to be re-trained when SOPs are revised.

You must also:

- follow a written training program (that is, a training SOP) and use qualified trainers to train personnel (including technical, maintenance and cleaning staff)
- ensure personnel have the education, training or practical experience to perform their assigned duties
- ensure personnel are aware of the principles of GMP, including good documentation practices, that affect them
    - they should receive initial and ongoing GMP training relevant to their job responsibilities
    - ongoing GMP training should be conducted according to an established schedule (for example, annually or bi-annually) and when changes are made to the GMP regulations or personnel require refresher training after a long leave (for example, parental leave) or performance deficiencies

Sometimes legislation, regulations or Health Canada guidance documents change. Provide your personnel with the most up-to-date training in Canadian NHP GMP requirements.

You must also:

- provide training on written procedures (SOPs) before implementing new or revised versions (for example, when changes to equipment or processes are made)
- give specific training to personnel working in areas where highly active, toxic or sensitizing materials are handled
    - they should have access to relevant information (for example, safety data sheets) and personal protective equipment (PPE)

- appoint qualified replacements to carry out their duties and functions when key personnel are absent
- maintain records of education and training for all personnel, including management, involved in handling NHPs and update the records when needed

Maintaining copies of resumés in addition to their records of GMP and SOP training helps to build a complete record of each employee's qualifications.

You must also:

- assess the effectiveness of training by reviewing personnel performance periodically
    - personnel must have both initial and ongoing training to ensure they stay up to date on changes to written procedures (SOPs) and regulatory requirements
- confirm that consultants and contractors have the necessary qualifications, training and experience to complete the tasks they were hired to do
    - for example, a consultant could be hired to act as your QAP (with product release responsibilities), which means they would need to meet the qualifications laid out in this guide (section 51)
    - keep their resumé on file

Only qualified staff can supervise the manufacture of NHPs. These operations are often technical in nature and require constant vigilance, attention to detail and a high degree of competence. Products often fail to meet required standards when staff are poorly trained or do not understand the importance of production control.

The persons in charge of your QA department (your QAP) and of your production department must:

- have the education, training or practical experience to control or supervise the activities
- supervise each working shift that involves activities under their control
    - the person in charge can be off-site if they are fully accessible and have enough knowledge of the on-site operations to do their job
- delegate duties and responsibilities when needed (for example, to cover all shifts) to a person who is qualified while still being accountable for those duties and responsibilities
    - the designated person (that is, the QAP designate) must have the relevant education, training or practical experience

- in this guide when we say QAP, it means the QAP or one of their designates
- refer also to QAP training, experience and technical knowledge under section 51 in this guide

Companies must demonstrate how decisions made by the QAP are independent from other business decisions. A QAP who holds additional responsibilities within a company must still follow established written procedures (SOPs) and make decisions that are not influenced by their other company obligations, especially decisions that could impact financial gains. For example, when the QAP is also a company executive, a returned damaged product should be actioned as outlined in the relevant SOP. The QAP should not accept or justify the result and then return the damaged product to saleable stock.

GMP evidence

You must demonstrate GMP compliance for personnel with supporting evidence. The type of GMP evidence for personnel may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates related to the appropriate education, training and work experience for all personnel
- job descriptions that outline the role and responsibilities of the position
- list of qualified designates
- resumé, copy of educational degrees that show the person meets their job description
- certificates of completed training that relate to the person's assigned duties and responsibilities (such as GMP training)
- employee training schedule or attendance records that demonstrate initial and on-going relevant training

6.6 Sanitation program (section 48)

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.

Intent

Sanitation of a building, as well as employee hygiene, influence the quality of NHPs. The GMP requirements under the regulations say to perform activities in areas that are free from:

- environmental contamination
- contamination by another product

A written sanitation program lays out for employees the expectations and necessary steps to ensure sanitation is maintained. It provides assurance that levels of cleanliness in the facility are upheld.

Manufacturer, packager, labeller requirements

You must have a sanitation program for the facility and a health and hygiene program for employees as outlined in this section.

Requirements for importers and distributors responsible for storage

You must have a sanitation program for the facility that is focused on the storage area.

Facility sanitation program

A written sanitation program that will prevent a product from being contaminated should include:

- cleaning procedures for facilities, in particular the production and storage areas
    - consider all surfaces such as floors, walls, ceilings, work surfaces, light fixtures and ventilation filters

- identification of cleaning compounds, sanitizing agents, pesticides and other toxic materials
    - should be labelled, used and stored to prevent contamination
- procedures for:
    - cleaning and sanitizing equipment and utensils
    - verifying a production area has been cleaned before it is used for manufacturing, packaging and labelling activities
    - destroying and disposing of waste materials and debris
- provisions for:
    - protecting raw, in-process, bulk and packaging materials against contamination and cross-contamination
    - containing or ventilating dusty operations to prevent other areas from being contaminated (if applicable)

Cleaning is the process of removing visible dirt, dust and other soils from surfaces. Cleaning generally involves using a cloth or wipe and a detergent, soap or solvent. Rinsing is required.

Sanitizing reduces the number of microorganisms on a surface to a safe level. Sanitizing generally involves using a sanitizing agent such as a weak bleach or alcohol solution. Rinsing is usually not required after sanitizing. Sanitizing may be performed after routine cleaning or before the next usage of clean equipment, or both.

Equipment cleaning and sanitizing

Establish written procedures (SOPs) for cleaning equipment that is used in production. Include enough details so operators can clean the equipment easily and effectively.

Include the following in your procedures:

- personnel responsible for cleaning equipment
- cleaning schedules
    - state how often equipment and lines should be cleaned between the production of different products or different batches of the same product
- sanitizing schedules (if applicable)
- full description of the methods and materials, including dilution of cleaning agents, used to clean equipment
- instructions for:

    - disassembling and reassembling each piece of equipment to ensure proper cleaning (if applicable)
    - removing previous batch identification
    - protecting clean equipment from contamination before next use
    - inspecting cleanliness of equipment immediately before use
    - identifying equipment reserved for handling contaminated materials or waste
- steps for evaluating and confirming the efficacy of the equipment cleaning process

Always consider the materials used in your facility even when they don't come directly into contact with your products. Materials should be easy to clean repeatedly. For example, use plastic or metal shelves and pallets, not wooden ones, in production areas.

Clean primary contact surfaces for manufacturing and filling equipment in a way that consistently ensures there is no visible product or cleaning agent residues. Protect all equipment from contamination and keep it clean and dry. You should control the level of microbial contamination and ensure that methods to detect microbial contaminants when evaluating cleaning are effective.

Clean and, if applicable, sanitize all contact surfaces before use and after any interruption where there is a possibility it may have become contaminated.

In consecutive operations:

- for batches of different NHPs, adequately clean and, if applicable, sanitize the contact surfaces to prevent cross-contamination
- for different batches of the same product, inspect and adequately clean the contact surfaces to prevent buildup and carry-over of contaminants

Also clean when necessary any surfaces that do not come into direct contact with components, in-process products or finished products.

Use effective systems to reduce the potential of non-contact surfaces from becoming sources of contamination. For example, use floor sticky pads between different production areas and have a shoe policy in place.

Identify and separate dirty and clean equipment and utensils, making sure their cleaning status is clearly stated.

Contact surfaces used for manufacturing or holding low-moisture components or products must be clean, dry and sanitary before use. For surfaces that are wet-cleaned,

sanitize if applicable and ensure that they are thoroughly dry before subsequent use. If wet processing is used during manufacturing, clean and, if applicable, sanitize all contact surfaces to protect against the introduction of microorganisms.

Store single-use (disposable) articles (such as utensils intended for one-time use, paper cups and paper towels) in appropriate containers. Handle, dispense, use and dispose these articles in a manner that protects against contamination of components, products or any contact surface. Clean, sanitize (if applicable) and store portable equipment and utensils in a manner and location that protects them from contamination.

Cleaning compounds, sanitizing agents, pesticides and other toxic materials

Cleaning compounds and sanitizing agents must be:

- suitable for their intended use
- safe under their conditions of use
- free from undesirable organisms

You are responsible for selecting suitable cleaning products for use in your facility. Use food-grade cleaning products on any surfaces that may come in contact with raw materials and in-process and bulk products. Your QAP should evaluate all cleaning products to ensure they do not present a risk of contaminating materials and products.

All toxic materials that you purchase should have a safety data sheet. Do not use or keep toxic materials where components, materials, products and contact surfaces are exposed. The exception are materials required to:

- maintain clean and sanitary conditions
- conduct laboratory test procedures
- maintain or operate the facility or equipment used in your operations

Identify, handle and maintain toxic materials in a manner that protects against contamination of components, materials, products and contact surfaces. Follow all relevant federal, provincial and local government regulations for using and storing these toxic materials.

If you must use pesticides (such as insecticides, fumigants, fungicides or rodenticides), remember to:

- take precautions to protect against the contamination of components, materials, products and contact surfaces

- choose pesticides that are registered and use in accordance with the Pest Control Products Act
- follow provincial or territorial and municipal rules on pesticide use

Learn more:

- Pesticides and pest management: Frequently asked questions

Substances associated with the operation of equipment (such as lubricants, heating fluids and coolants) must not come into contact with materials or products. This would alter the quality of the materials or products beyond established specifications. If there is contact, you should evaluate any deviations to ensure the material or product can still be used.

Use food-grade lubricants and oils when there is a risk of direct or indirect contact between a substance and an NHP material or product. An example would be the lubricants used for the tablet press during the compression of tablets.

Health and hygiene program

Make sure that the following personnel follow appropriate practices to protect products against contamination:

- those who are in direct contact with raw, in-process or bulk materials
- those who use processing equipment

A written health and hygiene program should indicate that you have to:

- wear:
    - intact, clean and sanitary gloves made of impermeable material when there is a potential for contamination of, among other things, raw materials, primary packaging components, in-process products or equipment
    - hairnets, caps, beard covers or other effective hair restraints when working with exposed materials or products
    - as required, face masks in production and packaging areas when working with exposed materials or products
    - outer garments, including shoe coverings, that protect against contamination of materials, products or equipment, where necessary
- remove:

    - cosmetics that may come in contact with raw, finished and packaging materials, and process equipment when working in the production area
    - unsecured jewellery, hand jewellery and other objects that might fall off, when applicable
        - hand jewellery that cannot be removed may be covered with a material that will not fall off, is clean and is in sanitary condition
- maintain personal cleanliness
- wash hands thoroughly before starting work and at any other time when they may become soiled or contaminated
- store clothing or other personal effects outside of processing areas
- not consume food and drink, chew products or smoke in manufacturing, packaging, labelling, storage or testing areas

In the health and hygiene program, you should also:

- ensure periodic eye examinations are conducted for personnel responsible for visual inspections
- respect quarantine times imposed by public health authorities
- report to supervisors and remove anyone who has or may have a health or personal hygiene condition that could adversely affect materials or products, such as:
    - an illness (including fever, coughing and sneezing)
    - an infection
    - an open lesion
    - any other source of microbial contamination (including contaminated clothing or other objects)
- ensure personnel is not allowed back until the health or hygiene condition no longer poses a risk to the product
- take necessary precautions to protect against allergen cross-contact and contamination with microorganisms, allergens, filth, foreign substances or other extraneous materials, such as:
    - food
    - hair
    - tobacco
    - cosmetics
    - perspiration
    - personal medicines
    - chemicals (for example, pesticides, cleaning products, perfumes)

GMP evidence

You must demonstrate GMP compliance for your sanitation program with supporting evidence. The type of GMP evidence for a sanitation program may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for a sanitation program that include the following elements:
    - cleaning premises, production and storage areas, and equipment, with information on:
        - areas to be cleaned (for example, equipment, production line, rooms)
        - cleaning methods (for example, wet or dry mopping, dusting)
        - tools to be used
        - cleaning and storage of the cleaning tools
        - cleaning and sanitizing agents to be used
            - must be suitable for their intended use and not pose a contamination risk
            - information on dilution specifications (if any) and expiration date
        - cleaning frequency for each task (for example, batch-specific, daily, weekly, monthly)
        - procedures to prevent cross-contamination between any equipment and utensils to be shared between NHPs and other substances (for example, pharmaceutical drugs, cannabis), where applicable
        - procedures for destroying and disposing of waste materials and debris (including expired or rejected materials and products, and recalled or returned products)
        - storage of equipment after cleaning
        - verification of the cleaning before usage (for example, equipment, production room)
    - health and hygiene program (including verification to ensure employees are correctly applying the procedures)
        - guidance related to personal hygiene
        - personnel hygiene training log
- approved facility cleaning schedule and cleaning completion logs that:
    - identify the personnel responsible for both cleaning and verifying the cleaning by signing and dating all log entries
    - describe what is being cleaned

- identify the cleaning frequency for each task (for example, batch-specific, daily, weekly, monthly)
  - include an explanation when a cleaning task does not take place as per its intended frequency
- show the records of sanitation have been verified by the QAP, with any changes that may affect the cleaning process documented

Cleaning logs must reflect the procedures that are outlined in the sanitation written procedures (SOPs). Include cleaning log templates in the appropriate SOPs and the relevant parts of a sanitation log in the batch production record (for example, equipment cleaning and verification of sanitation before use).

6.7 Operations (section 49)

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.

Intent

The regulations require that measures be taken to maintain the integrity of an NHP. This ranges from when raw materials enter the facility to the time the finished dosage form is released for sale and distributed.

Requirements for manufacturers, packagers, labellers, storers (as well as importers, distributors responsible for storage or transportation)

Make sure that practices and procedures are in place, as applicable, for:

- controlling materials
- controlling processes
- evaluating contracted parties (where applicable)

Manufacturer, packager, labeller requirements

Processes related to the following require controlling, as applicable:

- raw materials
- in-process materials
- bulk products
- packaging and labelling materials
- manufacturing, packaging and labelling operations

Make sure that practices and written procedures (SOPs) are in place and up to date for both material and process control.

Transporting, handling and storing raw, packaging and labelling materials

Develop written procedures (SOPs) for transporting, handling and storing raw, packaging and labelling materials. As applicable, include procedures for:

- following sanitary procedures for conveying materials, including specific design specifications (for example, to help with pest control) and cleaning procedures
- ensuring vehicles and transportation equipment have adequate temperature control to prevent materials from becoming spoiled, contaminated or damaged during transportation
- taking precautions to ensure frozen materials transported with dry ice do not come into contact with the dry ice, which may affect the material's quality
- packaging or separating to protect materials from being contaminated by other articles in the same load
- establishing a strictly controlled or electronic inventory system for materials that are quarantined and kept separate from approved goods before they are used in manufacturing
- providing appropriate conditions, including temperature and humidity, for storing materials to ensure they do not deteriorate or become contaminated
- ensuring competent supervisory personnel are in place to ensure that transportation and storage operations are carried out adequately
- ensuring personnel engaged in preparing materials for transport (including those loading and unloading shipments) are trained in procedures designed to preserve the quality of materials during transportation
- maintaining records on transportation requirements, including agreements, procedures, maintenance, cleaning, temperature control and training records

Receiving, examining and identifying raw, packaging and labelling materials

Develop written procedures (SOPs) for receiving, examining and identifying raw, packaging and labelling materials. As applicable, include procedures for:

- performing visual inspections of shipments (trucks and containers) for appropriate content, container damage or broken seals to determine if container condition has caused the materials to be contaminated or become deteriorated
- verifying that the temperature of refrigerated trailers, if used, is correct before unloading
- identifying each lot of raw, packaging or labelling material with a distinctive lot number, along with date received, name of material and status (quarantined, approved or rejected)
    - the lot can be traced to the supplier
    - differentiating the same lot of a material that is received in multiple different shipments makes it easier to trace
        - adding a sequential number to the lot number helps (for example, Lot #12345-1, Lot #12345-2)
- confirming that the supplier's invoice, guarantee or certification for each shipment is consistent with the purchase order

Sampling, testing and approving or rejecting raw, packaging and labelling materials

Develop written procedures (SOPs) for sampling, testing and approving raw, packaging and labelling materials. As applicable, include procedures for:

- identifying and controlling each lot of materials according to its quality status (such as quarantined, approved or rejected)
- assessing each lot of material against specifications (such as appearance, identity and composition)
- setting a time limit (re-test period) beyond which materials that are subject to deterioration may not be used in production without additional testing
- retesting materials after they have been exposed to conditions that may affect their purity, quality or composition
    - could include temperature excursions during transportation, extended periods of time in storage or extended exposure to light or humidity

- review and approval by the QAP of the results of any tests or examinations conducted on the materials
- releasing the materials from quarantine by the QAP for use in manufacture, packaging or labelling

Water added to the product is also a raw material. Establish appropriate systems and controls to ensure that water used in production is of appropriate quality. Refer to the Quality of natural health products guide for more information on water as an ingredient.

Manufacturing the bulk and finished product

Develop written procedures (SOPs) for manufacturing the bulk and finished product. As applicable, include procedures for reviewing, approving and maintaining:

- a master formula for the product to ensure that it adheres to regulatory requirements and claims
    - includes the strength and potency (if applicable) stated on the label and on the product licence
- a master production document for each product
- batch records for each batch of product
    - must accurately reflect the master production document
    - indicate that each significant step in the manufacturing process was completed

The manufacturing section of a master production document is a template for the batch record. It includes the master formula, manufacturing instructions, in-process controls, a list of equipment to be used, and timelines for significant steps in manufacturing. Refer to the glossary for a full description of a master production document.

Batch records (manufacturing section)

Record the details of each batch processed at the time of its actual manufacturing in a batch record that has its own unique number. Make sure the batch record reflects the currently approved master production document.

Prepare and verify the batch record (this is a task for qualified personnel). Include the following information:

- name and batch or lot number of the product
- dates and times when manufacturing operations and any significant intermediate stages were started and completed

- a list of the raw materials and quantity required for each to achieve the expected batch size
    - document and verify the calculations made to determine required quantities for the specific batch size (for example, calculation of the amount of a liquid ingredient required based on the percentage noted in the master formula)
- batch number and quantity of each raw material actually weighed and dispensed
- equipment and processing lines used to produce the batch
    - give enough details to make it easy to trace the usage, maintenance and cleaning records for each piece of equipment and processing line
- name or identifier of each operator who performed each significant step of the process and the person who checked these steps, including:
    - for manual operations, significant steps may include:
        - weighing or measuring each ingredient
        - adding the ingredient to the batch
        - recording steps requiring specific times
        - recording temperatures or speeds
        - recording any other steps critical to producing a consistent product
- results of any quality checks done at appropriate stages of the process and the person who did the checks
- batch yields at appropriate stages of processing, as required, and final yield
    - explain any deviations from an expected yield
    - evaluate against the acceptable range for the final yield
- notes on problems, including details of any deviation from the manufacturing instructions
    - provide written approval by qualified personnel, including the QAP
- signature of the person responsible for the processing operations

If you use documents in your company that are not written in English or French, make sure that:

- processes are clear and controlled
- your staff has access to documents they can read and understand

Documents requested by Health Canada must be provided in either English or French. For more information, refer to the translation of records into English or French section of this guide.

Packaging and labelling the finished product

Develop written procedures (SOPs) for packaging and labelling the finished product. As applicable, include procedures for:

- preparing, reviewing and approving a master document (packaging order)
- completing records for each product batch to reflect the currently approved master document
    - document that each significant step in the packaging and labelling operation was completed
- identifying equipment and packaging and labelling lines
    - lines for packaging different products should be properly separated and, if necessary, dedicated
- issuing packaging materials for use only by authorized personnel and ensuring label control and reconciliation
- destroying and disposing outdated or obsolete material, unused printed packaging and rejected materials
- making sure that work areas, packaging and labelling lines, printing machines and other equipment are clear of products, materials or documents previously used if these are not required for the current operation
    - you could use a checklist to document the line clearance
- overseeing the printing of lot numbers and expiry dates, with special attention paid to printing done by hand
    - check it regularly
    - make sure printed and embossed information on packaging materials is distinct and will not fade or erase

Label control and reconciliation

Develop written procedures (SOPs) for label control and reconciliation. As applicable, include procedures for:

- attaching samples of the printed packaging and labelling materials used to package orders, when possible
    - include evidence of confirmation of the lot number, expiry date and any overprinting
- labeling right after filling and sealing, whenever possible
    - have measures to ensure that no mix-ups or mislabelling will occur if labelling is delayed

- destroying unused batch-coded materials and recording their disposal after packaging and labelling is done
    - follow a procedure if non-coded printed materials are returned to stock
- destroying outdated or obsolete packaging and labelling materials and recording their disposal
- comparing the amount of printed packaging and labelling materials issued to the line with the number of units packaged during reconciliation
    - investigate and account for any discrepancy before releasing the materials
- making sure printed packaging and labelling materials are:
    - stored in an area with access restricted to designated personnel who are supervised by qualified personnel
    - withdrawn against a packaging order
    - issued and confirmed to match approved master copies by qualified personnel
- using roll-fed labels instead of cut labels, whenever possible, to prevent mix-ups
    - avoid printing more than 1 type of label on a sheet of material
    - automated electronic verification can be used to preventing mix-ups
    - conduct checks to ensure that any electronic code readers, label counters or similar devices are operating properly
- taking special care when using cut labels, carrying out overprinting off-line and in hand-packaging and labelling operations
    - in these cases, have 1 operator perform a 100% examination for correct labelling during or after labelling operations
    - have a second operator independently verify this
- checking and recording the performance of any printing (such as the printing of lot numbers and expiry dates) to ensure it's correct
- ensuring every package is identified by a lot number and an expiry date

For information on labelling NHPs and complying with Canadian requirements, consult:

- Guidance document: Labelling of natural health products

It's not only valuable to labellers and product licence holders, but also for importers, to evaluate product labels for compliance with Canadian requirements.

Batch records (packaging and labelling section)

Record the details of each batch packaged and labelled in a uniquely numbered batch record (packaging and labelling record). Make sure the batch record is based on the

currently approved master production document. Qualified personnel must prepare and verify the batch record.

Include the following information, as applicable:

- name and batch and lot number of the product
    - including the natural product number (NPN) can help identify the product
- dates and times when packaging and labelling began and ended, and any significant intermediate stages
- quantity, batch number or analytical control number of each packaging and labelling material and bulk NHP issued
- equipment and packaging and labelling lines used
    - give enough detail so that their usage, maintenance and cleaning records can be traced
- if possible, an actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master document
- identification of the personnel who are supervising packaging and labelling operations and the movement of the bulk NHP to the line
- identification of the operator who performed each significant step and the person who checked these operations, including:
    - verification of labels
    - line clearance
    - movement of the bulk NHP to the line
    - verification of the lot number and expiry date
    - recording of specific times, temperatures or speeds
    - label reconciliation
- checks for identity and conformity of the packaging and labelling
    - including the results of any in-process controls used
- verification that inline printing (such as the printing of lot numbers and expiry dates) is correct
- verification of the proper functioning of line monitors, electronic imaging or vision systems
- how precautions applied to a partly packaged product are handled
- notes on any special problems, such as:
    - details of any deviation from the packaging and labelling instructions (with written approval by qualified personnel, including the QAP)
- the quantity of finished product obtained
- reconciliation of the quantity of printed packaging and labelling material and bulk NHP used, destroyed or returned to stock
- signature of the person responsible for the packaging and labelling operations

A review of completed batch records or acceptable alternatives outlined in this guide should be part of your QAP's finished product release procedure and done when reviewing the finished product test results.

Importing and distributing

Although not specifically set out in this regulation, importers and distributors are often responsible for transporting and storing finished products. Manufacturers, packagers, labellers, importers and distributors are responsible for ensuring products are stored in accordance with up-to-date practices and written procedures (SOPs).

Transporting and storing finished product

Develop written procedures (SOPs) for transporting and storing the finished product. As applicable, include procedures for:

- conducting transportation and storage operations according to appropriate sanitation principles
    - perform these operations in a manner that protects against adulteration and in conditions that minimize the potential for contamination
    - consider worst-case scenarios, including seasonal fluctuations
- equipping and maintaining, as necessary, conveyances to provide adequate temperature control
- taking precautions to ensure frozen products transported with dry ice do not come into contact with the dry ice
    - may affect the quality of the product
- assigning competent supervisory personnel to ensure that transportation and storage operations are carried out adequately
- training personnel responsible for transportation and storage in procedures that maintain the quality of products
- outlining all necessary specifications for the carrier's vehicle and transportation equipment
    - include specific design specifications (for example, temperature control or monitoring using calibrated devices) and cleaning procedures
- maintaining records on transportation requirements, including agreements, procedures, maintenance, cleaning, temperature control and training
- storing quarantined products away from released products
    - separated physically or through a strictly controlled physical or electronic inventory system

- storing products in appropriate conditions, including temperature and humidity, to protect against quality deterioration
- identifying all products, samples, containers and major equipment at all times regarding their contents and status
- ensuring adequate procedures are in place to:
    - prevent extraneous materials from being included in the product packaging
    - identify, store and dispose of rejected or contaminated or adulterated products
- accepting or rejecting shipments containing reprocessed or reworked batches
- investigating significant or unusual discrepancies observed during reconciliation of the product
- restricting access to storage areas to authorized personnel
    - access can be restricted by locks, passcodes, alarms, guards or other means

Standard operating procedures (SOPs)

SOPs play a major role in a company's QA system. An SOP is a written procedure describing in detail the steps needed to complete tasks consistently.

Ensure your company's SOPs describe how company operations comply with the GMP requirements and are:

- available to all required personnel
- up to date and reflect all requirements and practices
- reviewed regularly by qualified personnel

You should set up a regular schedule to review your SOPs (such as during annual self-inspection). Regular reviews help to identify Health Canada regulatory and guidance updates, changes to internal and external contact information, and outdated practices. Keep a record of your reviews, even when the SOP does not require any updating. Also make sure to review and approve changes to SOPs (including the reasons for the revisions), and ensure only current SOPs are in use.

At a minimum, in addition to its main content, a well-written SOP will include the:

- company name
- SOP title
- document number
- version number

- page number on each page

You should keep an up-to-date list of all your SOPs, including their SOP number, title and version number. When assigning SOP numbers, a coding system can be helpful. For example, the first issuance of the first SOP related to sanitation may be numbered as SAN-001-00. The “00” version number indicates the document has not yet been revised because it’s new. After its first approved revision, it would be numbered as SAN-001-01.

Approval and effective dates:

- date of approval of the SOP is the date that it is approved by the QAP
    - includes their name, signature and date
- effective date is the date on which the SOP is put into use

The effective date is the date when everyone must use the new procedure. You should leave enough time between the approval and effective dates so that everyone who needs to use the SOP may be trained on it.

Also include in the SOP the following, as applicable:

- Scope: describes the purpose of the SOP and items that are not covered by the procedures
- Responsibilities: lists departments or job positions that must follow the SOP
- Materials: lists materials, equipment or devices needed to perform this activity
    - for example, detergents required to clean a particular piece of equipment
- Safety: any safety considerations specific to the task
    - for example, wear a mask
- Procedure: detailed steps to perform the activity in a consistent and repeatable manner, including illustrations or pictures and cross-references to other SOPs, as needed
    - for example, speeds, temperatures, measurements and time periods to be used
- List of attachments: any associated forms to be completed when an activity is performed
    - for example, equipment cleaning logs used to track cleaning details, including the personnel responsible and the date performed
- Revision history: date of revision, detail of changes and reason for revising the SOP
    - reference to related deviation reports or CC documents may also be included

Companies should create an SOP outlining how the company's SOPs will be numbered, formatted, controlled, approved and stored.

Quality agreements (written agreements)

A quality agreement (written agreement) is a formal document between 2 or more parties outlining the specific GMP duties and responsibilities of each party involved with respect to Part 3 of the regulations. It defines the specific duties, responsibilities and expectations of each party involved in the agreement. A quality agreement between parties should include every activity or operation that is carried out when more than 1 party is involved.

The regulations outline who is ultimately responsible to ensure processes are in place to control outsourced activities. (For example, section 52 of the regulations states that manufacturers and importers are responsible for determining the period of time that the NHP will continue to comply with its specifications.) The regulations do not distinguish between manufacturers that produce products under their own NPN and those that contract manufacture them for others. In all instances where the GMP refer to manufacturers or manufacturing, the requirements also apply to contract manufacturers or contract manufacturing.

Your quality system should include the control and review of any outsourced activities. You must ensure that all documents and records that you are required to maintain are available at your premises, even if you outsource the related activities. Failure to demonstrate that outsourced activities meet GMP may lead to regulatory actions.

You should monitor, review and assess the records and results of all your outsourced activities to ensure that all materials, products and services provided by the contracted party comply with the:

- GMP requirements
- site licence
- product licence
- quality agreement

The quality agreement that you draft for the contracted party (such as your contract manufacturing, packaging, labelling, importing, storage partner) should include, as applicable, a:

- description of who is responsible for:
    - writing and approving raw material, packaging material and finished product specifications
    - purchasing, sampling, testing and releasing raw materials and packaging materials
    - writing and approving the master formula
    - undertaking production, quality and in-process controls
    - conducting analytical tests
    - overseeing the stability program
    - overseeing transport and storage logistics and conditions
    - retaining lot or batch samples
    - coordinating and executing recalls
- clause stating there should be no subcontracting of any work without written authorization
- clause that allows you to audit the contracted facility
- description of how information will be communicated between contracted parties
- procedure used to ensure that each lot or batch being released for sale has been manufactured, packaged, labelled or imported in compliance with GMP and product licence requirements
- requirement to investigate any deviations and OOS results that may have an impact on the quality of the products
- description of how to handle rejected raw and packaging materials, and in-process, bulk and finished products
- description of how complaints and information about potentially defective products are to be handled and investigated
- requirement for changes to be governed by a CC system and approved by the QAP

Quality agreements (written agreements) covering all testing activities, if testing is done at a contract laboratory, should:

- permit audits of the external lab's facilities and operations
- describe (at a minimum) who is responsible for:
    - overseeing collection, transportation and storage conditions of samples before testing

  - keeping stability samples at predetermined temperatures and humidity, if applicable
  - testing methods to be used, acceptance criteria to be applied and, when applicable, test method validation or suitability
  - retaining analytical results and supporting documentation

GMP evidence

You must demonstrate GMP compliance for operations with supporting evidence. The type of GMP evidence for operations may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for operations activities, including for:
  - transporting, receiving, handling, storing and distributing raw, packaging, labelling materials or finished products, as applicable
  - manufacturing (including all aspects of the production run), packaging, labelling and storing NHPs
  - an inspection program for contractors
  - creating and maintaining quality agreements (written agreements)
- master production documents, master labels and batch records, certificates of manufacture or batch certificates (for importers, when applicable)
- specifications, certificates of analysis and records of release for all raw materials (medicinal and non-medicinal ingredients)
- product disposition, distribution, return and disposal logs and records
- records for OOS results, including investigations into root causes
- product complaint logs, records and resulting action
- audit reports or completed records of pre-evaluation for approved contractors
- list of all contract manufacturers, packagers and labellers used (both internationally and in Canada)

Ensure you have a signed quality agreement (written agreement) for each contract manufacturer, packager, labeller, importer, storer, distributor and tester. The quality agreement should clearly outline the contracted party's duties and responsibilities. Note that the regulations outline who is ultimately responsible for ensuring processes are in place to control outsourced activities.

6.8 Operations (section 50)

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.

Intent

You must have a system in place for recalling a product. The system must include:

- tracking the product from manufacturing to distribution
- tracing the product from the raw material stage to when it's released in its final form

In this guide, we also provide guidance on how to comply with section 62 of the regulations (recall reporting).

Manufacturer, packager, labeller, importer, distributor requirements

You must:

- establish written procedures (SOPs) that outline how to initiate and undertake a product recall promptly and at any time
    - review and update these procedures regularly
- employ appropriately trained and experienced personnel who will manage complaints and investigations on defects
    - to decide measures for managing potential risks and conducting recalls
- ensure batch or product distribution records are available to the persons responsible for recalls
    - should contain contact details, as well as identifying information on product quantity and batch or lot
- designate a storage area for recalled products prior to the approved and documented disposition action
- ensure a quality agreement (written agreement) is in place for activities contracted to other parties

- should clearly establish and document the roles and responsibilities on recalls for each party involved in the contracted operations

You must also have a:

- system to proactively monitor foreign suppliers for issues that may require products to be recalled
  - includes recalls initiated by the foreign sites or regulatory compliance actions or warning letters issued by foreign authorities
- process for recording the progress of a recall and the issuance of a final report
  - includes the reconciliation between delivered and recovered quantities of the recalled products, and the corrective and preventive actions (CAPA) put in place
  - should also include effectiveness checks to ensure that everyone on the distribution list received the recall communication letter and was able to action it appropriately
- process for periodically evaluating the effectiveness of the recall system (for example, performing a mock recall)
  - will confirm it remains up to date with company procedures and current Health Canada requirements and guidance

Many foreign regulatory authorities have websites that list compliance actions in their respective jurisdictions. Use this information to help you monitor sites abroad, such as the:

- FDA Data Dashboard and Warning letters sites (US FDA)
- GMP non-compliance report site (European Medicines Agency)

You must also consult:

- recall reporting section of this guide
  - includes what information to provide to Health Canada and how to test your system through mock recalls
- Drug, natural health product and biocide recall guide (GUI-0039)

GMP evidence

You must demonstrate GMP compliance for recall systems with supporting evidence. The type of GMP evidence for recall systems may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for recalling an NHP and recall reporting
- distribution records for all products
- signed quality agreement (written agreement) outlining recall responsibilities

6.9 Quality assurance (section 51)

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 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 shall be approved by a quality assurance person before that natural health product is made available for further sale.

Intent

QA is the area of GMP concerned with sampling, specifications, testing, documentation and release procedures. The QAP is the person who maintains your quality system and assures that products are suitable for sale.

This regulation ensures that:

- the necessary and relevant tests are carried out
- products are not released for sale until their quality has been determined to be acceptable
    - includes confirming that the product's specifications are met

Manufacturer, packager, labeller, importer, distributor requirements

A comprehensive quality system will help you properly control manufacturing, packaging, labelling, storing, testing and distributing an NHP.

Ensure your quality system is maintained by a quality unit which is independent from where potential or perceived conflicts of interests may arise:

- independent from production, sales and marketing, and all other areas of your company or organization

A quality unit fulfills both QA and QC responsibilities. Depending on the size and structure of your organization, this can be in the form of:

- separate QA and QC units overseen by the QAP **or**
- a single person (that is, the QAP themselves)

For small companies, the senior official or business owner may be the most qualified to implement and run the quality system. In this case, you should have either:

- controls in place that are robust, efficient and well-documented to ensure that only products that meet their specifications are released for sale **or**
- a third-party QAP that has these controls in place

You should have a written job description for the QAP to ensure the individual makes decisions related to GMP requirements independently.

Support your QAP with a QA team to maintain an efficient oversight throughout your operations. This could be due to the size of your company, its business hours or when the

extent of the documentation requiring review becomes difficult to manage due to your company's growth.

To maintain an efficient quality system, your QAP will put in place, manage and run various quality system components.

To help you comply with the requirements in section 51 of the regulations, these components are presented as quality subsystems in this guide. We have also provided detailed information on each of the components. You do not have to organize your quality system along these specific quality subsystems but should make sure that those that apply to you are in place.

The components of an efficient quality system include:

- a quality management system for manufacturers, packagers, labellers, importers and distributors, where the QAP is responsible for:
    - maintaining and monitoring overall compliance with GMP, procedures and specifications
    - handling all review and approval duties
        - such as CC, reprocessing or reworking, batch release, specifications review and reports
    - monitoring and investigating product complaints, defects, returns and reprocessed or reworked products
- a laboratory control system for manufacturers, packagers and importers, where the QAP is responsible for:
    - implementing a system that controls laboratory testing and laboratory-related activities
        - such as procedures, testing and method development or verification
    - ensuring that the testing methods used are suitable for use, such as through preparatory testing (refer to the glossary) or system suitability, when required
- an importation control system for importers, where the QAP is responsible for:
    - ensuring that imported NHPs are manufactured, packaged, labelled and stored at sites that meet GMP requirements equivalent to those of the regulations
    - confirming that imported products meet their specifications and Canada's regulatory requirements
    - controlling products imported in case there are issues with the product's safety, efficacy or quality

- a risk management system for manufacturers, packagers, labellers, importers and distributors, where the QAP is responsible for:
    - assessing, controlling, communicating and reviewing the risks about the quality of a product across its lifecycle
        - from raw materials being received at a manufacturing site to expiry
    - coordinating risk management across the company's various functions and departments
    - managing change and continual process improvements through a documented change control or management process

Quality assurance person training, experience and technical knowledge

Every manufacturer, packager, labeller, importer and distributor must have a QAP. This person is responsible for assuring the quality of an NHP before it's made available for sale. Your QAP must have the training, experience and technical knowledge of the buildings, equipment, procedures and practices used to conduct each activity outlined in the regulations.

A qualified QAP has appropriate and sufficient training, experience and technical knowledge:

- Training:
    - a demonstrated understanding of the principles of GMP
- Experience and technical knowledge:
    - experience in:
        - applying and working with GMP
        - the ability to monitor good documentation practices
    - ability to:
        - develop, maintain and review written procedures (SOPs)
        - implement an efficient quality system
        - conduct internal GMP audits to proactively identify GMP issues
        - investigate appropriately and successfully different quality and GMP issues identified and initiate the proper follow-up actions
        - implement efficient risk-mitigation strategies
        - review finished product specifications, batch records (as required) and certificates of analysis
        - review raw material or in-process product specifications and certificates of analysis

        - understand and interpret different test results
        - implement an effective pest control program
        - implement, conduct and monitor product recalls
        - understand the elements of a stability study
        - implement an effective chemical handling system (for example, WHMIS) when required
    - technical knowledge in the manufacturing, packaging and labelling of NHPs as it relates to their responsibilities

You must have evidence that your QAP is qualified.

Refer also to the personnel section for additional guidance on the QAP.

Quality management system

The QAP, with the support of their team:

- establishes and follows written procedures (SOPs) to ensure that products conform to specifications and regulatory requirements
- approves or rejects formulations, procedures, specifications, test methods, controls and results that affect the purity, quality and composition of each ingredient and product
    - establish and implement written procedures (SOPs) for this
- approves or rejects raw, packaging and labelling materials, and finished products
    - includes products manufactured by contractors and is based upon conformance or non-conformance to their respective specifications
        - establish and implement written procedures (SOPs) for this
        - companies that only import finished products do not need to have written procedures (SOPs) for approving or rejecting raw, packaging and labelling materials
- reviews and maintains completed batch records
    - manufacturers, packagers and labellers must review batch records for completeness and adherence to good documentation practices
    - importers may have to review batch records in specific instances
        - refer to the importation control system section for more information
- approves or rejects products for release for sale or distribution against the completed certificate of analysis, batch record or other acceptable documentation
    - document the approval using, for example, a product release form

- a certificate of analysis must be issued for each lot of product and should include as applicable:
  - identifying information, such as name of the NHP or NPN
  - batch or lot number
  - date of manufacture
  - expiry date
  - test type, method or ID number and acceptance criteria
  - numerical results (when appropriate)
  - the certificate of analysis signed and dated by the approver

- approves or rejects product quality deviations and reprocessing or reworking in the manufacture of a product
  - establish and implement written procedures (SOPs) for this
- investigates deviations and OOS results and ensures proper controls are in place
  - establish and implement written procedures (SOPs) for this
  - document all deviations and OOS results
- approves the destruction of returned or quarantined products, unless the QAP determines, by documented assessment or investigation, that the products may be released for sale or resale
  - establish and implement written procedures (SOPs) for this
    - include steps for determining whether further investigation and corrective action is necessary at the manufacturing, packaging or labelling sites

The QAP also:

- maintains records for returned, reprocessed or reworked, and redistributed products, which should include the following:
  - name and description of the product
  - lot number
  - reason for return
  - quantity returned
  - date of return
  - means of final disposition
  - an investigation report that documents the findings and any follow-up action taken, when required
- handles internal product complaints (deviations) and issues identified during manufacturing, packaging, labelling, storing or transportation
  - establish and implement written procedures (SOPs) for this
    - include a step for determining whether further investigation and corrective action are needed

- documents external product complaints and issues
    - establish and implement written procedures (SOPs) for this
    - include the following:
        - name and description of the product
        - lot number and expiry date
        - source and nature of the complaint
        - any response taken
        - an investigation report that documents the findings and any follow-up action taken, when required
- monitors and maintains appropriate data integrity (refer to the records section for more information)

Evaluate returned products for defects that could lead to changes being made to your company's processes. Product returns can be caused by quality, manufacturing, packaging or labelling problems, which must be fixed.

Deviations

A deviation is the departure from an established or approved procedure, process, work instruction or form, or an accepted standard. An example would be an OOS result.

Some deviations are not planned (for example, when a manufacturing process is not followed because equipment failed during production).

Some deviations are planned (for example, when a piece of equipment not listed in the master production documents is used instead).

Investigating deviations under your quality system shows that your company:

- notices problems as they arise
- has investigative and control processes in place to deal with them

Note that deviations are not always a negative occurrence.

As well as identifying the deviation as planned or unplanned, the QAP should rate its scope and severity (critical, major or minor) by evaluating its potential impact on the following:

- product safety, efficacy and quality
- previous batches or lots that could be affected
- trends relating to similar products, including similar causes or issues on other products

- materials and equipment implicated
- testing processes

Types of deviations:

- Minor deviation: will probably not affect the finished product's safety, efficacy and quality
    - Example: a short temperature deviation on a product meant to be stored at room temperature
- Major deviation: will probably affect a product's safety, efficacy and quality
    - Example: not adding an ingredient during manufacturing
- Critical deviation: will lead to hazardous or unsafe products
    - Example: a machine leaking oil into or onto a product, or when there are product cross-contamination incidents

Document, investigate and resolve any deviation from established procedures and standards as quickly as possible. Major and critical deviations may lead to:

- CC put in place
- CAPA plans
- recalls

To investigate deviations efficiently, we suggest defining a reasonable timeline for this based on the deviation rating. For example, investigations into critical, major and minor deviations could be completed within 10, 20 and 30 working days, respectively. You should not release a product on the market before you confirm that the deviation did not affect the product's safety, efficacy or quality.

Out-of-specifications

An OOS is a specific type of deviation. An OOS occurs when:

- a material or product fails to meet an established specification
- things like machinery or monitoring equipment perform or are used outside established conditions or parameters
    - for example, mixing speed is too high or too low or a temperature excursion is recorded

Section 44 of the regulations states that every NHP available for sale must comply with the specifications submitted during the product licensing process. Thus, releasing OOS products for sale without following an approved written procedure (SOP) for

investigating OOS results and correcting the root cause is a serious GMP error and a non-compliance with the regulations.

When investigating an OOS, the QAP, with the support of their team, is responsible for:

- placing the OOS material or product in a quarantine area until the issue is resolved appropriately
- analyzing the data related to the OOS
- evaluating the impact on product safety, efficacy and quality
- revisiting previous batches or lots that could be affected and looking at related trends
- evaluating the materials, equipment and testing processes implicated
    - refer to the laboratory control system section for more information
- considering similar causes or issues on other materials or products
- developing a corrective action plan
- ensuring that any resampling or retesting are performed properly, according to a written procedure (SOP)
- ensuring the OOS material or product is appropriately disposed of (such as raw materials being returned to the supplier), as required
- initiating a recall of batches or lots that were distributed in the Canadian market, when required

As the QAP, ensure that OOS test results are investigated in accordance with a written procedure (SOP). This procedure should include the following aspects:

- an investigation (or requesting an investigation from the testing laboratory) to determine the cause of the OOS result
    - When caused by a clearly identified laboratory error: You can invalidate the original results, then repeat the test and report the results. Record an explanation, including the source of the error and the corrective actions to prevent recurrence.
    - When not caused by a clearly identifiable laboratory error: The investigation should focus on a review of the manufacturing processes and any other factors that could have impacted the results.
- any retesting or resampling must be approved in advance by the QAP with the number of retests to be performed
    - The original sample should be sufficiently large to accommodate a retest. Include a justification if a resampling is performed.
- testing your hypothesis may be required to demonstrate the presumptive root cause

OOS results may require you to implement CAPA. Refer also to the CAPA process section of this guide.

Remember that repeated testing or sampling until a passing result is obtained to invalidate the OOS is not an acceptable practice. This is commonly referred to as "testing into compliance".

- Report all valid test results (both passing and suspect) and fully consider them in batch release decisions.
- Averaging compliant and OOS results is not appropriate.

Laboratory control system

A laboratory control system may differ greatly from one organization to another. It will depend on how a manufacturer, packager or importer decides to test (analyze) their material or product to ensure specifications are met prior to sale. Companies may completely outsource product testing or do it entirely in-house. Some may do a limited subset of simple analysis (such as brix, density or pH) and outsource the rest.

Testing is fundamentally linked to sections 44 and 51 of the regulations. Although testing is not a licensable activity under Part 2 of the regulations, manufacturers, packagers and importers must have a laboratory control system. The breadth and depth of this system will depend on whether you have an in-house laboratory or use a third-party laboratory.

The following pharmacopoeias and international standards are included in Schedule B to the Food and Drugs Act (always reference the most current version):

- *European Pharmacopoeia* (Ph.Eur.)
- *Pharmacopée française* (Ph.F.)
- *Pharmacopoeia Internationalis* (Ph.I.)
- *The British Pharmacopoeia* (B.P.)
- *The Canadian Formulary* (C.F.)
- *The National Formulary* (N.F.)
- *The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals*
- *The United States Pharmacopoeia* (U.S.P.)

Third-party laboratory testing

If your company outsources testing to a third party, your QAP must still be involved in maintaining the laboratory control system. The QAP, with the support of their team, ensures that:

- any third-party laboratory can do all the tasks and responsibilities assigned to them and that they apply acceptable laboratory practices
    - ideally, you should use an accredited laboratory
        - refer to the Standards Council of Canada to identify laboratories
        - laboratories holding a Health Canada drug establishment licence (DEL) for testing
        - laboratories meeting the ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories
    - if not, your QAP should confirm that the third-party laboratory is acceptable, such as by:
        - performing a virtual or in-person audit of the laboratory
        - reviewing the laboratory credentials
- all testing methods used:
    - are suitable for use
    - are applicable to the product being analyzed
    - yield valid test results
- testing is done according to pharmacopoeial (such as the USP) or other acceptable methods
    - refer to the Quality of natural health products guide for more information on test methods
- product sampling is performed properly, according to a written and approved procedure
- microbial contamination testing is done at the finished product stage
    - if done prior to packaging, a manufacturer or importer should maintain an acceptable scientific rationale, supported by efficient process controls and risk management strategies
- manufacturers and packagers keep records of material or in-process testing
- manufacturers and importers keep records of all finished product testing
    - importers must keep the certificate of analysis from the manufacturer as well as other additional testing they had performed
        - refer to the importation control system section for more information

Regardless of who conducts the testing, the Canadian manufacturer or importer must make sure that:

- products comply with their specifications before they are released for sale
- records of finished product test results are maintained in accordance with sections 51, 53 and 56 of the regulations

In-house laboratory testing

In addition to what is needed for third-party laboratory controls, the role of the QAP expands when testing is done in-house. The QAP is typically supported by personnel who have the appropriate scientific background to do testing.

The QAP, with the support of their team, ensures that:

- the in-house laboratory can do all the tasks and responsibilities assigned to them and is following acceptable laboratory procedures
- laboratory procedures, testing, method development and verification are properly controlled by qualified personnel
- procedures to handle and prepare the reagents or standards are implemented
- sampling and retesting are performed properly, according to a written procedure (SOP)
- laboratory records of tests, including test results, and investigations are maintained
- laboratory operations training records of staff implicated in the laboratory are maintained
- staff follow proper hygiene practices
- water used in the laboratory's operations is appropriate to the methods used
    - such as USP grade, purified or potable

Only qualitative methods (as opposed to enumerative or quantitative methods) for specific microorganisms are acceptable when determining their presence or absence.

Importation control system

The importer is the final party responsible for products imported into Canada and thus plays a critical role in ensuring that the products are safe, effective and of high quality. Part of this role is monitoring foreign manufacturers, packagers and labellers to ensure

that imported NHPs meet appropriate standards and have been manufactured in a GMP environment. Refer to the operations section for more information.

When you import products, the QAP, with the support of their team:

- confirms that the imported products meet their specifications and Canada's regulatory requirements
    - establish and implement written procedures (SOPs) for this
- controls the products imported in case of safety, efficacy or quality issues (such as by doing additional tests or initiating recalls when needed)
- approves or rejects finished products manufactured by foreign sites based on conformance or non-conformance to their respective specifications
    - establish and implement written procedures (SOPs) for this
- approves or rejects test methods, controls and results done on behalf of the foreign site if the site does not completely test the product specifications, especially those that affect the product's purity, quality and composition
    - establish and implement written procedures (SOPs) for this
- reviews and maintains completed batch records when applicable
    - a certificate of manufacture for a product manufactured in a non-MRA or PIC/S inspected facility may be an acceptable alternative to a batch record when the process in place meets the following:
        - the content of the certificate meets the definition of a certificate of manufacture in this guide (refer to the glossary)
        - the master production document has been reviewed and approved by the importer's QAP
        - periodic review of batch records is conducted (for example, at least once a year)
        - complete batch documentation is available upon request
        - the product's medicinal ingredients have not been quantified by input
        - the product's medicinal ingredients are not on a rotational testing schedule
        - the batch has not been reworked or reprocessed
    - refer to the specifications section for more information on importing from buildings inspected by a regulatory authority under an MRA or PIC/S
- approves or rejects the product for release and distribution against the completed certificate of analysis, batch record or other acceptable documentation
    - document this approval (for example, use a product release form)

    - importer (or a third-party laboratory contracted by the importer) must conduct any tests required by the specifications but not completed by the foreign site before releasing the product
    - importer must maintain documentation that includes the following:
        - identifying information, such as name of the NHP or NPN
        - batch or lot number
        - date of manufacture
        - expiry date
        - test type, method or ID number and acceptance criteria
        - numerical results (when appropriate)
        - quantity of product released
        - reference to any applicable deviation reports
- investigates OOS results and ensures proper controls are in place at the foreign and importing sites
    - establish and implement written procedures (SOPs) for this
    - document and investigate all OOS results from imported products
- approves the destruction of returned or quarantined imported products unless the QAP determines, by assessment or other investigation, that they may be released for sale or resale
    - establish and implement written procedures (SOPs) for this
- handles complaints for imported products
    - establish and implement written procedures (SOPs) for this
        - include steps for determining whether further investigation and corrective action is necessary at the manufacturing, packaging, labelling or importing sites
- monitors issues related to importation, such as transportation:
    - establish and implement written procedures (SOPs) for this
    - include steps for determining whether further investigation and corrective action is necessary

Risk management system

Risk management involves assessing, controlling, communicating and reviewing risks that could affect the quality of an NHP across its lifecycle. A quality risk management process can help a company comply with GMP requirements. Refer to the quality risk management section for more information.

A risk management system for quality involves CC and CAPA. It also includes internal audits (self-inspections) to proactively identify potential issues.

For examples of quality risk management processes and applications, consult the ICH's guideline, adopted by Health Canada:

- Q9: Quality risk management

Although NHPs are not within the scope of ICH guidelines, such references are helpful to the NHP industry and other stakeholders. The guidelines may help you gain a better understanding of GMP concepts and processes that also apply to NHPs.

Change control

A CC process will help you:

- monitor changes that could affect the manufacturing, packaging, labelling, importing, distributing and quality of your NHPs
- ensure that premises, equipment, methods or product-related changes are made in a controlled and efficient manner
- reduce the possibility of process disruptions or the introduction of faults, errors or problems during the implementation of a change

Establish and implement written procedures (SOPs) to support your CC process. When implementing a CC process, the QAP, with the support of their team:

- identifies and supports a qualified team to lead the change
    - such as the production team or laboratory analysts
- analyzes the potential impacts of the planned changes on:
    - product quality
    - manufacturing, packaging, labelling, importing or distributing processes, as applicable
- monitors the process and signs off on the implementation of the planned CC
- documents, reviews and approves changes
    - process should describe measures made to ensure that all documents affected by the change are revised appropriately
- includes a classification system based on the nature and scope of the change (critical, major or minor) and identifies its impact on the process using clear terminology
    - the classification system will help determine the appropriate level of effort and documentation required to justify the change (such as testing, validation and support)
- evaluates the impact and effectiveness of the change
- signs off on and closes the CC record once the change is fully implemented

Corrective and preventive actions

CAPA are taken to eliminate the cause of a detected non-conformity or undesirable situation. Always have in place a process for CAPA so that personnel can correct an undesired, unacceptable or improper issue or practice. This will also help to prevent it from happening again. An efficient CAPA process supports a company's ongoing and long-term GMP and QA standards.

Key terms related to CAPA:

- Immediate correction: to immediately correct or contain a GMP deficiency or product issue
    - these corrections usually do not fully address the issue
- Corrective actions: to control a current event
- Preventive actions: to avoid an event from happening again

The key steps of a strong CAPA process are:

1. Identify a GMP deficiency or product issue
2. Document and record
3. Assemble a team of subject matter experts to review and investigate
4. Use immediate correction measures to contain the problem
5. Identify the root cause
6. Evaluate the impact
7. Implement a CAPA plan
8. Monitor the effectiveness of the plan
9. Close the CAPA with QAP approval

Refer to the CAPA process section of this guide for more information.

The following events may trigger the need to initiate a CAPA process:

- deviations
- complaints
- investigations
- internal findings
- external findings

Your QAP is responsible for establishing, monitoring and maintaining a CAPA process, which includes:

- a tracking system for events (such as deviations, OOS results) and actions taken (CAPA and CC)
- a team of appropriate subject matter experts (such as QA, QC, manufacturing) to:
    - determine and document the root cause of the problem
    - plan, develop and implement appropriate CAPA
    - undertake the following steps if the issues are product-related and the products are available on the Canadian market:
        - evaluate and mitigate the issues identified that are related to product safety, efficacy and quality
        - revisit previous batches or lots that could be affected and look at related trends
        - evaluate if similar causes or issues could apply to other products
        - determine if amendments to regulatory submissions are necessary
        - initiate a recall for batches or lots already distributed in Canada, when required
    - describe and document short- and long-term CAPA
    - determine a reasonable timeline to correct issues and plan for CAPA implementation, when required
- revisiting the CAPA within a specified timeline to monitor and evaluate their effectiveness
- signing and closing the CAPA when complete

Your CAPA process may lead you to identify or consider that the issue may affect other products or processes. Your CAPA investigation should include those products or processes.

Importers are responsible for the products they import into Canada. Also note:

- products imported must be manufactured, packaged, labelled, imported, distributed and stored with equivalent GMP to Canadian GMP for NHPs
    - section 43 of the regulations
- products must meet their specifications and be approved by the QAP before they are for sale (before release)
    - sections 44 and 51 of the regulations
- the importer or Canadian manufacturer is responsible for establishing and maintaining data on product shelf life
    - section 52 of the regulations

When product-related issues are identified, the importer must develop and implement a strong CAPA plan. Although this plan may leverage the foreign manufacturing, packaging

or labelling sites, the importer must ensure that processes and controls are in place to prevent the event from occurring again.

You should do periodic self-inspections to monitor GMP and proactively correct issues. During the self-inspection, ensure to cover all GMP that apply to your activities. For more information, consult the self-inspection chapter in the PIC/S's Guide to good manufacturing practice for medicinal products, part I.

GMP evidence

Your QAP must be qualified. You must have evidence to support this and the responsibilities of this position. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates outlining responsibilities and activities, such as:
    - QAP job description that outlines roles and responsibilities, required training, experience and technical knowledge
    - review and approval of methods, procedures and systems used to manufacture, process, label and import NHPs
    - approval of raw, packaging and labelling materials
    - finished product release, including:
        - direction on how to assess each lot for compliance with its Canadian specifications and the product licence after testing has been performed
        - direction on how to confirm the lot number and expiry date on the label
        - a description of what conditions would stop the release of a product
    - disposition, distribution and disposal of products, including returns released for re-sale
    - complaint investigation and resolution
    - corrective actions addressing deviations, non-conformities and OOS results
- approved finished product specifications for products manufactured, packaged, labelled and stored at the site, including confirmation that:
    - the medicinal ingredients, including quantity and potency (if applicable) amounts, are the same as on the product licence
    - all required test results, test methods and acceptance criteria are within Health Canada requirements
- approved finished product release records that include:

    - product identification, NPN and lot number
    - date of manufacture, packaging and labelling, and expiry
    - quantity of product manufactured or imported and released
    - results of the finished product testing and the product status (released or rejected)
- QAP's resumé (C.V.), including education, that demonstrate the person meets their job description
- QAP's training record that demonstrates ongoing and relevant training
- organizational structure or chart that clearly demonstrates that the QAP operates independently

6.10 Stability period (section 52)

Section 52

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

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

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

Intent

A written stability program is used to:

- determine the shelf life of an NHP
- provide evidence that the product will remain within its specifications over its shelf life
    - occurs under the recommended storage conditions in the packaging available for commercial sale

Examples of environmental factors that can affect a product's shelf life during storage include:

- light
- oxygen
- humidity

- temperature

A product's shelf life may also be affected by a product's:

- pH range
- moisture content
- chemical hydrolysis
- chemical interactions
- oxidizing or reducing agents

Environmental factors and product characteristics may cause a product to degrade, lose medicinal ingredient strength or show an increase in microbial contamination.

Manufacturer, importer requirements

Manufacturers and importers must put written procedures (SOPs) and practices in place for product stability studies to ensure that finished products comply with approved specifications.

You must:

- have a completed stability study for each NHP marketed in Canada
- implement and make available a stability protocol for each study
- maintain a stability report that summarizes the data generated and includes the evaluation and conclusions

You are responsible for obtaining, maintaining and reviewing up-to-date records on the stability program. It does not matter if you or the product licence holder, foreign manufacturer, distributor or other responsible person performs the stability testing.

For imported products, stability studies from foreign sites may be accepted. As the importer, you must:

- ensure that the stability protocols used comply with Canadian requirements
- review, evaluate and maintain the stability results
- obtain any required tests that are not included in the stability studies collected from foreign sites
- maintain a complete stability report for the NHP released in Canada

Stability program written procedure

To implement an effective stability program, you must have a stability program written procedure (SOP). The SOP should include details on the following:

- assigning the initial expiry date
- conducting real-time stability studies
- collecting additional stability data, if needed
- designing a stability protocol
- maintaining a stability report

You may be able to reduce the number of stability studies for products with multiple package types by using bracketing or matrixing. For more information on using bracketing and matrixing, consult:

- ICH guideline Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products

Although NHPs are not within the scope of ICH guidelines, such references are helpful to the NHP industry and other stakeholders. The guidelines may help you gain a better understanding of GMP concepts and processes that also apply to NHPs.

Assigning the initial expiry date

Each finished NHP sold in Canada must have a lot number and an expiry date on the label. To determine the initial expiry date, use known data to predict the product's shelf life, such as:

- results of accelerated or real-time stability studies on the product
- information that has been gathered from similar products in similar packaging

While accelerated testing generates preliminary shelf-life data in a relatively short timeframe, it may be unreliable when used to assign an expiry date. You will need to determine if it's appropriate to use accelerated stability studies, especially for products that can easily separate, melt, soften, crack or degrade under high temperatures and humidity. Use real-time stability testing to confirm data from accelerated testing.

When using stability data from similar products, maintain evidence of their manufacturing and packaging process (for example, a batch record) to thoroughly evaluate and document any differences between the products that might affect stability.

Maintain the stability study results from any similar products used to support your product's initial shelf life.

In general, similar products would be those with similar formulations and manufacturing and packaging processes (premises and equipment):

- similar formulations would differ only in processes and ingredients that are assessed to have no or minimal effects on product stability
    - for example, colourants or flavours
- similar packaging would differ only in components that are assessed to have no or minimal effects on product stability
    - for example, label content or other secondary packaging components

Differences in raw materials and finished products can change the product's properties, including the material in which they are packaged, how the package is sealed and package size. Interactions between ingredients, added preservatives and the manufacturing process must also be considered.

Conducting real-time stability studies

Real-time stability studies must be conducted and used to verify any shelf life that was proposed based on extrapolation. Use the data collected through real-time studies to ensure that each finished product meets its label claims at the expiry date (when stored according to its labelled storage conditions).

Real-time stability studies must follow an established stability protocol. This means the:

- product lots must be of the same formulation and packaged in the same container closure system (or scientifically demonstrated equivalent) as those sold commercially
- manufacturing process used for lots that are in a stability program must match that used for lots sold commercially, provide the same quality and meet the same specifications as those intended for sale.

A product held in bulk before it's packaged or any time throughout its manufacture could affect stability studies. You should consider including batches that have been stored at the limits of extended hold times (for example, more than 1 month) in your study. This would represent a worst-case scenario.

The shelf life is established through stability studies (for example, data show that the product is stable for 24 months). The studies are used to assign an expiry date to each lot of packaged product. The expiry date printed on the product packaging must be assigned

from the date of original batch manufacture, not the date of packaging. For example, a 24-month shelf life would be indicated by printing an expiry date on the product packaging that is 24 months after the date of manufacturing. This would occur even if the product was held in bulk for 6 months before being packaged.

Stability sample storage areas may include specialized chambers or dedicated rooms. They must be monitored for temperature, humidity and, where applicable, light levels. Storage conditions should be maintained within the ranges specified in the stability protocol and in accordance with the product licence and label. Document and maintain records of the storage conditions.

The regulations are not prescriptive on the time points required for conducting stability testing on NHPs. However, additional test time points can help manufacturers, importers and product licence holders gather useful information and compile trending data on the product over its shelf life.

By tracking stability test results at several time points over the course of the stability study, trends may be observed in the preservative strength, microbial contaminant levels and medicinal ingredient strength. These may lead to OOS test results before the product expires. Results that are out-of-trend (OOT) should be investigated. Remember, OOS test results can lead to product recalls.

When medicinal ingredients in the finished product are quantified by input, they cannot be assayed at expiry. Instead, you may evaluate other observed changes to the product over its shelf life, such as changes in colour or odour, viscosity, disintegration and microbial contamination. These may indicate changes in the product's quality and stability.

We recommend assigning a shorter shelf life for those products where medicinal ingredients cannot be quantified by assay. Remember to make changes to your stability program when new test methods that can be used for your product become available.

You should confirm and adjust the expiry date when required. Base any updates to the shelf life on real-time studies performed on products stored:

- under the conditions noted on the label
- for the period indicated by the expiry date

Re-evaluate the product shelf life when significant changes are made to the formulation, the manufacturing process, or the packaging. These may affect the product's stability.

Collecting additional stability data

You may choose to gather additional stability data to expand your knowledge of how various factors affect product quality. This would be in addition to assigning the initial expiry date and confirming the shelf life through real-time studies. Gathering additional data can help to:

- resolve complaint investigations
- extend expiry dates
- improve storage conditions
- justify hold times
- understand effects of temperature deviations
- support the approval of rework

Reworking means using an alternate manufacturing process for a single batch of an in-process, bulk or finished NHP due to an unexpected failure to meet predetermined specifications.

The regulations do not specifically require expiration dates for bulk products. However, it's valuable to collect data on various hold times to provide assurance that the product remains stable for the intended period of use. Consider including batches that have been stored in bulk at the limits of extended hold times (for example, more than 1 month) in your stability program.

Any rework performed may affect the stability of the finished product. Enrolling reworked lots into the stability program can provide support for releasing these products and assurance that the lots are still of good quality.

Storage conditions for NHPs need to be in accordance with label requirements, unless you have an acceptable scientific rationale that allows for brief deviations (for example, during shipping). Stability data may support planned temperature deviations and worst-case scenarios (frequency and severity) throughout the distribution chain.

The data are also useful in assessing the effects of unplanned deviations. If you conduct studies such as freeze/thaw or high temperature cycling, you should evaluate the early exposure to extreme temperatures, as stability at the end of shelf life may be affected.

NHPs are not within the scope of USP <1079> Risks and mitigation strategies for the storage and transportation of finished drug products. However, the concepts and

mitigation strategies presented in that reference may help to guide best practices related to temperature excursions.

Initial shelf life may be extended if real-time stability studies show that the product is stable for longer than anticipated. Carrying out these studies past the current expiry date and evaluating the test results according to your stability protocol may allow you to make changes to your stability period and extend your expiry date for future lots.

The desire to extend expiry dates requires pre-planning in the protocol stage. You need to enrol additional samples in the program and document the additional test time points you will use.

Consumer complaints, such as those dealing with product colour, odour and appearance, may give additional data on the stability of your product. A product that changes in appearance or smell over time may indicate microbial growth or unwanted chemical reactions.

Designing a stability protocol

A stability protocol should be designed to provide data from the study in a form and quantity that permits a realistic analysis. It should be created for each stability study.

Your stability protocol should include, as applicable, the:

- study scope and purpose
- name or NPN of each product included
- reference to the master formula, and master manufacturing documents, packaging and labelling documents or ID numbers used for lots being tested
- type, size and composition of each container and closure system or reference to the packaging ID number
- total number of containers required of the pack size to complete the study
- lot or batch code, date of manufacture and proposed expiry date of each product included
- procedures for evaluating the stability of products before or after constitution, reconstitution or dilution (if applicable)
- sample size and test intervals (for example, frequency of sample testing) for each test parameter
- storage conditions (and tolerances) of samples, with conditions such as temperature and humidity maintained and controlled for length of the study
    - use stability chambers or dedicated and controlled rooms, where practical

- orientation of samples (for example, upright, inverted, horizontal) that reflect the worst-case scenario, if applicable
- stability specifications, including:
    - tests that can detect any changes to the physical, chemical and microbiological characteristics of the product dosage form over its shelf life
    - acceptance criteria for each test parameter
- procedures for evaluating the packaging, which may include:
    - appearance of inner walls and cap
    - integrity of seals
    - appearance and adhesion of the label
    - readability of the lot number and expiry date
- method of data evaluation, including any statistical analysis or trending graphs or tables used to establish shelf life
- format and structure of the stability report coming out of the study
- procedures for evaluating OOS test results or negative trends
    - assess confirmed OOS, borderline or significant atypical trend that may have impact product quality
    - may require further actions (such as further stability studies, an increase in testing frequency or change in shelf life)
    - consider the impact on all batches or lots available on the market

The properties selected for testing during a stability study should include those that may be subject to change during storage or could affect the label claims, product safety, efficacy or quality. Although many minerals are known for their stability over time, mineral medicinal ingredients should still be included in stability studies. Ingredients can change over time in unexpected ways. This includes when they are mixed with other ingredients, manufactured into their finished dosage form and packaged in various packaging materials.

For more information on stability specifications for various dosage forms, consult:

- Quality of natural health products guide

Maintaining a stability report

The stability report summarizes the data generated from each stability protocol, including the study's evaluation and conclusions. Include the following in this report, as applicable:

- study details that were outlined in the stability protocol, including test intervals

- storage conditions
- sample orientation
- stability specifications, including test methods and acceptance criteria
- product specific details, including:
    - product name or NPN
    - batch or lot code
    - date of manufacture
    - expiry date
    - packaging details
- reference to any deviation reports outlining discrepancies from the stability protocol
- evaluation of appearance of inner walls and cap, and integrity of seals
- evaluation of appearance and adhesion of label, and readability of lot number and expiry

Also include:

- test results for each parameter included in the stability specifications
- scientific evaluation of the data generated by the study
- overall assessment of the findings
- assessment of any OOS, borderline or atypical trends observed
- signature and approval of the report by the QAP

The stability study should provide data in a form and quantity (such as number of test time points) that permits scientific evaluation and realistic statistical analysis. Study results should include results from:

- physical, chemical (when appropriate) and microbiological testing
- tests on particular attributes of the dosage form
    - for example, disintegration results for solid oral dosage forms

Use the data gathered through real-time studies to confirm and adjust the expiry date, as needed.

If you observe OOS, borderline or atypical trends during the study, you must take further action, such as conducting an investigation, additional stability studies, changing the shelf life or recalling the product. Consider also the impact of the stability study on all batches of the product that are on the market.

Review and evaluate the data collected against Canadian requirements. As the manufacturer or importer, you should do this whether you or the product licence holder,

distributor, foreign manufacturer or other responsible person did the stability testing. The QAP for the party responsible for the stability of the product in Canada will review, approve, sign and date the stability reports, and address any deficiencies.

Keep a record of how you determined each shelf life for 1 year after the last lot of the NHP to which that stability record relates has expired.

The record must include the:

- information used to determine the initial shelf life
- real-time stability protocol
- associated stability report supporting the expiry date of each NHP released in Canada

The regulations do not distinguish between a manufacturer and a contract manufacturer. Both have the same responsibilities for stability and related records:

- Section 52: Every manufacturer and every importer shall determine the period of time during which, after being packaged for sale, the NHP will maintain its purity and physical characteristics and its medicinal ingredients will maintain their quantity per dosage unit and their potency.
- Section 53: Every manufacturer who sells a natural health product shall maintain the following records at the site at which the NHP is manufactured: a record of each determination made by the manufacturer in accordance with section 52 and the information that supports that determination.

GMP evidence

You must demonstrate GMP compliance for stability with supporting evidence. The type of GMP evidence for stability may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for stability data or testing or determining expiry date, including a:
    - description of testing procedures and schedule
    - direction on storage of samples at recommended conditions
    - direction on actions to be taken when:
        - a product fails stability
        - stability failure investigations and recalls are needed

        - establishing a longer shelf life
    - description of how product shelf life is re-evaluated when significant changes are made to:
        - formulation
        - manufacturing process
        - packaging that may affect the product's stability
- laboratory results demonstrating that every product meets specifications at expiry
    - corresponding testing results for each time point as indicated in the stability testing protocol
        - if real-time testing is not yet complete, include a timeline or schedule for completion
    - acceptable test methods and acceptance criteria are used
    - chemical contaminants do not need to be tested to support stability (for example, heavy metals, pesticides, solvent residues)

6.11 Records (sections 53 to 58)

Sections 53 to 58

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 by or for the manufacturer 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.

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 by or for the packager 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.

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.

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 by or for the importer 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.

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.

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 1 year following the expiry date of the natural health product to which that record relates.

Intent

Good documentation is a key part of a quality system. It promotes and supports compliance with GMP requirements. Documentation may be paper-based, electronic or photographic media.

Your quality system should define the various types of documents and media that you are using. The documentation system's main objective is to establish, control, monitor and record all activities, especially those that directly or indirectly impact the quality of your product. This includes information from all stages of the product lifecycle and all records on product quality.

Records must be reliable, complete, consistent and accurate.

Your company, QAP and employees must view documentation and record-keeping as a fundamental element of GMP and of your quality system.

Manufacturer, packager, labeller, importer, distributor requirements

You must have a documentation control system that properly documents, records and tracks all stages of manufacturing, packaging, labelling, storage, testing and distribution.

Table 2 lists the minimum record-keeping requirements for manufacturers, packagers, labellers, importers and distributors.

Table 2: Record-keeping requirements for various activities

Record	Manufacturer	Packager	Labeller	Importer	Distributor
Master production document	Maintain	None	None	Maintain	None
Batch record	Maintain	Maintain	Maintain	Access[1]	None
Test results: raw materials	Maintain	None	None	Access[2]	None
Test results: packaging materials	None	Maintain	None	Access	None
Test results: finished product	Maintain	None[3]	None	Maintain	None
Specifications: raw materials	Maintain	None	None	Access	None
Specifications: packaging materials	None	Maintain	None	Access	None
Specifications: finished product	Maintain	None[3]	None	Maintain	None
Stability	Maintain	None	None	Maintain	None
Ingredients list	Maintain	None	None	Maintain	None
Products List	Maintain				

Table 2: Record-keeping requirements for various activities

Record	Manufacturer	Packager	Labeller	Importer	Distributor
Complaints	Maintain				
Recall	Maintain				
Sanitation program	Maintain				

1. As an importer, maintain batch records when a medicinal ingredient is quantified by input. Use the batch record to control the release of products where 1 or more medicinal ingredients are quantified by input.

2. As an importer, maintain certificates of analysis for medicinal ingredients quantified by input. Use these certificates to ensure that the finished product contains the correct medicinal ingredient and that it was tested correctly prior to use.

3. For packagers of liquid products, documents demonstrating microbial controls to mitigate the risk of contamination during the filling process, or microbiological test results obtained after packaging, must be maintained.

Maintain: Indicates the party will keep and make readily available such records.

Access: Indicates the party does not need to keep these records but will have ready access to them.

None: Indicates the party does not need to have such records.

As an importer you may want to maintain copies of product licences and of product labels to confirm, during the release process, that products meet their label requirements.

You must:

- make any documentation requested by Health Canada for evaluation available in 1 of Canada's official languages (refer to the Official Languages Act)
- apply good documentation practices, as outlined in this section of the guide, to records and documentation
- not backdate or postdate records or other documentation
- maintain, as applicable, records to demonstrate that each batch of product was manufactured, packaged and labelled according to the procedures described in the master production document
    - Importers: a certificate of manufacture or batch certificate is an acceptable alternative to a batch record (when it meets the requirements outlined in this guide). However, complete batch documentation must be made available upon request.

- maintain, as applicable, records to demonstrate that each batch or lot of product was manufactured, packaged, labelled and imported according to Part 3 of the regulations:
    - when using a contractor to manufacture, package or label within Canada or import product, the site licence holder should:
        - keep a copy of the contractor's site licence, when applicable
        - document and keep records of all tasks that the contractor carries out on your behalf
        - establish and maintain a valid quality agreement (written agreement) covering the contracted manufacturing, packaging, labelling, importing, storing, distributing or testing activities in accordance with Part 3 of the regulations
        - ensure all arrangements for contracting, including any proposed changes to quality agreements (written agreements), are in accordance with GMP requirements and the product licence
        - make available to Health Canada the quality agreement (written agreement) (or relevant parts thereof) if further assessment or additional clarification is required
    - Importers: ensure that records can be accessed in a timely manner when manufacturing, packaging or labelling are done outside of Canada

You must also maintain, as applicable:

- evidence showing compliance of each finished product with its established specifications
- distribution records on your premises in Canada, with sufficient information to enable the recall of every batch or lot that has been made available for sale
    - refer to the recall reporting section of this guide for more information
- all manufacturing, packaging, labelling, testing and distribution records for at least 1 year after the expiry date of the finished product
    - although not required, we recommend keeping these records for a longer time so your company can do retrospective analyses

When the manufacturer is located outside of Canada, specific parts of a master production document may be a trade secret or confidential. They may be held on behalf of the Canadian importer by an independent party in Canada.

- The importer and independent party will ensure that Health Canada can access the data in a timely manner.

- The master production document will describe in general terms what, if anything, was redacted.

Specific requirements:

- Manufacturers and importers: maintain evidence establishing the expiry date of each product
- Manufacturers: maintain evidence or records of raw material testing that is used in the manufacture of the NHP
- Packagers: maintain evidence or records of packaging material testing that is used to package the NHP

You must also:

- retain authorized written procedures (SOPs) for all applicable sections of these requirements for reference and inspection
    - review written procedures (SOPs) regularly and have authorized employees keep them up to date
    - document the reasons for revising procedures and establish a system to ensure that only current versions are in use
- have the QAP approve, sign and date all relevant documents related to GMP
    - includes records of actions taken, conclusions reached and procedures followed
- ensure that any alteration of a document is explained, signed and dated, and that the original information can still be read
    - do not alter documents without authorization

Good documentation practices

Good documentation practices is a term used to describe standards that one follows to create and maintain documents. These common standards support GMP.

For more information about good documentation practices principles, consult the pharmacopoeial references on this topic (for example, USP <1029> Good documentation guideline).

Not following good documentation practices may lead to unreliable, incomplete, inconsistent or inaccurate documentation and cause multiple GMP-related failures. Good documentation practices are an essential part of a comprehensive GMP training program.

Good documentation practices generally include the following elements:

- Document creation:
  - ensure your documents are free of errors by checking for accuracy
  - avoid having handwritten documents in your quality system (except for handwritten entries)
    - refer to the handwritten entries item
  - record data entries promptly (when the activities are being performed) and in a format that makes it easy to evaluate trends (when applicable)
    - notebooks, data sheets and worksheets should contain identifying information to make them easier to trace
- Document approval:
  - ensure your documents are approved, signed and dated by appropriate authorized personnel
- Handwritten entries:
  - provide adequate space for expected handwritten entries
  - use indelible ink
  - ensure critical entries are independently checked (verified by second person)
  - do not leave blank spaces, if unused, cross out or write "n/a" (or similar text)
  - do not use ditto marks or continuation lines
  - use a handwritten signature, not a stamp
- Copies of documents:
  - ensure copies of documents are clear and legible, so that errors are not introduced
  - label copies as such (“COPY”) and initial and date
  - make copies of documents if the ink can fade over time (thermal paper)
- Document maintenance:
  - review documents regularly and keep them current
  - make sure documents are available and will last over the appropriate duration
- Document modification:
  - sign and date any handwritten modifications
  - do not cover altered text with heavy use of strikethroughs or with correction tape or fluid
  - note the reason for alteration (for example, "E.E." is a common abbreviation used to indicate "Entry Error")
  - implement controls to prevent the unintended use of outdated documents (documents where there is a more recent version)

Other good documentation practices:

- Do not remove or discard pages in documents (for example, in notebooks).
    - removing a page means that any data on that page will be lost
- Number the pages of documents.
    - page numbers, especially in a "page x of y" format, means you can confirm if any pages are missing
- Use a consistent and understood format for dates and times.
    - a date written as "07-05-10" can have numerous different meanings and lead to confusion and errors (consider using the internationally recognized ISO 8601 standard, which presents dates as YYYY-MM-DD)
    - write out times using the 24-hour clock system to reduce the potential of errors (use the ISO 8601 standard, which presents time as HH:MM or HH:MM:SS if seconds are required)
- Keep the original document when transcribing, especially when the original is of poor quality or physically damaged. Clearly mark the document as a transcription.
- Do not record raw data on non-official records, such as scrap paper or sticky notes.
- Avoid using asterisks when making a handwritten change, even if there is not enough white space to write out a change by hand in full.
    - the asterisk could be a problem if additional changes are made by another person who uses the same mark (instead use a numbering system, such as "1 entry error. KAM 2025-01-13", where KAM is the person's initials)

Electronic signatures and records

Sections 84 and 85 of the regulations on electronic signatures and electronic records state:

- 84: Any signature that is required by these regulations to be shown on a record or document may be an electronic reproduction of the required signature.
- 85: Any record that is required to be maintained by these regulations may be maintained in any electronic format from which a printed copy of the record can be produced.

If you keep your records in an electronic format (instead of paper), be sure those records are reliable and can be accessed.

You must:

- have written procedures (SOPs) for operating and maintaining computerized systems
- check that electronic documentation is accurate
- test and evaluate electronic document management systems to make sure they are suitable and reliable
    - your evaluation should take into consideration the general principles of good documentation practices regardless of whether records are paper or electronic
- back up electronic records
- implement controls to prevent older documents from being used rather than the most recent version
- allow only authorized personnel to modify electronic versions
- control access to electronic versions by password or other means
- keep a history (audit trail) of changes and deletions to electronic versions
- ensure electronic data is printable and all alterations are tracked
- use electronic signatures instead of handwritten signatures only if the electronic signature identification system is:
    - tested and evaluated for security, validity and reliability
    - secured from abuse and includes electronic protection against willful or accidental damage
    - documented as it goes through development

You must also ensure that:

- you can access your electronic records and documents at least 1 year after a product has expired
- all access and user rights in electronic systems are properly controlled to prevent system users from compromising data integrity

Most PDF editing software have an electronic signature identification system that would be an acceptable alternative to handwritten signatures. These systems have been:

- tested and evaluated for security, validity and reliability
- secured from abuse and include electronic protection against willful or accidental damage

Data integrity

The general principles of good documentation practices apply to the management of a record throughout its lifecycle. This is from the time that data is first generated to any modifications made after, regardless of format (including paper records and electronic records).

Establish a data governance system to ensure data integrity is maintained for all GMP records.

Make sure to:

- trace records to the source from which the record was generated, through:
  - initials and signatures
  - secure user identification
  - document revision history (for example, reasons for changes)
- create legible records, with no parts of the data obscured or removed
  - if archived, they can be retrieved quickly
  - any changes to records must also be documented and easily traced
- record, document or save data at the time that it is generated, with reliable evidence that this was done
- maintain your records in an original format as an original record or as a true copy that has been converted to a format such as a PDF that maintains data integrity
- ensure your records are accurate through a quality system that provides oversight for record generation and maintenance

Translating records into English or French

All documents requested by Health Canada (for example, during an inspection or a site licence application review) must be provided in English or French. Any document written in another language must be translated into either of these official languages. Keep a copy of the document in its original language along with the translated version.

Documents that are already in English or French do not have to be translated into the other official language. For example, records completed in French may be accompanied by another document in English. A translation of the English document is not required.

Using a certified translator: Use a certified translator for your translation needs. A certified translator will have a certification that can be confirmed by a seal or stamp. This will show the translator's membership number from a professional translation

association, either in Canada or abroad. All stamps and seals that are not in English or French must also be translated.

If the translation is not done by a certified translator, have a certified translator confirm its accuracy (provided as a signed attestation). In other words, you could do the translation in-house and then have it checked by a certified translator.

When translation is done in Canada: Use a translator who is in good standing with their provincial or territorial organization (who represents translators and interpreters) and is certified to translate documents.

When translation is done outside of Canada: Use an accredited translator who is officially recognized or authorized in the country where the translation is being completed.

Using an affidavit: If the translation cannot be provided or checked by a certified translator, rely on an affidavit to support an uncertified translator. The translator attests to their language proficiency and that their translation accurately represents the contents of the original documents or records. This is done in front of a commissioner authorized to administer oaths in the country where they live. The commissioner or notary public must be proficient in English or French to administer the oath. All stamps and seals that are not in English or French must also be translated.

Who can take an affidavit:

In Canada:

- a notary public
- a commissioner of oaths
- a commissioner of taking affidavits

Outside of Canada:

- a notary public or equivalent

Affidavits must not be prepared by you or by members of your family (even if a member is a lawyer, notary or certified translator).

Documents without translations: We do not accept documents that are not accurately translated into English or French. This includes those that are evidence to demonstrate GMP compliance or those that are required to be maintained under the regulations.

Translated documents that have expired: A translation is valid indefinitely unless the original document has changed or has expired. The signature of a certified translator or

notary that has expired does not invalidate the translation. As long as the translator's certification was valid at the time of signature, the translation is valid.

The only time a new translation is required is if you change the original document.

GMP evidence

Maintain records and have evidence to show that your records maintenance system demonstrates GMP compliance for records. Examples of evidence include:

- relevant written procedures (SOPs) related to the maintenance of records by manufacturers, packagers, labellers, importers and distributors, including as applicable the following:
  - CC
  - record control
  - record retention
  - control of electronic records
  - use of electronic signatures
  - good documentation practices
  - document translation
  - review and approval of GMP documents
  - written procedure (SOP) creation and maintenance
- a list of NHPs manufactured, packaged, labelled, imported or stored at the site
- for an electronic system:
  - information that supports the suitability and reliability of your system
  - documentation that outlines the development and maintenance of your system

6.12 Sterile NHPs (section 59) and ophthalmic use (section 60)

Sections 59 and 60

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.

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”.

Intent

The regulations require that proper GMP be implemented to ensure a product meets the definition of a sterile product. This is achieved either through manufacturing processes or terminal sterilization.

Manufacturer, packager requirements

The manufacturing of sterile products is subject to special requirements to minimize the risk of microbial and particulate contamination. Success depends on the skill, training and attitudes of the personnel involved. QA is very important, as this type of manufacturing must adhere to carefully established and validated or suitable methods of preparation and procedure. Do not rely only on a terminal process, finished product test for sterility or other quality aspects to ensure sterility.

Health Canada is an active member of PIC/S. We have adopted the PIC/S guidance on the manufacture of sterile medicinal products.

For more information on how to manufacture sterile products in compliance with the regulatory requirements, consult:

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

Treat all sterile NHPs as any other sterile health product. Be sure to:

- follow the guidance for sterile products provided in GUI-0119 in addition to the non-sterile GMP guidance provided in this guide
- test your product for sterility as per a defined pharmacopoeial method (for example, USP <71> Sterility tests)
    - for parametric release, consult:
        - Guidance on parametric release - Pharmaceutical Inspection Co-operation Scheme (PIC/S)

- validate and control your sterilization process
    - for irradiation sterilization, consult:
        - Annex 1 to the Good manufacturing practices guide - Manufacture of sterile drugs (GUI-0119)
        - Guide to validation of terminal sterilization process of drugs (GUI-0074)
    - for terminally sterilized products, have:
        - documented evidence to show each sterilizer load was sampled appropriately from the potentially coolest part of the load (sample must be tested individually for sterility, unless subject to parametric release)
        - summaries of re-qualification of sterilization processes when required
    - for aseptically filled products, have evidence to show that samples tested for sterility include:
        - the first container filled
        - the last container filled
        - those filled after any significant intervention or stoppage
- validate and control your product-specific processes for all critical steps of the manufacturing process, including:
    - validation approach used (prospective or concurrent)
    - reference numbers and dates of approval for the master production document, including:
        - packaging
        - process validation protocol and study
        - validation of the test methods
    - the lot numbers involved and dates of completion of these studies
    - copy of the approved conclusions from product validation studies

Importer requirements

In addition to the records listed in Table 2 for non-sterile NHPs, you should maintain summaries of the:

- validation, re-qualification and controls of the sterilization processes
- product-specific process validation for all critical steps of the manufacturing process

You should also ensure you have access to copies of complete protocols and related studies for all validation activities.

GMP evidence

You must demonstrate GMP compliance for sterility with supporting evidence. The type of GMP evidence for sterility may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for sterility, such as:
  - manufacturing and packaging processes for sterile products
  - environmental control of particulate and microbial contamination
  - clean room entry and exit process for personnel and materials
  - clean room maintenance
  - laminar flow maintenance
  - product sterilization
- a detailed floor plan showing the movement of personnel and materials during sterile production
- in-process and finished product testing results
- validation of sterilization process documentation
- sterilization and environmental monitoring records
- microbiological surface swab test results
- records for QAP and product support staff on their qualifications and specialized training in microbiology

Note that GMP evidence for sterility is in addition to all of the GMP evidence expectations that apply to non-sterile NHPs.

6.13 Lot or batch samples (section 61)

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 1 year has elapsed since the expiry date of that natural health product.

Intent

Samples of units from a batch of finished product must be kept for:

- analysis by you or by Health Canada
- identification (such as confirming labelling, lot number, expiry date)

The retention samples also serve as a record of the batch of finished product and can be assessed if there is:

- a quality complaint
- a query about compliance with the product licence
- a labelling or packaging query
- an adverse reaction report

You may also choose to keep samples of raw materials and packaging materials, to help you when conducting thorough investigations in the case of quality defects or OOS tests.

Manufacturer, importer, distributor requirements

You must:

- manage retention samples according to written procedures (SOPs)
- maintain records so you can trace retention samples that may need to be reviewed
- maintain a retention sample of sufficient size to allow duplicate testing on the batch according to finished product specifications and the product licence
- keep representative samples of the finished product
    - for a batch that is packaged in 2 or more distinct packaging operations (for example, 2 separate lots, 2 separate packaging lines) or has been repackaged, take at least 1 retention sample from each individual packaging or labelling operation
    - so you can assess the actual packaging operation or inspect labelling, insert, lot number or expiry date
- store retention samples in a temperature and humidity monitored area
    - use the storage conditions listed on the label, in accordance with the product licence (for example, refrigerated storage where relevant)

Health Canada may request a sample. The sample must be large enough to complete full finished product testing in duplicate. Some companies keep retention samples in triplicate, to use for their own investigation. Retention samples that are stored in optimal storage conditions may be used as comparison samples. They may be useful when investigating product quality complaints where storage conditions are the suspected root cause.

You must also:

- keep samples from each lot of finished product for at least 1 year after they have expired in the original packaging
    - if multiple containers are required to complete full testing, keep containers of the same material and construction (supported by documented evidence) with at least 1 containing the label with which the product is marketed in Canada
- ensure there is a quality agreement (written agreement) when more than 1 site is involved in importing, manufacturing, packaging or labelling a product
    - agreement should outline the responsibility for taking and storing retention samples between the parties concerned
- store retention samples at another building in Canada (or outside Canada if necessary) only if there is a quality agreement (written agreement) that outlines the responsibilities of each party
- if other arrangements for retaining samples are made, information on the arrangements must be provided to Health Canada upon request
- any alternate site must adhere to GMP and keep the samples in the same containers as those marketed in Canada and the samples must be accessible within a reasonable timeframe (for example, 72 hours)
- ensure that all necessary analytical materials and equipment are still available, or easily obtained, to carry out tests given in the specification until 1 year after the last batch manufactured has expired
    - very important if a product is discontinued or a manufacturing facility or testing laboratory closes down
- make detailed arrangements to transfer retention samples (and relevant GMP documentation) to an appropriate storage site if a manufacturer, importer or distributor closes and unexpired batches of products remain on the market

Retention samples and stability samples are not the same. When collecting samples to complete stability testing from a particular lot, keep a separate set of retention samples of that same lot. Refer to the glossary for more information.

GMP evidence

You must demonstrate GMP compliance for lot or batch samples with supporting evidence. The type of GMP evidence for lot or batch samples may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates related to sampling, including the following:
    - sampling protocol
    - sample retention
        - samples to be stored under the environmental conditions listed on the product label in accordance with the product licence
        - samples to be kept for each lot of product for at least 1 year after the product has expired
- a list of all samples being held, with product name, lot number and, expiry date and retention date
- a signed quality agreement (written agreement) outlining sample storage responsibilities

6.14 Recall reporting (section 62)

Section 62

Every manufacturer, importer or distributor who commences a recall of a natural health product shall, within 3 days after the day on which the recall is commenced, provide the Minister with the following information in respect of the natural health product:

(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 the manufacturer, importer or distributor who commenced the recall;
(f) the reasons for commencing the recall;
(g) the name and address of each person to whom the recalled product was sold by the manufacturer, importer or distributor who commenced the recall;

(h) the quantity of the recalled product that was sold by the manufacturer, importer or distributor who commenced the recall;
(i) the quantity of the recalled product remaining in the possession of the manufacturer, importer or distributor who commenced the recall;
(j) if the recall was commenced by a manufacturer, the quantity of the recalled product that they manufactured;
(k) if the recall was commenced by an importer, the quantity of the recalled product that they imported and the name and address of each person that sold it to them;
(l) if the recall was commenced by a distributor, the quantity of the recalled product that was sold to them and the name and address of each person that sold it to them; and
(m) a description of any other action, in respect of the recall, that the manufacturer, importer or distributor who commenced the recall is taking.

Note that section 25 of the regulations states that every licensee who recalls a NHP must provide the Minister with the information referred to in section 62 within 3 days after the start of the recall.

Intent

The requirements for recall reporting are in place to ensure a product is recalled successfully. The manufacturer, importer and distributor must ensure that all the pertinent information is available and all products on the market are given the correct disposition.

Manufacturer, importer, distributor requirements

You must:

- establish written procedures (SOPs) that:
    - identify individuals responsible for initiating and coordinating recall activities
        - the production department or management should not overrule QA decisions
    - ensure the recall procedure can be implemented at any time, during and outside normal working hours
    - ensure the recall procedure outlines the steps for implementing a recall:
        - determines the extent of the recall

        - assigns the health risk classification (Type I, II or III) (refer to the glossary)
        - establishes how affected parties will be notified
    - include a statement that you will provide the required information to Health Canada within 3 days after you begin the recall process
    - include the information on who to notify at Health Canada
        - foreign sites should reference contacting the respective Canadian importers
    - keep distribution records so each lot may be traced
    - identify and store recalled products separately in a secure quarantine area until further action is determined
    - assess at intervals and record in writing the progress and effectiveness of the recall, and issue a final report, including a final reconciliation
    - notify all Canadian and foreign sites involved in manufacturing, importing or distributing the recalled products
        - notification templates must be in both English and French

Even if no health risk is identified, a product may still need to be recalled if it contravenes the regulations (for example, when there is an error in the NPN on the product label).

When recalling an NHP, follow your recall written procedure (SOP) as outlined in section 50, and submit product recall information to the appropriate Health Canada regional office within 3 days of initiating the recall.

Refer to section 62 of the regulations for the list of information that you must provide.

Section 62 does not specifically apply to packagers and labellers. However, many recalls are the result of product packaging and labelling issues. Packagers and labellers must have appropriate systems in place in case they are affected by a recall.

You must also consult:

- Recall policy for health products (POL-0016)
- Drug, natural health product and biocide recall guide (GUI-0039)

These documents contain guidance on the following:

- recommended recall written procedure (SOP) format
- mandatory actions required when a recall is initiated

- how to determine the health risk classification assigned to the recall (Type I, II or III)
- information that should be incorporated into a recall record or recall report (including a recall strategy and communications plan)
- how recalled products should be stored in quarantine until disposition is determined
- sample templates and links to forms, such as the:
    - recall communication template (recall letter and product return form)
    - Drug, natural health product and biocide recall reporting form (FRM-0356)

As with all your written procedures (SOPs), you should review your recall SOPs periodically to ensure your procedures and contact information for reporting recalls are up to date.

Mock recalls

A mock recall program may help you comply with the sections of the regulations on recalls. Be sure to include all departments that may be involved in the recall.

Mock recalls should:

- have a comprehensive written procedure (SOP) that describes the functions of the mock recall program
- be done periodically by personnel who are qualified to perform and evaluate them and documented (include a simulation exercise)
    - consult the USP <2750> Manufacturing practices for dietary supplements for more information
- produce a report on the findings and corrective actions taken, which should:
    - be reviewed by appropriate senior or executive company management
    - show that corrective actions were implemented in a timely manner
    - include a conclusion on how effectively the simulation was performed
    - include metrics on the percentage of product that would likely have been recovered from the marketplace

GMP evidence

You must demonstrate GMP compliance for recall reporting with supporting evidence. The type of GMP evidence for recall reporting may vary. Examples of evidence include:

- relevant written procedures (SOPs) and associated blank record templates for recall reporting, including:

    - procedures that allow for a recall of an NHP to be performed
    - recall information that you need to provide to Health Canada when there is a recall (and contact information for the appropriate Health Canada regional office)
- recall records or recall reports if a recall took place, including:
    - documentation of all recall information (English and French recall notices, communications and final report)
    - documentation of the recalled product's final disposition
- a list of previous recalls and reasons for them
- a mock recall report (if no actual recall was conducted)

Appendix A – Glossary

Acronyms and abbreviations

CAPA:	corrective and preventive action(s)
CC:	change control
GLP:	good laboratory practices
GMP:	good manufacturing practices
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO:	International Organization for Standardization
MRA:	mutual recognition agreement
MSDS:	material safety data sheet
NHP:	natural health product
NPN:	natural product number
OOS:	out-of-specification
OOT:	out-of-trend
PIC/S:	Pharmaceutical Inspection Co-operation Scheme
PPE:	personal protective equipment
QA:	quality assurance
QAP:	quality assurance person
QC:	quality control
SOP:	standard operating procedure
US FDA:	United States Food and Drug Administration
USP:	United States Pharmacopeia
WHMIS:	Workplace Hazardous Materials Information System
WHO:	World Health Organization

Glossary

The following definitions apply to the terms used in this guidance. Certain terms may have different meanings in other contexts. If there is a conflict between a definition in this section of the guide and a definition in the Food and Drugs Act or the Natural Health Products Regulations, the definition in the act or regulations prevails.

Acceptance criteria (tolerance limits): Numerical limits, ranges or other suitable measures for acceptance of the results of analytical procedures. (ICH Q7)

Batch: A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. For continuous production, a batch may

correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. (ICH Q7)

Batch certificate: A certificate issued by the manufacturer of a lot or batch of a product imported from buildings inspected by a regulatory authority under a mutual recognition agreement (MRA) or under the Pharmaceutical Inspection Co-operation Scheme (PIC/S). For more information on the content of a batch certificate, refer to the International harmonized requirements for batch certification.

Batch number: A distinctive combination of numbers, letters or both that:

- identifies a product batch **and**
- appears on documents such as the batch record

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

Bulk preparation: A homeopathic preparation not in its final packaging, usually in quantities larger than the largest commercially available package size.

Bulk product: A product in dosage form not in its final packaging, 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 containing the:

- name and address of the lab performing the test(s)
- name and specifications of the material(s)
- test(s) performed
- test method(s) used
- actual numerical results
- approval date(s)
- signature of approver

Also contains other technical information deemed necessary for its proper use.

Certificate of manufacture: A document issued by a vendor to a distributor or importer attesting that a specific lot of product has been produced according to its master production document. Such certificates include a detailed summary of 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.

Change control: A written procedure that describes the action to be taken if a change is proposed:

- to facilities, materials, equipment or processes used to manufacture, package and test natural health products **or**
- that may affect the operation of the quality or support system

Compliance: The state of conformity of a regulated party (including a corporation, institution, individual or other legal entity) or a product with a legislative or regulatory requirement, or a recognized standard.

Compositing: A process that involves:

- taking multiple samples from a portion of units or containers
- combining or blending the samples together to form a composite
- taking a single sample from the composite and testing it once (composite testing)

Confirmatory testing: Tests done by a third-party laboratory to confirm results obtained from another facility. The goal is to confirm the validity of results already obtained for the same lot.

Contractor or contract manufacturer: A legal entity that carries out activities on behalf of a company according to a quality agreement (written agreement). This includes other sites within the same corporate structure. For example, a company that manufactures, packages or labels a natural health product (NHP) or performs any other activity or operation concerning an NHP, under the terms of an agreement with another party.

Conveyance: A vessel, aircraft, train, motor vehicle, trailer or other means of transportation, including a cargo container. (Safe Food for Canadians Act)

Corrective and preventive action (CAPA) plan: A set of actions that eliminate the cause of an identified non-conformity or other undesirable situation. Corrective actions are taken to control a current event. Preventive actions are taken to prevent them from occurring again.

Critical equipment: Equipment that if not properly controlled may cause significant variation in the quality of the finished product.

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

Data integrity: The extent to which all data are complete, consistent and accurate throughout the data lifecycle. (PIC/S)

Deviation: A departure from an established or approved procedure, process, work instruction, form, or accepted standard. Deviations can be planned (known in advance) or unplanned.

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 that 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: Knowledge or skills acquired by:

- actively participating in events or activities
- 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 into its final container and labelling.

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

Good documentation practices: Measures that collectively and individually ensure paper or electronic documentation is secure, attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate. (WHO)

Health risk classification: A numerical designation that Health Canada may assign to a product to indicate the relative degree of risk to human health presented by the product:

- Type I: A situation in which there is a reasonable probability that the use of or exposure to a product will cause serious adverse health consequences or death

- Type II: A situation in which the use of or exposure to a product may cause temporary adverse health consequences or where the probability of serious adverse health consequences is remote
- Type III: A situation in which the use of or exposure to a product is not likely to cause any adverse health consequences

Homeopathic medicine: Refer to the Supplementary GMP for homeopathic medicines for a description.

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

Importer: A person who imports a natural health product (NHP) into Canada, for the purpose of sale (includes bulk NHPs).

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

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

In-process tests: Tests performed during the manufacture of the natural health product, rather than as part of the finished product tests conducted before release. (ICH Q6A)

International Organization for Standardization, ISO: A worldwide non-governmental organization of national standards bodies that maintains a group of global standards.

Label (noun): 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 (verb): 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 its label.

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

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

Manufacturer: A person who fabricates or processes a natural health product (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 an 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 natural health product in dosage form.

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 as well as the processing instructions, including the in-process controls.

Master production document: A document that includes:

- specifications for raw materials, packaging materials and packaged dosage form
- master formula
- sampling procedures
- critical processing related standard operating procedures
    - whether or not these procedures are specifically referenced in the master formula

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 product formulation
- manufacturing and process control instructions
- in-process testing requirements
- 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
- dates and times (if applicable) of commencement and completion of significant intermediate stages, such as blending or heating, and of completion of production

MRA country: A country that is a participant to a mutual recognition agreement (MRA) with Canada. (section C.01A.001(1), Food and Drug Regulations)

Mutual recognition agreement: An international agreement that provides for the mutual recognition of compliance certification for good manufacturing practices for drugs. (section C.01A.001(1), Food and Drug Regulations)

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:

- the diagnosis, treatment, mitigation or prevention of 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

However, an NHP does not include a substance set out in Schedule 2 of the regulations or any combination of substances that includes a substance set out in Schedule 2.

Observation: A written or verbal comment used to identify a deviation or deficiency of good manufacturing practice (GMP). A GMP deviation or deficiency noted by an inspector during the inspection of a site, and confirmed in writing to the company in the inspection exit notice. Observations are assigned a risk classification ranging from 1 for "critical" to 2 for "major" to 3 for "other".

Out-of-specification, OOS: A testing result that does not meet the approved specifications or established acceptance criteria.

Outsourced activity: Activities conducted by a contract acceptor under a written agreement with a contract giver. (ICH Q10)

Package: To put a product in its immediate container.

Package or packaging material: Includes:

- immediate container
- labels
- printed packaging materials
- any suitable material intended to protect the natural health product during storage and transport
- 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.

Pest: Any objectionable insect or other animal, including birds, rodents, flies, mites and larvae. (USP 2750)

Potency: The amount of the standardized components per dosage unit that further characterizes the quantity of the ingredient. It is necessary when a claim on the potency is required on the label or is required for a specific product (for example, when literature supports the product with that standardized component). In the Supplementary GMP for homeopathic medicines section of this guide, "potency" refers to the degree of dilution of a homeopathic medicine.

Preparatory (suitability) testing: A demonstration that the natural health product tested does not inhibit the assay or the recovery, multiplication or growth of microorganisms that may be present within it. Preparatory testing thus controls the risks of false negatives or lower-than-expected results.

Production: All operations involved in preparing a finished product, from materials received, through processing and packaging, to the finished product, including storage. (ICH Q7)

Product licence holder: An individual with legal ownership of and responsibility for the natural health product. The product licence holder may be located in or outside of Canada. Product licence holders who are located outside of Canada must identify a Canadian representative.

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 (personnel): To make competent or eligible for a job, position or task by having the proper or necessary skills, knowledge, credentials, accomplishments or qualities.

Quality assurance: Planned and systematic activities applied within the quality system give confidence that the predetermined standards for quality and safety will be met.

Quality assurance person: The person responsible for assuring the quality of the natural health product before it's made available for sale. This person has the training, experience and technical knowledge related to manufacturing, packaging, labelling, importing and/or distributing. Also understands the good manufacturing practices requirements of Part 3 of the Natural Health Products Regulations.

Quantity: The amount of medicinal ingredient(s) per dosage unit.

Quarantine: Effective restriction of the availability of material or product for use (physically or by system), until released by the quality assurance person. The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. (ICH Q7)

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

Recall: A responsible party's removal from further sale or use, or correction, of a distributed product that presents a risk to the health of consumers or violates the Food and Drugs Act or the Natural Health Products Regulations.

Recognized institution: A post-secondary educational facility (such as a university, college or professional institute) that has a solid 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 single batch of an in-process, bulk or finished natural health product to a previous step in the approved manufacturing process due to foreseen quality concerns with the batch. Reprocessing procedures are looked on as necessary from time to time. They are pre-approved by the quality control department and as part of the marketing authorization, where applicable.

Retention sample: A sample of a fully packaged unit from a lot or batch of finished product stored for identification purposes. For additional product testing, a sample is considered necessary to determine if the natural health product complies with its specifications. (European Commission Annex 19 Reference and retention samples)

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

Reworking: Subjecting all or part of a single batch of an in-process, bulk or finished natural health product to an alternate manufacturing process due to a failure to meet predetermined specifications. Occurs unexpectedly and is not pre-approved as part of the marketing authorization.

Sale: See "Sell".

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

Scientific rationale: A justification that is in accordance with the principles and methods of science, and is systematic and exact. In the natural health product context, this justification should be supported by an acceptable pharmacopoeial reference or data to explain the

underlying issues that led to the need of preparing such a rationale. When such acceptable references are not available or when such data is difficult to obtain, the justification must nevertheless be sound and reasonable.

Secondary package: A container in which a natural health product is wholly or partly contained without coming into direct contact with the dosage form.

Secondary packaging/labelling: To place a natural health product already in its immediate package or container into a secondary package or container.

Sell: Includes offer for sale, expose for sale, have in possession for sale, or distribute to 1 or more persons, whether or not the distribution is made for consideration for lease, offer for lease, expose for lease or have possession for lease. For clarity, the word "consideration" can take various forms, including:

- monetary payment
- promise to do something
- promise to refrain from doing something

Shelf life: The time period during which a natural health product is expected to remain within the approved shelf-life specification, provided it's stored under the conditions defined on the container label. (ICH Q1A)

Site: A place of or for an activity specified under the Natural Health Products Regulations.

Specifications: Quality standards include tests, references to test methods and appropriate acceptance criteria (tolerance limits), which are numerical limits, ranges or other criteria for the tests described. Specifications establish the criteria to which a finished product should conform to be considered acceptable for its intended use. (ICH Q6A)

Stability: The ability of a natural health product to keep its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf life. (adapted from the WHO definition)

Stability sample: A representative sample of a fully packaged unit from a lot or batch of finished product stored under controlled conditions for the stability tests to define its shelf life under specified packaging and storage conditions.

Stability tests: A series of tests done to obtain information on the stability of a natural health product in order to define its shelf life under specified packaging and storage conditions. (WHO)

- Accelerated testing: Studies designed and performed according to an approved stability protocol, to increase the rate of chemical degradation or physical change of a product by using exaggerated storage conditions as part of the stability studies. Data from these studies, in addition to real-time (long-term) stability studies, can be used to assess longer-term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes. (adapted from the ICH Q1A description)
- Real-time (long-term) stability studies: Stability studies, performed according to an approved stability protocol, under the recommended storage conditions for the shelf life proposed for labelling. The results are used to establish the shelf life, to confirm the projected shelf life, and to recommend storage conditions. (ICH Q1A)

Standard operating procedure, SOP: An authorized written procedure giving detailed instructions for performing operations consistently and in a repeatable way. They are not necessarily specific to a given product or material but are of a more general nature (for example, equipment operation, maintenance and cleaning, product release, training procedures). Certain standard operating procedures may be used to supplement product-specific master production documents.

Sterile: Free from viable microorganisms.

Sterile dosage form: A dosage form that is free from viable microorganisms.

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

Appendix B - References

Laws and regulations

Food and Drugs Act
Food and Drug Regulations
Natural Health Products Regulations
Official Languages Act
Pest Control Products Act

Guidelines and other documents

Health Canada

Adulteration of natural health products
Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)
Canadian drinking water guidelines
Canadian guidelines for food processing during adverse water events
Compliance and enforcement policy for health products (POL-0001)
Drug, natural health product and biocide recall guide (GUI-0039)
Evidence for homeopathic medicines guidance document
Good manufacturing practices guide for drug products (GUI-0001)
Guidance document: Labelling of natural health products
Guidance on parametric release: Pharmaceutical Inspection Co-operation Scheme (PIC/S)
Guide to validation of terminal sterilization process of drugs (GUI-0074)
International harmonized requirements for batch certification
Lists of acceptable polymers for use in food packaging applications
Mutual recognition agreements
Natural health products management of applications policy
Pesticides and pest management: Frequently asked questions
Quality of natural health products guide
Recall policy for health products (POL-0016)
Risk classification guide for drug good manufacturing practices observations (GUI-0023)
Site licensing guidance document

Canadian Food Inspection Agency

Canada Organic Regime

European Union

Guidelines on good distribution practice of medicinal products for human use

United States

Homeopathic Pharmacopoeia of the United States
United States Pharmacopeia (USP) and National Formulary (USP–NF)

- USP <51> Antimicrobial effectiveness testing
- USP <71> Sterility tests
- USP <1029> Good documentation guidelines
- USP <1079> Risks and mitigation strategies for the storage and transportation of finished drug products
- USP <1112> Application of water activity determination to nonsterile pharmaceutical products
- USP <2091> Weight variation of dietary supplements
- USP <2232> Elemental contaminants in dietary supplements
- USP <2750> Manufacturing practices for dietary supplements

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

- ICH guideline Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products
- ICH guideline Q7: Good manufacturing practices guide for active pharmaceutical ingredients
- ICH guideline Q9: Quality risk management

International Organization for Standardization (ISO)

ISO 8601 Date and time format

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

GMP guide PIC/S
Good practices for data management and integrity in regulated GMP/GDP environments

World Health Organization (WHO)

Expert Committee on Specifications for Pharmaceutical Preparations report
Good storage and distribution practices for medical products
Guidance for organizations performing in vivo bioequivalence studies
Guidelines for drinking-water quality
Guidelines on GMP for herbal medicines

Appendix C – Supplementary GMP for homeopathic medicines

1. About homeopathic medicines

To be considered a homeopathic medicine, a product must be **both**:

- manufactured from, or contain as medicinal ingredients, only substances referenced in a homeopathic monograph in 1 of the following homeopathic pharmacopoeias, as amended from time to time:
  - *Homeopathic Pharmacopeia of the United States*
  - *Homöopathisches ArzneiBuch* (German homeopathic pharmacopoeia)
  - *European Pharmacopoeia* (Ph.Eur.)
  - *Pharmacopée française* (Ph.F.)
  - *Encyclopedia of Homeopathic Pharmacopoeia* **and**
- prepared according to the methods outlined in 1 of the homeopathic pharmacopoeias listed in the first point, as amended from time to time

Homeopathic medicines are NHPs. They are made from a wide range of materials, such as plants, animals, minerals and chemicals. Many of these can be highly toxic in the raw material form. Nosodes are also a type of homeopathic medicines (they are preparations of pathological tissues, excretions or secretions).

Manufacturers and importers must make sure to carry out the critical processes (for example, raw material identification, raw material handling, attenuations) under controlled conditions when producing homeopathic medicines.

The guidance presented in this section of the guide is specific for homeopathic medicines. It supplements the guidance provided in the overall guide. As homeopathic medicines are NHPs, the rest of this guide also applies to the activities related to them. Follow the guidelines provided specifically in this section of the guide in addition to the guidance provided in the main part of the guide.

If you are producing tinctures, also refer to ICH guideline Q7: Good manufacturing practices guide for active pharmaceutical ingredients. This is regardless of whether the tinctures are sold to consumers or used for further processing of finished products.

Although NHPs are not within the scope of ICH guidelines, such references are helpful to the NHP industry and stakeholders. They may help you gain a better understanding of GMP concepts and processes that also apply to NHPs.

Note also that "potency" refers to the degree of dilution of a homeopathic product. In this section of the guide, there is more information on the terminology applied in the homeopathic context.

1.1 Premises and equipment

To meet the requirements

Due to the infinitesimal dose of active ingredients, prepare homeopathic medicines in a manner that eliminates the possibility of cross-contamination and outside contamination.

For manufacturers and packagers:

- Design your premises so that the homeopathic attenuations are prepared in rooms or workstations that:
    - have appropriate environmental controls, such as a room with filtered air under positive pressure or in a laminar airflow workstation
    - are distinctly separate from products that are volatile or have permeating odours
- Design your premises to accommodate hazardous raw material storage and processing requirements, including:
    - isolating toxic or infectious raw materials from other materials
    - handling raw materials in segregated areas with appropriate environmental controls suitable for each material
        - pharmacopoeias may provide more information on storing dangerous raw materials
- Use equipment and utensils exclusively for homeopathic preparations, which are:
    - made of materials that do not shed particles
    - cleaned and maintained using products (such as lubricants) that do not contaminate the homeopathic medicine
        - your cleaning written procedure (SOP) should include the cleaning of vessels and containers used in successive attenuations or triturations

For importers:

- Ensure the facilities that manufacture, package or label the homeopathic medicine meet the premises and equipment requirements

1.2 Personnel

To meet the requirements

For manufacturers and packagers:

- Provide training specific to the attenuation or trituration of homeopathic medicines

For manufacturers:

- Have a personnel qualification program that:
    - ensures trained personnel are observed performing the manual operations and that the materials produced meet their pre-determined acceptance criteria
    - provides training that is appropriate to the tasks being done
    - schedules annual training and reviews to ensure the production methods are not inappropriately modified over time
    - maintains supporting documents that detail the training content and completion dates
    - restricts the entry of untrained or unnecessary personnel in processing areas designated for attenuation and trituration

For importers:

- Ensure the facilities that manufacture, package or label the homeopathic medicine meet the personnel requirements

1.3 Sanitation

To meet the requirements

For manufacturers and packagers:

- Ensure the sanitation program does not contaminate the homeopathic medicine with chemical or particulate matter
- Put in place:

- cleaning, microbial and environmental monitoring parameters for all processing areas, and focus on areas designated for attenuation and trituration
- methods to ensure cleaning and maintenance products do not contaminate your product
- methods to ensure there is no cross-contamination of your product, including:
  - any remaining traces of the product previously manufactured
  - any cleaning agent residue

For importers:

- Ensure the facilities that manufacture, package or label the homeopathic medicine meet the sanitation requirements

1.4 Operations

Manufacture your homeopathic medicines according to the preparation methods outlined in 1 of the 5 accepted homeopathic pharmacopoeias listed in this section of the guide.

There are several distinct manufacturing steps for homeopathic medicines. Each step involves repeating attenuation (dilution) and succussion (vigorous shaking). Source materials for these medicines are typically divided into 2 basic categories: soluble or insoluble. Insoluble source material must be triturated (ground with a soluble powder, typically milk sugar) until it can be dissolved in water.

The 3 basic manufacturing steps are:

- Source material is transformed to a mother tincture or soluble trituration.
  - Mother tinctures are a relatively concentrated aqueous alcoholic extract from which subsequent attenuations are prepared.
  - The tincture potency may vary depending on the soluble or insoluble nature of the source material.
  - Detailed manufacturing processes are stated in the homeopathic pharmacopoeias listed in this section of the guide, and each monograph references a specific manufacturing process.
- Mother tincture is diluted to a target medicating potency, when required.
  - The target medicating potency is typically used to impregnate pellets or other solid dosage forms.

    - As it has a high alcohol content, it should not be sold directly to consumers.
- Targeting the medicating potency (or mother tincture) to the finished product.
    - This step can be for either single or combination homeopathic products.

To meet the requirements

For manufacturers:

- Control the 3 basic manufacturing steps following GMP, which means generating up to 3 different types of manufacturing batch records:
    - record for source material to mother tincture or to a soluble trituration
    - record for the mother tincture to the target medicating potency
    - record for target medicating potency to the finished product

As you have to rely solely on production controls to ensure the product has reached its defined potency, you must document each critical step. The person performing the task and the person performing the verification must sign and initial each step.

Perform all verifications in a timely manner and at the same time as the batch production. Critical processes include measuring tasks (such as using scales, pipettes), attenuation processes (trituration or succussion methods) and impregnation.

For importers:

- Put in place proper processes to monitor the GMP of foreign manufacturers
- Include ongoing control measures to ensure each imported product meets its specifications before the product is released

For manufacturers, packagers and labellers:

- Keep separate written procedures (SOPs) for homeopathic medicines
- Carry out the following critical production processes that relate to your activity:
    - harvest or produce raw materials according to the homeopathic pharmacopoeias
        - verify and record the identity of all raw materials
        - label raw materials that are toxic or potentially infectious as to their safety status (such as allergen or toxic) or a material safety data sheet (MSDS) equivalent
- Ensure mother tincture batch records contain sufficient information, such as:
    - the duration of maceration 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
    - sterility of nosodes, such as heat processing of the first attenuation in the preparation
- Ensure the process for in-process attenuations or triturations (critical in production) is consistent, reliable and free of contaminants
- Include the following information in the master formula and batch record:
    - potency scale (X or C scale or Korsakovian)
    - written procedures (SOPs), or reference to SOPs, for each processing stage
    - number of succussions during each attenuation
    - duration of trituration, when 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 that differs from the batch number assigned to the product
    - attenuation or trituration number at the particular stage of preparation (for example, could be designated by potency)
    - name, dosage form, batch number and batch size of the preparation for which it's intended
    - composition or reference to the master formula
    - an internal code and analytical control number of each raw material or mother tincture used
    - precautions to be adopted during handling ingredients, when applicable
        - schedule manufacturing to ensure continuity within the attenuation or trituration series, and avoid prolonged storage of intermediate homeopathic potencies
- Ensure the following is in place when manufacturing impregnated pellets from medicating potencies made by a separate company:
    - raw material identity testing and a batch record showing that the raw material was added during manufacturing
    - studies showing the impregnation procedure is adequate
    - written procedures (SOPs), or reference to SOPs, for washing, drying and, when applicable, sterilizing packaging materials
    - stability studies or challenge studies showing that the procedures and materials used ensure there is no microbial contamination until expiry
- Ensure your QAP documents the release between the different manufacturing steps (unless performed as 1 continuous process from source material to finished product)

- Ensure your batch records document the critical steps and the person performing the task and the person performing the verification must sign or initial the records
    - verifications are done in a timely manner and at the same time as batch production
    - critical processes include measuring, attenuation processes and impregnation

1.5 Specifications

Specifications of homeopathic medicines must meet the requirements set out in homeopathic pharmacopoeias. Consult the list of homeopathic pharmacopoeias provided in this section of the guide.

Manufacturers and importers must:

- identify the source material used to make the homeopathic medicine
- have evidence of identification (defined in 1 of the recognized homeopathic pharmacopoeias)

For homeopathic medicines, testing for identity can only be performed on the source material. To do so, use the methods and criteria set out in the homeopathic pharmacopoeias.

Manufacturers and importers must keep evidence of identity testing of the source material of homeopathic medicines. The quality of homeopathic products can only be assured by strictly controlling starting materials and diluents and using a thorough QC system.

Health Canada has monographs specific for nosodes and organotherapy, which include criteria for identification, sterilization and GMP. Manufacturers and importers must keep the information and records mentioned in these monographs, when applicable.

To meet the requirements

For manufacturer and importers:

- Keep written specifications that describe the homeopathic medicine and the required test methods

For specifications pertaining to identity, purity, quantity, potency and tolerances, consult:

- Evidence for homeopathic medicines

This guidance document also lists the conventional testing protocols for the dosage form, for example:

- tablets: uniformity of weight, hardness and disintegration
- liquids: alcohol type and percentage
- ointments or syrups: viscosity or rheology

For manufacturers:

- Keep records and evidence of identity testing of the source material of homeopathic products

For importers:

- Keep records and evidence of identity testing of the source material of homeopathic products **or**
- Have access to the records and evidence of identity testing
    - if you receive a certificate of manufacture or batch certificate that meets the requirements outlined in this guide

For manufacturers and importers:

- Ensure that identification, sterilization and GMP criteria from the monographs specific for nosodes and organotherapy are met when those apply

1.6 Stability

To meet the requirements

For manufacturers and importers:

- Develop and maintain written procedures (SOPs) that confirm the stability of homeopathic medicines
- Keep records of ongoing purity testing as outlined in Evidence for homeopathic medicines
    - due to the unique nature of homeopathic medicines, stability evidence focuses on:
        - microbial contamination
        - non-medicinal ingredients (for example, alcohol concentration, hardness of granules or tablets and disintegration stay consistent)
        - packaging materials, such as bottles and caps, do not contaminate the product or leak

- labels do not fade or peel from the packaging

1.7 Terminology

Inconsistent or different interpretation of terminology used in homeopathic medicines manufacturing can make it difficult to demonstrate a sound GMP process. Definitions cannot be substituted for novel manufacturing practices or to avoid maintaining critical documents required to demonstrate GMP.

Terminology must be consistent with either:

- the definitions listed in Evidence for homeopathic medicines
- 1 of the 5 homeopathic pharmacopoeias listed in this section of the guide

Review the definitions to make sure you understand them. Generally recognized definitions of terms used in the homeopathic field include:

- **Attenuation:** Material prepared by dissolving 1 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 (such as 1X, 1CH).
- **Finished product:** A product that has undergone all stages of production, including packaging in its final container and labelling. The final potency of a homeopathic medicine is in the final packaging that is to be sold to consumers.
- **Maceration:** Processing method using unheated solvent (cold or room temperature water, alcohol or other organic solvent) to extract medicinal properties from a raw material.
- **Medicating potency:** The final liquid potency of a homeopathic medicine. This potency is typically used to impregnate pellets or other solid dosage form, as it has a high alcohol content and is not expected to be sold directly to consumers.
- **Mother tincture:** A relatively concentrated aqueous alcoholic extract from which subsequent attenuations are prepared. Synonyms are mother liquor, stock solution and starting solution. The actual tincture potency may vary depending on the soluble or insoluble nature of the source material. Detailed manufacturing processes are stated in the homeopathic pharmacopoeias and each homeopathic medicine monograph references the specific manufacturing process (also called class).
- **Nosodes:** These are:
  - attenuations of pathological organs or tissues
  - causative agents such as bacteria, fungi, ova, parasites, virus particles and yeast

- disease products
- excretions or secretions

- **Percolation:** A method used to extract dried substances that have been reduced to the proper degree of fineness.
- **Potency:** The degree of dilution of a homeopathic product.
- **Source material:** Substances referenced in a monograph in a homeopathic pharmacopoeia and is the undiluted, physical form of the substance. Additional clarification on source materials can be found in the section on source information in Evidence for homeopathic medicines.
- **Starting material:** The active ingredient used at the beginning of the manufacturing stage. Ingredient may be the source material, mother tincture or medicating potency, for example, depending on the manufacturing phase of the product.
- **Succussion:** The agitation step of attenuation (also known as dynamization or potentization). Vigorous agitation is obtained by a rapid bi-directional movement of the container, with each movement or stroke abruptly interrupted to create significant turbulence throughout the liquid. Rotation movements (stirring) alone cannot achieve the degree of turbulence required.
- **Trituration:** Attenuations of solid substances are prepared by trituration of the crude substance with lactose.

Appendix D – Risk classification

1. Risk classification of NHP GMP observations

During a NHP site licence assessment or a site inspection, a Health Canada officer or inspector notes deviations from Part 3 (GMP) of the regulations as explained in this guide. These deviations appear as risk-rated GMP observations in Health Canada documents, such as information request notices and inspection exit notices, provided to regulated parties.

1.1 Purpose

Health Canada wants to ensure consistency by our:

- assessment officers during NHP site licence assessment
    - new application, amendment or renewal
- inspectors during NHP site inspections

This consistency applies to:

- classifying GMP observations according to risk
- assigning an overall compliance rating to the paper review of GMP evidence or to an inspection

We also want industry to be aware of the situations we consider unacceptable and that may result in a non-compliant rating or compliance and enforcement actions or both.

This tool can also be used by your company when conducting a GMP self-inspection to proactively identify issues.

1.2 Background and scope

As part of the continuous improvement of the NHP program, we updated our risk classification tool to:

- ensure a transparent and consistent approach to evaluate GMP compliance
- align with the rest of this guide

GMP deviations can result in an NHP that is harmful to the patient, consumer or other end user. Therefore, our evaluation of a company's overall compliance with GMP considers the nature and extent of the deviations.

As the list of GMP observations in this guide is not exhaustive, additional observations may be added where appropriate.

1.3 Risk classification guide

You must follow the GMP outlined in this guide. For any observations that are noted, your QA personnel must document and take appropriate CAPA to eliminate the cause and prevent future non-compliance.

In addition to following the risk classification categories and giving examples of observations for the GMP requirements, we may use other relevant documents and information when:

- reviewing a company's compliance history
- determining risk classification and compliance and enforcement measures

Not all of the observations listed in this section of the guide may apply to all types of activities.

1.4 Risk categories

GMP observations are classified into 1 of 3 risk categories. They are based on the nature of the deviation from GMP and extent of occurrences.

Risk 1: Critical observation

- A GMP deviation that results in or is likely to result in a non-compliant product or an immediate or latent health risk

This includes an observation of:

- fraud
- product adulteration
- misrepresentation or falsification of data
- widespread cross-contamination, infestation or unsanitary conditions

Risk 2: Major observation

- A GMP deviation that may result in an observation of:
  - a product that does not consistently meet its marketing authorization
  - a failure to follow procedures to approve batches of products prior to sale
  - a failure of the QAP to fulfil their responsibilities

Certain Risk 2 observations may be upgraded to a Risk 1 and are identified with an arrow (↑). This indicates that the site does not control its processes and operations effectively.

Risk 3: Other observations

- A GMP deviation that does not meet Risk 1 or Risk 2 criteria but is a departure from the GMP

Certain Risk 3 observations may be upgraded to a Risk 2 and are identified with an arrow (↑).

A repeated Risk 2 or Risk 3 deviation or unresolved deviations from a previous site licensing assessment or inspection may result in a higher classification.

1.5 Assigning the overall GMP compliance rating

As part of an NHP GMP assessment and inspection, we will assign:

- GMP observations a corresponding risk category
- an overall GMP compliance rating (compliant or non-compliant)

This rating is a determining factor in our site licensing decision or inspection outcome.

The risks we identify will be used to evaluate the effectiveness of your company's QA team or department in terms of their knowledge, training and ability to function independently.

Regardless of the compliance rating assigned, the company should make every effort to resolve any noted deviations in a timely manner.

Non-compliant rating

In general, a Risk 1 observation will result in a non-compliant (NC) rating. As a result, we may suspend, cancel or refuse to issue, amend or renew a site licence.

When the products present a significant health hazard, we may take appropriate enforcement action, such as requesting a recall or detaining or seizing the products.

We may also assign an NC rating in other situations, including:

- when numerous Risk 2 observations are identified indicating that the site does not control its processes and operations effectively
- when repeated Risk 2 observations are not adequately resolved
    - indicates the required corrective actions following the previous assessment or inspection were not implemented

Compliant rating

We may assign a compliant (C) rating in different situations, including where we have made:

- no observations
- only a few Risk 2 observations focused on isolated issues
- only Risk 3 observations

1.6 Risk classification of GMP observations

The following lists the observations for each section of Part 3 of the regulations.

Take note:

- Text in parentheses is additional optional information that we may include in the risk observation at our discretion.
- The use of the word ‘or’ indicates that the statements are related, so we may select either or both statements.

Specifications (section 44)

Risk 1 (critical) observations:

- addition of adulterants (for example, ingredients listed in the Prescription Drug List, narcotic substances or any ingredients not listed in the Natural Health Products Ingredients Database) or fraudulent replacement or mixing of medicinal or non-medicinal ingredients
- misrepresentation or falsification of testing records

Risk 2 (major) observations:

- products not assessed or tested according to their approved finished product specifications (including test methods and acceptance criteria) (↑)
- inadequate finished product specifications available for products (↑)
- finished products that do not comply with their specifications are distributed or released for sale (↑)
- modifications to testing records not documented
- inadequate scientific rationale for using quantification by input (↑)
- no review of batch records for imported products using quantification by input
- inadequate rationale or process for using reduced or rotational testing program
- inadequate testing parameters (for example, test methods, target quantities, upper and lower acceptance criteria)
- reduced testing program applied by importer without a certificate of analysis for each lot received
- reduced testing, rotational testing or quantification by input not supported by adequate documentation
- failure to ensure third-party laboratory is acceptable for intended use
- finished product specifications and any changes made to specifications are not approved and documented by the QAP
- inadequate written procedures (SOPs) related to finished product testing or specifications (↑)

Risk 3 (other) observations:

- failure to maintain a copy of the certificate of compliance when using batch certificates for imported products (↑)

Premises (section 45)

Risk 1 (critical) observations:

- inadequate segregation of raw material dispensing, manufacturing, storage or testing areas to prevent cross-contamination, with evidence of cross-contamination
- inadequate building maintenance, resulting in premises in poor condition (for example, major structural defects or damages such as holes, cracks or peeling paint) with evidence of product contamination
- inadequate pest management, resulting in premises with evidence of contaminated product, extraneous pest matter or visible signs of infestations

Risk 2 (major) observations:

- inadequate segregation of raw material dispensing, manufacturing, storage or testing areas to prevent cross-contamination (↑)
- malfunctioning of the ventilation or filtration system resulting in possible localized or occasional cross-contamination
- outlets for liquids and gases or accessory supplies (for example, steam, air, nitrogen, dust collection) not properly installed or identified
- maintenance (such as air filter replacement), periodic verification and monitoring of pressure differentials not performed, when applicable
- temperature or humidity not controlled or monitored where or when necessary (for example, conditions not monitored daily) (↑)
- light not controlled where or when necessary (for example, storage not in accordance with label requirements of the product)
- inadequate precautions to prevent temperature, humidity or light level excursions of raw, in-process or finished products
- inadequate building maintenance, resulting in premises in poor condition (for example, major structural defects or damages such as holes, cracks or peeling paint) with direct exposure to contaminant
- damage (for example, holes, cracks or peeling paint) to walls, ceilings and floors immediately adjacent to or above manufacturing areas or equipment where the product is exposed (↑)
- accumulation of dust, powder or other contaminants on hard-to-clean pipes, fixtures or ducts directly above products or manufacturing equipment
- surface finishes (floors, walls and ceilings) do not permit effective cleaning
- unsealed porous finishes (for example, on floors, walls and ceiling) in manufacturing areas that may lead to contamination (such as mildew, mould, powder from previous productions) (↑)
- insufficient manufacturing, packaging, labelling and storage space that could lead to mix-ups
- quarantine area accessible to unauthorized personnel or quarantine area not clearly marked
- insufficient precautions to prevent contamination or cross-contamination of the materials and product
- grounds around manufacturing buildings not suitably maintained
- inadequate refuse receptacles or improper waste disposal practices that may lead to contamination of the product or harbourage of pests (↑)
- doors giving direct access to exterior from manufacturing and packaging areas used by personnel during production
- inadequate measures to prevent pests from entering the premises and contaminating products
- inadequate pest control record

- inadequate written procedures (SOPs) related to the maintenance of the premises (↑)

Risk 3 (other) observations:

- unscreened and untrapped floor drains
- damage to surfaces not directly adjacent or above exposed products
- non-production activities performed in production areas
- inadequate rest or break, change, wash-up or toilet facilities
- insufficient lighting in production or inspection areas
- untidy conditions that do not permit effective cleaning

Equipment (section 46)

Risk 1 (critical) observations:

- evidence of a malfunction that could affect the quality or safety of the product

Risk 2 (major) observations:

- contamination or potential for contamination of a product by foreign materials (for example, grease, oil, rust, leaking gaskets, particles) from the equipment or utensil due to inadequate equipment or utensil maintenance, installation or use (↑)
- equipment not suitable or operating within its specifications (↑)
- inadequate provisions in place for storing or protecting clean equipment to avoid contamination (↑)
- production equipment or utensils made of porous, reactive or toxic materials, or not designed to withstand repeated cleaning, are in direct contact with materials (raw, in-process or finished product)
- inadequate covers for tanks, hoppers, or similar manufacturing equipment
- equipment location or identification may lead to cross-contamination or possible mix-ups (for operations performed in a common area)
- water system not maintained or operated to provide water of acceptable quality (↑)
- inadequate calibration program or records not maintained for automatic, mechanical, electronic or measuring equipment (↑)
- inadequate equipment preventive maintenance program or equipment is not maintained properly (for example, according to its maintenance schedule)
- inadequate equipment calibration, maintenance, usage or cleaning logs

- temperature-, humidity- or light-sensitive compartments are not controlled or inadequate records maintained, where appropriate (↑)
- inadequate written procedures (SOPs) related to the functioning, maintenance or calibration of equipment (↑)

Risk 3 (other) observations:

- insufficient distance between equipment and walls to permit proper cleaning (↑)
- base of immovable equipment not adequately sealed at points of contact
- temporary means for repairs (for example, with tape, cardboard) in use
- defective or unused equipment not removed or appropriately labelled

Personnel (section 47)

Risk 1 (critical) observations:

- individual or team responsible for the supervision of manufacturing, packaging, labelling, storing or importing (with storage or transportation) does not demonstrate adequate education, GMP knowledge or training, or does not have practical experience in their area of responsibilities

Risk 2 (major) observations

- individual or team responsible for manufacturing, packaging, labelling, storing or importing not qualified by education, training or experience to perform their respective tasks
- insufficient training (initial or ongoing) for personnel responsible for QA and manufacturing, packaging, labelling or storage operations resulting in related GMP deviations
- insufficient personnel with the necessary qualifications for QA and manufacturing, packaging, labelling or storage operations with evidence of error (↑)
- personnel using unapproved written procedures (SOPs)
- inadequate written procedures (SOPs) related to the appropriate training, education and work experience of personnel (↑)

Risk 3 (other) observations:

- inadequate training records or training is not reflective of the personnel's responsibilities (↑)
- inadequate written training program (↑)
- personnel using outdated written procedures (SOPs)

- inadequate job descriptions that outline the role and responsibilities of each position

Sanitation program (section 48)

Risk 1 (critical) observations:

- widespread accumulation of residues and extraneous matter or gross infestation, indicating inadequate cleaning
- inadequate written sanitation program in place for premises or equipment resulting in premises in an unacceptable state of cleanliness (unclean or unsanitary manufacturing, packaging, labelling or storage areas)

Risk 2 (major) observations:

- personnel with illnesses that could affect the safety or quality of a product are permitted to work around or near production materials or products (↑)
- inadequate written sanitation program (↑)
- inadequate written health and hygiene procedures
- personnel having direct contact with materials or using processing equipment and not following appropriate hygienic practices to protect products against contamination (↑)
- inadequate equipment cleaning
- inadequate written procedures (SOPs) for cleaning (including cleaning frequencies) of production or storage areas (↑)
- for shared equipment, no cleaning is performed between production runs of different products (↑)

Risk 3 (other) observations:

- inadequate equipment or facility cleaning records (↑)
- cleaning not completed as scheduled
- inadequate identification of cleaning compounds or sanitizing agents (↑)
- personnel responsible for cleaning not identified
- sporadic dust, powder or residue observed in some manufacturing areas or on equipment (↑)
- inadequate procedures for the destruction and disposal of waste materials and debris (↑)

Operations (section 49)

Risk 1 (critical) observations:

- contracting out manufacturing, packaging, labelling or storage services from a site that does not comply with the applicable GMP or does not hold a site licence
- no written procedures (SOPs) in place for the critical activities conducted at the site
- material (raw, in-process, bulk or finished) adulteration or contamination
- unsuitable treatment of raw agricultural materials that contain soil or other contaminants
- materials (raw, packaging, in-process or finished) stored under inappropriate conditions with evidence of quality deterioration or cross-contamination
- raw materials improperly identified or labelled (for example, failure to include appropriate name, description, lot number, expiry date, quality status and potency, as required) which has led to mix-ups
- presence of material not authorized for use in NHPs (for example, prescription drug, controlled drug), unless permitted under a separate licence
- use of raw materials that are beyond their shelf life without approval from the QAP or added without testing or scientific rationale
- no written master formula or master production document
- master formula or manufacturing order showing gross deviations or significant calculation errors
- inappropriate control of labels with evidence of mix-ups

Risk 2 (major) observations:

- evidence that approved procedures are not followed by personnel (↑)
- upon receipt, raw, bulk, in-process or packaging materials not held in quarantine until released by the QAP
- inadequate or inaccurate labelling of raw, bulk, in-process, or packaging materials or finished products
- no retest period or expiry date established for raw materials
- production personnel do not respect the quarantine status of raw or packaging materials
- inadequate written procedures (SOPs) for conditions of storage (including transportation) (↑)
- inadequate written procedure (SOP) for material or product receiving or sampling
- water used in manufacturing or processing not of acceptable quality (↑)

- successive attenuations completed in area other than laminar airflow workstation (applicable to homeopathic medicines)
- failure to destroy outdated or obsolete printed packaging materials and record the disposal
- certificate of analysis shows incomplete testing results (↑)
- inadequate or incomplete raw material or primary packaging specifications available for products (↑)
- each batch of raw material was not evaluated against specifications
- inadequate written master formula or master production document (↑)
- inadequate batch record, certificate of manufacture or batch certificate (↑)
- production processes not controlled
- inadequate investigations and corrective action plans pertaining to deviations, OOS testing results or complaints
- deviations or CC processes not documented or not approved by the QAP
- lack of proper identification of in-process materials resulting in a high probability of mix-ups
- inaccurate or incomplete information in manufacturing, packaging or labelling orders or procedures
- significant or unusual discrepancies observed during reconciliation of bulk product or printed packaging materials not investigated by qualified personnel prior to release
- failure to record duration (of mixing, maceration or percolation, for example) and other significant manufacturing steps as specified in the procedure, when applicable
- activities performed were not attributable to the person who performed them
- no quality agreement(s) (written agreements) with contractors
- insufficient controls in place to ensure that records cannot be deleted (↑)
- insufficient controls in place to ensure that changes made to data are tracked and justified (↑)
- activities were not documented at the time they were performed

Risk 3 (other) observations:

- inadequate written procedures (SOPs) for handling materials (↑)
- failure to establish complete and comprehensive written procedures (SOPs) (↑)
- written procedures (SOPs) not systematically reviewed on a periodic basis, do not reflect current practices or do not contain instructions or directions that are applicable to NHPs
- access to production areas not restricted to authorized personnel

- inadequate or unsigned quality agreement(s) (written agreements) with contractors
- no inspection or audit program for contractors (↑)

Operations (section 50)

Risk 2 (major) observations:

- inadequate distribution records for products (↑)
- recalled products are not identified appropriately and placed in quarantine until disposition is determined
- inadequate written procedures (SOPs) related to product recall (↑)

Risk 3 (other) observations:

- incomplete recall procedure
- incomplete list of all previous recalls
- inadequate process for recalled product reconciliation or effectiveness checks
- mock recall not performed (when applicable)
- quality agreement (written agreement) does not outline recall responsibilities

Quality assurance (section 51)

Risk 1 (critical) observations:

- no QAP who is responsible for assuring the quality of the product before it is released (made available) for sale
- individual or team responsible for QA not qualified by training, experience and technical knowledge relating to the activities conducted and GMP
- QA is not a distinct and independent function or unit, with evidence that QA decisions are overruled by other departments or management
- no testing of finished products before they are released for sale
- test results that indicate a negative impact on product quality were not documented, reported or investigated by the QAP
- misrepresented or falsified analytical samples, tests results or raw data
- information, test results or raw data used to support release were not available, deleted or destroyed

Risk 2 (major) observations:

- inadequate testing of finished product (not according to finished product specifications) (↑)
- use of materials in manufacturing, packaging, labelling or storage without prior assessment and approval by the QAP (↑)
- products made available for sale or resale without assessment and approval by the QAP (↑)
- batch or lot records, raw material test results and product label not reviewed as part of the determination to reject or approve product for distribution or sale (↑)
- product released for sale that does not comply with its product licence (↑)
- inadequate system for complaint handling or returned goods (↑)
- inadequate written procedures (SOPs) available for sampling, inspecting, testing of materials (raw, packaging, in-process or finished product) or product release, where applicable (↑)
- inadequate investigation or documentation of OOS test results, OOT test results, deviations or borderline conformance
- rework done without prior approval of the QAP
- decisions made by the QAP are not documented (includes signature or date)
- returned products unsuitable for resale are not identified, segregated or destroyed
- inadequate records maintained for returned, reprocessed, reworked or redistributed products (↑)
- inadequate written procedures (SOPs) for investigating and documenting OOS test results, OOT test results, deviations or borderline conformance (↑)
- inadequate written procedures (SOPs) for handling product complaints (↑)
- no process in place to identify and prevent the importation of product from sites not included on the site licence, with evidence of importation from these sites (↑)

Risk 3 (other) observations:

- written procedures (SOPs) for manufacturing, packaging, labelling, importing or storing products are not approved by the QAP
- incomplete or missing documentation for a written complaint
- failure to provide a written job description of the QAP

Stability period (section 52)

Risk 1 (critical) observations:

- stability data collected does not support the product shelf life

Risk 2 (major) observations:

- inadequate data (for example, real time or accelerated, number of lots) or scientific rationale or program available to establish or confirm shelf life (↑)
- stability data or records not reviewed and approved
- no action taken when data shows that product does not meet its specifications prior to the expiry date (↑)
- inadequate stability program (↑)
- no stability studies pertaining to changes in manufacturing and packaging materials, if applicable
- samples retained for stability studies are not stored under recommended storage conditions
- inadequate testing parameters (for example, test methods or specifications, upper and lower acceptance criteria) (↑)
- inadequate written procedures (SOPs) related to stability data or testing or the determination of expiry date (↑)

Risk 3 (other) observations:

- insufficient quantities retained for complete testing
- failure to follow stability procedure or protocol

Records (sections 53 to 58)

Risk 1 (critical) observations:

- evidence of falsification or misrepresentation of records (for example, release and stability testing results, manufacturing documents, sales documents)

Risk 2 (major) observations:

- documentation not readily available from site licence holder (for example, unable to access records from products that are manufactured, packaged and or labelled outside of Canada in a timely manner)

- failure to maintain master production documents at the manufacturing or importing site
- failure to maintain a listing of all ingredients contained in each lot or batch of the NHP
- failure to maintain testing records in respect of a lot or batch of raw or packaging material used in the manufacturing or packaging of the NHP
- failure to maintain testing records in respect of a lot or batch of the NHP by the manufacturer or importer
- failure to maintain a copy of the specifications for each NHP that is being manufactured or imported at the site
- failure to maintain general records demonstrating that each lot or batch of the NHP was manufactured in accordance with GMP
- failure to maintain stability data to establish or confirm the expiry date of each NHP
- failure to maintain records containing sufficient information to enable the recall of every lot or batch of the NHP that has been made available for sale (manufacturing, testing and distribution records)
- failure to maintain a list of all the NHPs that are being manufactured, packaged, labelled, imported or stored at the site
- failure to maintain a copy of the sanitation program that is in use at the site
- records not signed or dated
- incomplete records
- failure to maintain records for 1 year following the expiry date of the NHP
- records required to be maintained were not retained in a readable and readily accessible format for their required period
- records were not named and organized in a manner that allowed for adequate traceability
- inadequate written procedures (SOPs) related to the maintenance of records (↑)

Risk 3 (other) observations:

- good documentation practices not followed (↑)
- lack of version control of written procedures (SOPs) or forms
- illegible records
- inadequate electronic documentation or electronic signature system in place

Sterile NHPs (section 59) and ophthalmic use (section 60)

Note that risk classifications for sterile NHPs are based on those outlined in Risk classification guide for drug GMP observations (GUI-0023).

Risk 1 (critical) observations:

- inadequate validation of critical sterilization cycles
- water systems not validated
- evidence of water system problems such as microbial or endotoxin counts not within specifications
- no media fills performed to demonstrate the validity of aseptic filling operations
- no environmental controls or monitoring for viable microorganisms during filling for aseptically filled products
- aseptic filling operations continued following unacceptable media fill results obtained
- batches failing initial sterility test released for sale based on a second test without proper investigation
- inadequate environmental conditions for aseptic operations
- absence of leak test for ampules

Risk 2 (major) observations:

- aqueous-based products not subject to terminal steam sterilization without proper justification
- inadequate room classification for processing or filling operations (↑)
- aseptic manufacturing suites were under negative pressure compared to clean areas (C-D) (↑)
- clean areas (C-D) were under negative pressure compared to unclassified areas (↑)
- insufficient number of samples taken for environmental monitoring or inadequate sampling methods (↑)
- insufficient environmental controls or insufficient monitoring for viable microorganisms during filling for aseptically filled products (↑)
- premises and equipment not designed or maintained to minimize contamination or generation of particles (↑)
- inadequate maintenance of water systems
- inadequate re-validation of water systems after maintenance, upgrading, OOS trends
- inadequate training of personnel (↑)
- personnel involved in aseptic filling prior to completing successful media fill
- inadequate gowning practices for clean and aseptic areas
- access to sterile production areas not restricted to authorized personnel
- inadequate sanitation or disinfection program (↑)

- inadequate practices or precautions to minimize contamination or prevent mix-ups
- non-validated time lapse between cleaning, sterilization and use of components, containers and equipment
- no consideration given to bioburden prior to sterilization
- non-validated time lapse between start of manufacturing and sterilization or filtration
- inadequate program for media fill
- capability of media to grow a wide spectrum of microorganisms not demonstrated
- misinterpretation of results for media fills
- samples for sterility testing insufficient in number or not representative of the entire production run
- each sterilizer load not considered as a separate lot for sterility testing
- purified water is not used as the feed water the clean steam generator
- inadequate testing program for water system (↑)
- the water system used for the final rinsing of containers and components used for NHPs is not tested for endotoxins
- inappropriate environment or controls for crimping following aseptic filling
- inadequate inspection for particles and defects (↑)
- gases used to purge solutions or blanket products not passed through a sterilizing filter (↑)
- inadequate integrity testing of sterilizing or vent filters (↑)
- inadequate written procedures (SOPs) related to sterility (↑)

Risk 3 (other) observations:

- steam used for sterilization not monitored to assure suitable quality
- inadequate control on the maximum number of personnel present in clean and aseptic areas

Lot or batch samples (section 61)

Risk 2 (major) observations:

- failure to retain and store samples of each lot of product in its original container or in containers of the same material and construction for a period of 1 year past the expiry date of the NHP, as part of an established sample retention program
- failure to provide retained samples of finished products

- retained sample not stored under appropriate environmental conditions (as listed on the product label)
- inadequate written procedures (SOPs) related to sampling (↑)

Risk 3 (other) observations:

- insufficient quantity of samples retained for finished product testing
- quality agreement (written agreement) does not outline sample storage responsibilities

Recall reporting (section 62)

Risk 1 (critical) observations:

- misrepresented or falsified recall record(s) provided to Health Canada

Risk 2 (major) observations:

- failure to notify Health Canada within 3 days of commencing the recall and provide the information as outlined in section 62 of the regulations

Risk 3 (other) observations:

- incomplete recall information provided to Health Canada
- inadequate product reconciliation records

1.7 Compliance and enforcement

Compliance and enforcement measures by the Regulatory Operations and Enforcement Branch are based on the:

- nature of the deviations from GMP
- risks to health and safety that these deviations represent

Enforcement activities may include:

- asking for recall of NHPs
- issuing public advisories
- asking for voluntary detention, export or voluntary disposal of NHPs
- seizing NHPs
- cancelling, refusing or suspending a product licence (by the Natural and Non-prescription Health Products Directorate)

- cancelling, refusing or suspending a site licence
- issuing a stop sale request
- issuing an injunction preventing firms from selling NHPs
- prosecuting people
- having the Canada Border Service Agency refuse entry of NHPs into Canada

For more information on compliance and enforcement activities, consult:

- Compliance and enforcement policy for health products (POL-0001)

Appendix E – Corrective and preventive action process

Purpose

This section will help you develop a strong CAPA process so you may be able to efficiently correct issues and ensure they will not reoccur.

It will also help you develop a comprehensive CAPA plan. A CAPA plan is used to respond to issues, deficiencies and non-compliances that could be identified by:

- personnel
- the QAP
- Health Canada
- consumers
- other sources (such as an audit)

There are also events that may trigger the need to initiate a CAPA plan:

- deviations (a written procedure is not followed)
- OOS test results
- internal findings (such as findings from a self-inspection)

This section describes:

- some of the information expected to be included in a CAPA plan
- best practices and suggestions to create a well-prepared CAPA plan
- expectations on the implementation of a CAPA plan
- the approach used by Health Canada to evaluate a CAPA plan

An issue is identified

Your QAP should have already developed and implemented a suitable CAPA process to follow. It will ensure the correct people are alerted if an issue is identified and that the steps that will need to be taken to address it are clear. This process must be part of your QA system.

Document and record

The whole CAPA process should be well documented and include a tracking system for events, to help you efficiently document and keep track of the ongoing issues.

The purpose of the CAPA process is to:

- collect information
- analyze the information
- identify and investigate product and quality problems
- take appropriate correction measures (to contain the situation immediately), corrective actions (to control a current event), and preventive actions (to prevent a problem from occurring again)

Thus, if you do not record and document every step of the process, the CAPA plan may fail at:

- dealing effectively with product and quality problems
- preventing issue reoccurrence
- preventing or minimizing GMP failures
- demonstrating due diligence was performed

Assemble a team of subject matter experts

Your CAPA process may require that you assemble a multidisciplinary team of appropriate subject matter experts (such as QA, QC, manufacturing). Such a team will be able to approach the problem from multiple angles to:

- implement immediate corrections
- investigate and conduct a root cause analysis
- evaluate the impact of the issue
- plan corrective actions and preventive actions (CAPA plan)
- put the CAPA plan into action and monitor its effectiveness

Make immediate corrections

When you identify an issue, it's important to immediately correct or contain it. A correction may involve repairing, modifying or adjusting a machine. Containment may involve putting a product lot or a machine in quarantine until you can gather more information.

Contain the issue until an investigation to identify the root causes can be conducted and corrective actions can be taken. High-risk issues require immediate correction measures to mitigate risks. You may need to use a series of short-term risk mitigation measures while long-term measures are being implemented.

Implementing a correction by itself without a broader set of corrective actions and preventive actions may not address the underlying problem. Immediate corrections will not prevent similar issues from happening again, but finding the root cause will.

It's not acceptable to continue to operate under conditions that may adversely impact the quality of NHPs or the safety of consumers.

Identify the root causes

Containment and immediate corrections are usually not enough to fully address an issue. You must identify the underlying causes of GMP deficiencies to:

- determine which actions are necessary to eliminate the root cause
- prevent the issue from happening again

Identify what caused the issue. Simply concluding that the problem was caused by human error or inadequate training can lead to ineffective CAPA.

Conduct the analysis using an appropriate investigation methodology or a combination of methods. Some methods that may be used to investigate root causes are described in Table 3.

Table 3: E: Examples of investigative methods.

Method	Considerations
5 whys	Identifies root cause quickly but may not identify all root causes, especially if the issue is complex or high risk. Asking why the deficiency occurred and drilling down by asking 4 (or more) questions beginning with a "why" will help to provide insights into the root causes.
Fishbone diagram	Uses a fishbone diagram to identify many possible causes for an issue. This structured approach helps to sort ideas into categories such as specifications, premises, equipment, personnel, sanitation, QA, stability

Table 3: E: Examples of investigative methods.

Method	Considerations
	and records. Doing so helps to identify relationships between different causes to fully address observations (immediate corrections, corrective actions, preventive actions).
Pareto analysis	Used to analyze and rank identified causes to determine which cause should be addressed first. Also known as the 80-20 rule. It will help you to prioritize actions.

Evaluate the impact

An impact evaluation will:

- ensure you have critically analyzed the breadth of the issue
- help you understand what went or may go wrong, the likelihood of occurrence and the severity of the consequences

Categories used to describe the level of impact (such as critical, major or minor, or high, medium or low) should be included in the CAPA plan. The categories should be defined in as much detail as possible.

During the impact evaluation, it's important to also consider if:

- similar issues could happen
- there might be an impact on the quality of marketed NHP lots or other products
    - if yes, you should investigate the previous lots of products that could be affected and look at related trends
- the data and information used to make previous decisions is reliable
- the level of control (such as over other products, internal processes, systems or suppliers) is adequate
- other actions are required to mitigate or eliminate the identified risks and gaps

The level of action taken to address observations should be proportionate to the risk and complexity of the GMP deficiencies.

Follow a written procedure (SOP) when determining the impact of the issue and its underlying causes. The quality of the analysis depends upon the robustness of the data used to assess the impact.

This data is often subject to information gaps or unexpected variables in processing. Revisiting the impact analysis when additional information becomes available is an important aspect of sustaining quality and compliance. This can be done even after you have completed the CAPA plan.

Implement corrective and preventive actions

Corrective actions are reactive. They are taken to control an existing issue. Preventive actions are proactive. They are taken to prevent the issue or similar problems from happening in the future.

Identifying the actions as corrective or preventive makes it easier to demonstrate that the CAPA plan fully addresses the issue and any possible underlying GMP deficiencies. This is why root cause investigations and impact analyses are essential when preparing a comprehensive CAPA plan.

As an example, if there is a product impact, part of your CAPA plan may include taking the following actions:

- adapting the manufacturing process, such as:
    - modification to equipment
    - new cleaning process for equipment
- a recall for batches or lots already distributed in Canada or abroad, as required

Determine and record the timeline to correct issues and implement the CAPA plan. Your plan should consider the resources (time, personnel, materials) needed for effective implementation.

It is important to set reasonable implementation timelines and monitor them. If extra time is needed to implement something, a justification should be documented.

Monitor effectiveness of action plan

Once you have implemented the CAPA, you need to revisit the issue. Answer these questions:

- Have the immediate corrections, corrective actions and preventive actions worked in addressing the issues and their root causes?
- Have employees completed training relevant to the immediate corrections, corrective actions and preventive actions?

- Have the immediate corrections, corrective actions and preventive actions resulted in any negative consequences? How may these be addressed?

Investing time and effort to prepare and implement a CAPA plan may also result in operational improvements.

Closure

Before the QAP approves and closes the CAPA plan, it's important to consolidate the related records and documents from each step of the process and their outcomes. In addition to helping prepare the CAPA plan itself, this information can be used to create or modify written procedures (SOPs).

Consolidating all records and analyzing the information generated will help you meet and maintain the regulatory requirements of the regulations.

Once the records are consolidated, you should confirm that the records include:

- a description of the immediate corrections or containment steps taken
- the results of your root cause and impact analyses
- the date that the CAPA were implemented
- the effectiveness of the actions taken

CAPA plans requested by Health Canada

We may inspect sites conducting licensable activities to assess their compliance. Inspectors issue an inspection exit notice after an inspection. This notice:

- gives an inspection rating of compliant or non-compliant
- describes any GMP deficiencies and non-compliances (observations) identified during the inspection
- provides an opportunity to prepare a CAPA plan in response
- indicates the date that a written response must be provided

During the site licensing process, we may issue an information request notice. This notice:

- describes any GMP deficiencies and non-compliances (observations) identified during the assessment
- provides an opportunity to prepare a CAPA plan in response
- indicates the date that a written response must be provided

The CAPA plan is mandatory, as it's an important part of the inspection or licensing process. CAPA plans provided by the deadline are reviewed and the information in these documents are taken into consideration. Responses received after the deadline are not reviewed.

During inspections or site licensing, only a sample of the NHP products processed by your company are looked at. Therefore, the observations describe a specific situation seen or identified. It is critical that your CAPA plan address the underlying GMP deficiencies tied to the observation made and is not limited to the specific product or process identified in the notice. As an example, if an inspector identifies a product lot with an issue, you must consider the impact of the observation on all the other lots and other products that could be affected by the issue.

A CAPA plan may be under way but not fully completed at the time the written response must be provided. Nevertheless, you must provide your ongoing CAPA plan to us by the due date.

Include in the CAPA plan:

- a clear summary of the steps completed
- immediate corrections and dates these actions were taken
- a description of preliminary or completed root cause investigations and impact analysis conclusions
- plans for ongoing investigations, impact analysis and target dates
- a description of implemented corrective actions and preventive actions, including dates completed for each observation
- a description of planned corrective actions and preventive actions and target completion dates for each observation

Health Canada may ask you to demonstrate and support your actions taken with documented evidence (for example, photographs, repair bills, updated SOPs).

If the target completion date extends over a long period of time, always include a justification. It's important not to commit to target dates that are overly optimistic or do not consider the actual time needed to complete the required work. CAPA must be implemented and evaluated as soon as possible.

Some CAPA may take a long time to implement (such as building renovations). For these, you must include the short-term actions taken to mitigate risks while the long-term actions are being implemented.

We expect you to address all observations and correct and prevent any underlying GMP deficiencies. When the observations are risk-rated, the CAPA plan that you submit must include the actions taken or planned to address:

- all critical (Risk 1) and major (Risk 2) observations
- any underlying GMP deficiencies

Complete all the actions and future commitments identified in the CAPA plan, including their dates of implementation. Failure to complete actions and meet commitments, including their target dates, can lead to compliance and enforcement actions.

Target completion dates that must be extended due to unforeseen consequences should be managed through quality management processes. You should:

- have a rationale as to why you cannot meet commitments or target dates
- have an updated action plan to address the issues, including revised target dates
- put in place interim control measures to mitigate risk (with date of implementation)

You should avoid vague responses. We require enough information to understand what your plans are and the reasons for those plans. Also, we consider timelines such as “from now on”, “in the future” or “to be determined” to be too vague.

Revision history

Table 4: Revision history

Version	Implementation date	Summary of changes
3.0	December 2015	n/a
4.0	September 4, 2025	The guide is presented in a more user-friendly format that follows the order of the regulations under Part 3 (GMP) of the Natural Health Products Regulations. Additional and clearer guidance is provided for most of the GMP topics presented in this guide, including more clarity on importer-related activities.