



Health Santé  
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# EVIDENCE FOR QUALITY OF FINISHED NATURAL HEALTH PRODUCTS

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Natural Health Products Directorate

June 2007  
Version 2

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

*Health Canada*

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

*Natural Health Products Directorate*

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## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a health product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the relevant sections of other applicable guidance documents.

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# SECTION 1. INTRODUCTION

## 1.1 Purpose

This guidance document is intended to provide applicants (manufacturers, packagers, labellers, importers, distributors) with the details necessary to comply with the *Natural Health Products Regulations* (the Regulations) at the time of submitting the product licence application (PLA) with respect to the manufacture and quality requirements of natural health products (NHPs).

## 1.2 Background

Based on valuable feedback received from stakeholders during various information sessions, and experience gained by reviewing PLAs by scientific reviewers/assessment officers and submission coordinators at the Natural Health Products Directorate (NHPD), the *Evidence for Quality of Finished Natural Health Products Guidance Document* has been revised.

## 1.3 Scope

The procedures outlined in this document apply to the quality assessment of all types of pre-market submissions of NHPs that fall under the purview of the Regulations. This document should be read in conjunction with other NHPD guidance documents such as the *Product Licensing Guidance Document*, *Good Manufacturing Practices Guidance Document*, *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document* and *Evidence for Homeopathic Medicines Guidance Document* to ensure the product requirements are comprehensively applied and documented in a product licence application. Further, reference has also been made to a number of national and international standards, such as the *United States Pharmacopoeia* (USP), *European Pharmacopoeia* (Ph. Eur.), and *Therapeutic Goods Administration of Australia* (TGA) where it is recommended that these standards be applied.

This document is intended for use by applicants, as well as by scientific reviewers/assessment officers and submission coordinators within NHPD and other stakeholders.

The NHPs available in Canada can be broadly classified into:

- Single ingredient products; and
- Multi-ingredient products.

The general quality requirements are outlined in **Section 2** of this document. Specific quality requirements of products containing particular items from Schedule 1 of the Regulations have also been included where they differ from the general requirements.

A multi-ingredient product is defined as a finished product containing more than one item from Schedule 1 of the Regulations (**Appendix 2**).

**Section 3** of this document outlines specific test requirements for the finished natural health product in various dosage forms.

**Section 4** of this guidance document outlines the quality requirements for homeopathic medicines.

## 1.4 General Overview

The regulatory requirements for the quality of the finished NHPs are set out in Sections 5 (License Application), 44 (Specifications), 98 (Medicinal Ingredient Representations) and 103 (Tablet Disintegration Times) of the Regulations.

PART 1  
PRODUCT LICENCES  
Licence Application  
Section 5

An application for a product licence shall be submitted to the Minister and shall contain the following information and documents:

(i) a copy of the specifications to which the natural health product will comply

PART 3  
GOOD MANUFACTURING PRACTICES  
Specifications  
Section 44

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

(2) The specifications shall contain the following information:

- a. detailed information respecting the purity of the natural health product, including statements indicating its purity tolerances;
- b. for each medicinal ingredient contained in 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 ingredients, 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.



PART 5  
GENERAL  
Medicinal Ingredient Representations  
Section 98

Section C. 01.012 of the *Food and Drug Regulations* applies in respect of natural health products.

C. 01.012. A manufacturer who makes representations on a label of a drug in oral dosage form, or in any advertisement, with respect to the site, rate or extent of release to the body of a medicinal ingredient of the drug, or the availability to the body of a medicinal ingredient of the drug shall

(a) before making the representations, conduct such investigations, using an acceptable method, as may be necessary to demonstrate that the site, rate or extent of release to the body of the medicinal ingredient of the drug and the availability to the body of the medicinal ingredient of the drug, correspond to the representations; and

(b) on request submit the record of such investigations to the Director.

PART 5  
GENERAL  
Tablet Disintegration Times  
Section 103

Subsection C. 01.015(1) and paragraphs C. 01.015(2) (d) to (f) of the *Food and Drug Regulations* apply in respect of natural health products.

C. 01.015. (1) Subject to subsection (2), no person shall sell for human use a drug in the form of a tablet that is intended to be swallowed whole unless, when tested by the official method DO-25, Determination of the Disintegration Time of Tablets, dated July 5, 1989,

(a) in the case of an uncoated tablet, the tablet disintegrates in not more than 45 minutes;

(b) in the case of a plain coated tablet, the tablet disintegrates in not more than 60 minutes; and

(c) in the case where the label of the drug indicates that the tablet carries an enteric coating or a coating designed to serve a purpose similar to that of an enteric coating, the tablet does not disintegrate when exposed for 60 minutes to simulated gastric fluid, but when it is subsequently exposed for a continuous period to simulated intestinal fluid the tablet disintegrates in not more than 60 minutes.

(2) Subsection (1) does not apply in respect of a drug in the form of a tablet where

(d) the drug is labelled as complying with a standard contained in a publication referred to in Schedule B to the Act;

(e) the drug has been demonstrated by an acceptable method to be available to the body; or

(f) representations regarding the drug are made on its label, or in any advertisement, with respect to the site, rate or extent of release to the body of a medicinal ingredient of that drug, or the availability to the body of a medicinal ingredient of that drug.

All NHPs that are to be sold in Canada need a product specification. The technical specifications submitted along with the product license application should include:

- tests for identity, microbial and chemical purity, quantity and potency, if applicable;
- test methods for identity, microbial and chemical purity, quantity and potency; and
- tolerance limits for microbial and chemical purity, quantity and potency.

Applicants should ensure that products are tested against the product specification requirements prior to release of the product for sale. If a claim is made on the label of a product for pharmacopoeial standard (e.g., USP grade), then applicants should strictly meet all requirements of relevant monographs including those requirements described in the general chapters, as stipulated in the specified pharmacopoeia.

The two basic streams of product licence applications are:

#### **1.4.1 Compendial Applications**

When a reference is made to NHPD monographs in the applications, applicants are not required to fill out the Quality Summary Report. Additional details in this regard are available in the guidance document *Compendium of Monographs*. In essence, applicants attest to meeting the relevant finished product specifications, as listed in the *Compendium of Monographs*.

#### **1.4.2 Non-Compendial Applications**

Applicants can also attest to meeting the relevant monographs and all other applicable requirements from one of the acceptable pharmacopoeia listed below. Where there are pharmacopoeial monographs for active ingredients only and the pharmacopoeia do not contain monographs for the finished product in the dosage form which is being applied for, the applicant should attest to meeting the relevant finished product specifications in the NHPD *Compendium of Monographs*. In this case, the applicant should provide a signed attestation that includes a complete description of the monographs to which they comply. In these cases, applicants do not need to fill out the Quality Summary Report (QSR).

In all other cases, applicants should complete the Quality Summary Report. Applications may also be submitted in ICH Common Technical Document (CTD) format.

If an applicant proposes finished product specifications that are outside the minimum requirements outlined in this guidance document, the applicant will be required to provide the proposed specifications, rationale for not meeting NHPD requirements and submit to NHPD additional scientific data to support the rationale. For instance, when an applicant proposes to use a different analytical method other than the one outlined in this guidance document, or proposes a tolerance limit exceeding the one described, proper justification is required and a risk-benefit analysis must also be provided. For any

new method used, the applicant should provide a detailed description of the methods, or a reference to the method if published.

NHPD will then assess the data provided by the applicant to determine whether the information is relevant and sufficient to support the quality of the NHP.

### **1.4.3 Acceptable Pharmacopeia**

The following pharmacopoeias are currently considered acceptable by NHPD:

United States Pharmacopeia (USP)  
British Pharmacopoeia (BP)  
European Pharmacopoeia (Ph. Eur.)

It is expected that if a monograph is published in one of these pharmacopoeia, the minimum specifications used for testing of the medicinal ingredient and finished products will be in accordance with the published monograph. The most recent version of the pharmacopoeia should be used in all cases.

## SECTION 2. GENERAL QUALITY REQUIREMENTS

In order to ensure quality of the finished products, manufacturers of NHPs should specify and implement quality requirements at every stage of manufacture of the raw material and finished product.

The quality requirements outlined in this chapter are general criteria for finished products containing NHPs, and additional product-specific requirements for items 1-8 of Schedule 1 of the Regulations (**Appendix 2**). Homeopathic product requirements, where unique, are detailed in Section 5.

In general, the guidelines encompass a list of tests, acceptance criteria, limits and ranges for the parameters prescribed that must be provided in finished product specifications, thus setting out the quality criteria for acceptance of NHPs for their intended use.

### 2.1 Characterization

Standardized plant extracts, all isolates of natural origin as well as their synthetic duplicates require characterization. For standardized extracts which use novel chemical(s) as marker compounds or bio-active compounds for standardization, characterization of the marker chemical may be required.

Characterization should include the chemical name and Chemical Abstract Service (CAS) Registry number. Additional details such as spectroscopic methods used to characterize the compound (e.g., Nuclear Magnetic Resonance (NMR), Infra-red spectroscopy (IR), Raman, Mass Spectroscopy) may be required.

#### 2.1.2 Identification Tests

Complete testing for identification purposes is usually performed at the raw material stage to identify the medicinal ingredient using physical and/or chemical identification tests.

Under section 44(2) (d) of the Regulations, the finished product specifications shall contain a description of the methods used for testing or examining the natural health product containing medicinal ingredients which are substances defined in Schedule 1 (see Appendix 2).

In the case of a medicinal ingredient where the constituents responsible for the biological activity are unknown or a chromatographic fingerprint cannot be established, or because of the complex nature of the finished product, it is sufficient to provide physical identity tests at the raw material stage.

Where possible, the medicinal ingredient should be identified by spectroscopic and/or chromatographic fingerprinting in the finished product. Spectroscopic methods include,

among others, Ultra Violet (UV), Infrared (IR), and Mass Spectroscopy, and chromatographic methods include, among others, High Performance Liquid Chromatography (HPLC), Thin Layer Chromatography (TLC), and Gas Chromatography (GC).

Botanical characteristics and other tests that lead to the identification of a plant material, an alga or a fungus are critical. These characteristics can be confirmed at the raw material stage, before the original form of the material is changed during the production process. Identification tests outlined in the pharmacopoeial monographs (such as USP or Ph.Eur.) or botanical text books can be used as a guiding tool.

- **Botanical Characteristics:**

- Macroscopic Characteristics – e.g., plant morphology that defines shape of leaf, flower etc.
- Microscopic Characteristics – e.g., plant tissue morphology that defines cellular characteristics.

- **Chemical Identification:**

Where possible chemical identification methods should be used (such as appropriate analytical methods like TLC, HPLC or GC) that characterize a specific chemical marker or a chemical reaction that is a representative test for a specific herb. Chromatographic fingerprinting where the proportions of chromatographic peaks are compared to a known standard can also be used for identification purposes.

The combination of botanical characteristics and chemical identification tests should be chosen to eliminate misidentification of the herb (e.g., eliminate use of a different species or a herbal drug that is likely to be falsified). Extracts of plant material can be identified by characteristics of the original material as mentioned above prior to the extraction process and chromatographic fingerprinting of the extract.

Isolates and synthetic duplicates of materials of natural origin (e.g., vitamins and minerals) should be identified at the raw material stage by physical description and physical form (e.g., colour, crystalline form, etc.) as well as other physical characteristics such as melting point, boiling point, optical rotation, etc. Appropriate identification tests such as Infrared spectroscopy should also be performed at the raw material stage. Essential fatty acids should be identified at the raw material stage and/or at the finished product stage by fatty acid composition of the oil, refractive index (for a liquid) and/or any other appropriate identification tests.

If the medicinal ingredient is an enzyme, it should be characterized at the raw material stage by chemical name, Enzyme Commission classification and CAS Registry number. Additional details such as gel electrophoresis, substrate specificity, isoelectric point, specific activity should also be provided, if available. Testing can be done according to pharmacopoeial methods or methods approved by the International Enzyme Commission.

If the medicinal ingredient is a bacterium which grows in readily visible colonies (e.g., cyanobacteria), tests for identity of the bacteria can include microscopic evaluation. A qualitative description of the bacterium should include parameters such as Latin binomial name (e.g., *Spirulina platensis*). The test methods used to identify the substance (e.g., organoleptic, macroscopic and microscopic) should also be provided in the raw material specifications. If the bacterium does not grow in readily visible colonies, the identity of the bacterial strains can be determined by the selective culture method, direct microscopic analysis, and DNA-based finger printing techniques.

For probiotic cultures, a qualitative description of the probiotic culture should be provided which should include identity parameters such as Latin binomial name (e.g., *Bifidobacterium longum*). The identity of probiotic strains should be determined preferably by using phenotyping and genotyping methods at the raw material and/or at the finished product stage. Identification should ensure the absence of mixed cultures at the raw material stage. Other commonly used methods for identification of probiotic strains are selective culture method, direct microscopic analysis, enzyme/metabolite analysis and DNA-based finger printing techniques. Testing should be done according to appropriate methods which are specific and reproducible.

#### **2.1.2.2 Specifications for Medicinal Ingredients**

A specification or a certificate of analysis for each medicinal ingredient should be provided with detailed information as to the testing performed to confirm the identity and purity of the medicinal ingredient.

### **2.2 Standardized Products**

Currently, there is no harmonized definition of standardization. Therefore, given that some manufacturing and finished product specification requirements differ for standardized products, this document assumes the definition of standardization used by NHPD.

Standardization is a process that manufacturers may use to ensure batch-to-batch consistency of their products. In some cases, standardization involves identifying specific chemicals (also known as markers) that can be used to manufacture a consistent product. The standardization process can also provide a measure of quality control of the product.

#### **2.2.1 Standardized Extracts**

Standardization refers to the process of delivering a product with a specified minimum level or a specified range of one or more of biochemical constituent(s) or marker compound(s), while maintaining the total characteristics of a product containing plant material, algae, bacteria, fungi, or non-human animal material. It is achieved by

characterizing and quantifying one or more biomarkers of either known pharmacological activity (medicinal or active compound) or unknown pharmacological activity.

Biomarkers are classified as follows:

- **Active constituent:** A known and acceptable therapeutically active biochemical component. This specific biochemical constituent can be adjusted by standardization to a level that is reproducible – either that naturally found in the plant or more concentrated in an extract.
- **Marker compound:** The active biochemical component is not known. The specified marker compound, which is characteristic of the natural health product, but does not contribute to therapeutic activity, is adjusted to serve an analytical purpose. Marker compounds can be used to control batch-to-batch consistency of the finished product.

The approach to standardization is to manufacture the product to ensure that each batch contains the same amount of the marker component. It is assumed that other chemical constituents in a given product will vary in proportion to the marker compound; if each batch contains the same standardized amount of marker, the content of other constituents will also be relatively consistent. Standardization of marker content can also be achieved by blending different batches of raw materials to achieve the target marker content. According to the American Herbal Products Association (AHPA) guidelines this is an excellent method for obtaining consistency.

Some methods for identifying and quantifying selected marker or active constituents are available in, among other sources, the *American Herbal Pharmacopoeia and Therapeutic Compendium* or in the scientific literature. When no method exists for the specific product, or when improved technology allows for a more accurate and precise method, an alternative method may be used as long as it is validated according to Organization for Economic Co-operation and Development (OECD's) Principles of Good Laboratory Practices (GLP), International Conference on Harmonization's (ICH) guidelines on Validation of Analytical Procedures or submitted to AOAC International for validation.

Many manufacturers employ various production processes to manufacture health products containing extracts with a target marker content, either by adjusting the extraction ratio and/or adding fillers to achieve the targeted marker content. This practice may be appropriate in cases where it has been established that the marker is responsible for the pharmacological activity. The extracts could be suitably blended with excipients such as starch, lactose or dicalcium phosphate. This process affords extracts of desired strength suitable for formulating into finished dosage forms.

A standardized extract can be characterized by its specifications and the ratio of the quantity dried equivalent of the herbal drug to the quantity of the extract. For a liquid extract, a ratio of 1:5 means that 1 g of crude dried material was used to prepare 5 ml of

extract and for a solid extract a ratio of 5:1 means that 5g of crude dried material was used to prepare 1g of extract.

The process of standardization as applied to products containing complex materials will facilitate consistency in quality of finished products in terms of quantity and potency. Presently, there are no universally accepted standards for the manufacturing of standardized extracts, however several monographs have been published and it is recommended that the analytical methods described in these monographs be used when available. Specifications for standardized products should include identity (e.g., chemoprofile, multiple fingerprints), potency and strength (quantity), purity (incidental compounds/contaminants). Manufacturing processes should be designed to ensure consistency, which requires controls on both raw materials quality and manufacturing processes. Standardization does have advantages as indicated below:

- ensuring consistency (i.e., batch-to-batch consistency)
- confirmation of the correct content of extract/dosage unit
- positive control to indicate possible loss or degradation during manufacturing or shelf-life

### **2.2.2 Non-Standardized Extract**

A non-standardized extract is made by soaking the plant, plant material, alga, bacterium, fungus, and non-human animal material in a liquid that removes specific compounds. The liquid can be used as is, or evaporated to make a dry non-standardized extract.

## **2.3 Manufacturing Requirements**

Manufacturing information is required for certain medicinal ingredients.

Considering the fact that Good Manufacturing Practices (GMPs) are implemented during processing of the finished product, manufacturing information is not required at the raw material stage or for the finished products containing a plant/plant material, an alga, a fungus, a bacterium or a non-human animal material. However, if required, NHPD may request manufacturing details on a case-by-case basis to support the quality of the raw materials and the final product.

### **2.3.1 Raw Material Manufacturing Information**

#### **2.3.1.1 Standardized Products**

The applicant is requested to provide the standardization method for the standardized products, e.g., a standardized extract of a plant material. It is recommended that the applicant choose one of the methods from the list below, which includes the most commonly used methods to adjust the quantity of marker in a product. This list can be modified to clarify the procedures used when necessary.



### *List of Standardization Methods:*

- selecting a specific variety of material with consistent content of marker (i.e., no adjustment of the product occurs)
- mixing raw material lots (e.g., equivalent amounts of 1 lot at 1% marker and a 2<sup>nd</sup> lot at 3% to give 2% marker)
- varying extraction ratio of source material to solvent
- varying extraction conditions (e.g., time, temperature, solvent strength: please specify)
- normalizing by varying excipient quantity in finished product
- other: please specify

Note: some products may be fortified or spiked with the marker or other ingredient which is added to the product. This is not to be referred to as a standardized product, but may be acceptable if declared on the PLA and label as fortified or spiked or with added ingredient (e.g., rose hips with added vitamin C).

The target marker(s) or active constituent(s) for each standardized extract medicinal ingredient should be provided with a range for the acceptance criteria for each marker. It is also necessary to indicate how the success of the standardization method is verified (i.e., by chemical assay, biological assay or another method which should be specified). Where a product is standardized to a group of compounds calculated against a single compound, this should be declared (e.g., Senna leaf standardized to x mg hydroxyanthracene glycosides, calculated as Sennoside B).

#### **2.3.1.2 Other Extracts**

For extracts of a plant or a plant material (e.g., tinctures), alga, fungus, bacteria or non-human animal material which are not adjusted, it may be necessary to provide basic manufacturing information such as extraction ratios, weight of the starting material used, as well as the solvents used in the extraction process.

If an extract conforms to an acceptable grade (e.g., pharmacopoeial grade), manufacturing information is not required at the raw material stage.

#### **2.3.1.3 Isolates and Synthetic Duplicates**

If an isolate or a synthetic duplicate conforms to an acceptable pharmacopoeial grade, raw material manufacturing information and raw material specifications are not required to be provided to NHPD.

If the isolate or synthetic duplicate does not conform to an acceptable grade, the applicant should provide at a minimum the following information:

- A brief description of the test methods, specification limits (lower and upper tolerance limits), and demonstration that the ingredient meets the specification limits, for:
  - Identity (physical description and/or chemical analysis);
  - Purity with respect to:
    - › Percentage purity of the medicinal ingredient;
    - › Process impurities specific to the method of synthesis or isolation;
    - › Potency where applicable (e.g., where assessed by bioassay).

All of the above information should be provided, but it may be provided by the applicant in various forms or combinations of documents, such as:

- a copy of the specifications sheet that provides the details outlined above; and/or
- a copy of the Certificate of Analysis or equivalent documents providing the specifications representative of the lot to be used in the manufacture of the finished product, providing the details outlined above; and/or
- a sequential description or flow diagram of the manufacturing process, with details on each manufacturing step including each solvent used (their ratio if in combination), temperature, pH, impurity profile and any other relevant conditions.

#### **2.3.1.4 Enzymes**

If the isolate is an enzyme (e.g., amylase), details of the manufacture of the enzyme at the raw material stage should be provided which should include source material, fermentation medium and isolation process. The source material should clearly indicate whether the enzyme is of microbiological origin and whether it is derived from genetically modified organisms. The taxonomic and genetic classification of the microbe should also be provided. In the case of immobilized enzymes, details such as composition and purity of the immobilizing agent and also the method of immobilization should be provided.

#### **2.3.1.5 Probiotics**

For each probiotic bacterial culture, the applicant should provide at a minimum the following information:

- A brief description of the test method, specification limits (lower and upper tolerance limits), and demonstration that the ingredient comes within the specification limits, for:
  - identity (microscopic, phenotypic, genotypic, serotypic methods etc.); and
  - purity with respect to:
    - › total viable count per gram of the raw medicinal ingredient; and
    - › microbiological contaminants.

All of the above information must be provided, but it may be provided by the applicant in various forms or combinations of documents, such as:

- A copy of the specifications sheet or Certificate of Analysis or equivalent documents providing the specifications representative of the lot to be used in the manufacture of the finished product, providing the details outlined above; and/or
- A sequential description or flow diagram of the manufacturing process, with details on preparation of mother culture, fermentation conditions (composition of media, process parameters such as temperature, pH), mixing, freeze drying and packaging conditions.

Further, in order to ensure maximum viability of the bacteria, the cells should be kept under conditions which promote maximum survival (e.g., refrigeration) at every stage of manufacture.

### **2.3.2 Proprietary Information Concerning the Manufacturing Process**

In cases where the details of the manufacturing process of the medicinal ingredient are proprietary and have not been provided to the importer or distributor, the proprietary information can be provided directly to the NHPD in the form of an NHP Master File (NHP-MF) or to the Therapeutic Products Directorate (TPD) in the form of a Drug Master File (DMF). This information will be kept confidential and an authorization letter from the Master File holder is required to allow access by the NHPD on behalf of the applicant during the assessment of a PLA. For details on using master files, refer to NHP-MF guidelines or to the TPD DMF guidelines.

Health Canada's quality assessment requirements for medicinal ingredients could be satisfied by a combination of a Certificate of Analysis that describes the tests and tolerances for the identity and purity of the ingredient, the citation of a manufacturer's Master File (MF) in which details of the identities and quantities of the process-specific impurities have been provided in confidence to Health Canada, and a description of a further assay that is used to assess potency.

This flexibility in the types of documents that may be used to support quality requirements will allow applicants to more easily provide Health Canada the required information while allowing industry to protect confidential manufacturing details that are not necessary for Health Canada's assessment of the product's safety, efficacy, and quality.

### **2.3.3 Finished Product Manufacturing Information**

Good Manufacturing Practices should be implemented at all stages of the manufacturing process. Manufacturing information is generally not required for the finished product manufacturing process. However for certain technically complex dosage forms or for dosage forms of NHPs with limited stability, e.g., vitamins and probiotics, NHPD may request manufacturing details of the finished product if required.

The NHPD would permit the use of the following processes to reduce the microbiological load of medicinal ingredients that are not susceptible to degradation as indicated. Manufacturing information may be requested for products where the following processes are used.

**Sterilization:** Sterilization may be allowed for certain products provided a scientific justification is included that ensures the potency of the medicinal ingredient is maintained. Sterilization method(s) and conditions, such as temperature and time, should be provided for sterilized raw materials or finished products.

**Irradiation of Natural Health Product:** Irradiation is not permitted as a method for microbiological reduction or as a sterilizing procedure where the finished products contain vitamins or amino acids, which are generally sensitive to this process. Irradiation may be permitted as a method for microbiological reduction or as a sterilizing procedure where the finished products contain plant/plant materials.

**Pasteurization:** Pasteurization may be allowed for certain products provided a scientific justification is included that ensures the potency of the medicinal ingredient is maintained. Pasteurization conditions, such as temperature and time, should be provided. Appropriate reduction of microbial load under the proposed conditions should be demonstrated.

## 2.4 Finished Product Specifications Requirements

Finished product specifications must be provided for every natural health product. They must include information on the identity, purity and quantity of the finished product along with corresponding tolerances. Additional specific tests that may need to be documented on the finished product specifications are detailed in **Section 3** and not covered in this section. The specifications should indicate which tests are carried out routinely on each batch of the finished product, and for those which are not carried out routinely, the frequency of the testing should be stated on the specification sheet.

### 2.4.1 Analytical Methods

Analytical methods used for testing should be indicated on the specifications by referring to the appropriate method number and the type of test involved, e.g., EPA Method 7000A (Graphite Furnace AAS). Where house methods are used, the QSR should include a brief description of the method and where appropriate, a literature reference to the origin of the method, e.g., HPLC method; Hoffmann, J.L. (1986) *Biochemistry* 25: 4444-4449.

### 2.4.2 Identity Testing on the Finished Product

Physical identification tests should be done on the final dosage form and should be documented in the finished product specifications. Tests for physical identification of the finished product might include tests such as organoleptic evaluation (sensory characteristics e.g., taste, odour, feel, appearance (colour and shape of the capsule or tablet), etc.). Where the medicinal ingredient is a defined chemical entity, or where a marker is present, chemical identification tests (e.g., comparison of a retention time of an HPLC peak with a standard) should be used.

If the medicinal ingredient conforms to an acceptable grade (e.g., USP, Ph.Eur., NHPD Compendial specifications), other than the pharmacopeial requirements, only physical identity testing of the finished product is required.

### 2.4.3 Purity

Under section 44 (2) (a) of the Regulations, the finished product specifications shall contain detailed information regarding the purity of the natural health product, including statements indicating its purity tolerances. The finished product specifications should include tests and methods and tolerance limits for the microbial and chemical contaminants as outlined in the following **Microbial Contaminants** and **Chemical Contaminants** sections.

Tolerances for purity must conform to the limits listed in Tables 1 and 2 of **Appendix 4**. The tolerance limits for microbiological contaminants and mycotoxins have been adapted from international standards such as World Health Organization (WHO) and National Sanitation Foundation (NSF). The microbial tolerance limits for a multi-component product would be based on the medicinal ingredient in the finished product that has the least stringent limit, however limits should be reduced if warranted by routine analysis showing lower levels of contamination.

If the applicant provides test methods and tolerance limits for the chemical contaminants at the raw material stage or if the medicinal and non-medicinal ingredients conform to an acceptable Pharmacopoeial grade, NHPD will accept this as exemption of testing at the finished product stage as long as a scientific rationale is provided ensuring that the finished product is free from any additional chemical contaminants.

If the applicant proposes purity testing that is not performed using a well-recognized method (e.g., an in-house method is proposed), the applicant may be required to provide additional information on the proposed method. When no method exists for the testing of a specific product, or when improved technology allows for a more accurate and precise method, an alternative method may be used as long as the method is validated.

Validation of analytical procedures should include a method description, justification for the use of the method and validation data. Copies of the validation report for the analytical procedures used during the development as well as those proposed for routine testing should be kept on file by the testing laboratory.

If testing for microbiological contamination is not performed on the finished product, the applicant must provide a scientific rationale justifying exemption of these tests.

#### 2.4.3.1 Microbial Contaminants

NHPD applies limits to the following organisms:

- **Total viable aerobic plate count**
- **Contaminating fungus (yeast and mould)**
- ***Salmonella* spp.**
- ***Escherichia coli***
- ***Staphylococcus aureus***

Testing should be done according to Pharmacopoeial (USP, Ph. Eur. etc.), WHO methods or any other internationally recognized methods.

Methods should be appropriate for the product and the expected bioburden, e.g., hypertonic solutions should not be tested using pharmacopoeial methods appropriate for purified water, as inhibition of microbial growth by the solution should be taken into account.

*Pseudomonas Aeruginosa* testing is required for liquid products unless alcohol is present at concentrations greater than 50%. Applicants should also consider carrying out other appropriate tests if required due to known issues of contamination or if another organism is considered a more appropriate indicator organism (e.g., *Enterococcus*, *Campylobacter*, *Shigella* or *Listeria* species).

For Probiotic products, the Total viable aerobic plate count is replaced by *Enterobacteriaceae* testing as a method of detecting specific microbial contamination. A method of enumerating viable members of the family *Enterobacteriaceae* should be used, e.g., USP <2021> "Enterobacterial count (Bile tolerant gram negative bacteria)" or the Health Canada test MFLP-43 "Determination of Enterobactericeae".

#### 2.4.3.2 Chemical Contaminants

In addition to considering the following contaminants to which the NHPD applies limits, applicants should also consider appropriate testing of the finished product for additional contaminants (e.g., aflatoxins in nuts and microcystin in cyanobacteria).

Chemical contaminant testing is not required for finished products containing only probiotics cultures.

**Heavy Metals (i.e., arsenic (inorganic), cadmium, lead and total mercury):** These should be tested individually or as total heavy metals expressed as lead at the finished product stage or at the raw material stage if all medicinal and non-medicinal ingredients

are tested. Testing should be done according to Pharmacopoeial or any other internationally accepted methods. Some commonly used methods are:

- Inductively Coupled Plasma-Atomic Emission Spectrophotometry (ICP-AES);
- Inductively Coupled Plasma-Mass Spectroscopy (ICP-MS);
- Atomic Emission Spectrophotometry (AES);
- Atomic Absorption Spectrophotometry (AAS).

The tolerance limits for arsenic, cadmium, lead and total mercury are consistent with relevant international standards. In Canada these limits are based on the following body weights: adult: 70 kg; 12-year-old child: 40 kg; six-year-old child: 20 kg. Please refer to the example of calculations given in **Appendix 5**. Limits for heavy metals should be provided in  $\mu\text{g}/\text{kg}$  b.w./day. When levels for individual metals are provided in ppm, the tolerance level for daily dose should not exceed to 9.8  $\mu\text{g}$  for Arsenic, 6.3  $\mu\text{g}$  for Cadmium, 20.3  $\mu\text{g}$  for Lead and 20.3  $\mu\text{g}$  for Mercury (calculated for 70 kg adult). The maximum daily intake should be documented in the Quality Summary Report and used to justify the proposed limit.

NHPD is willing to accept the use of the USP <231> test for total heavy metals under certain circumstances. The tolerance limit of not more than 10 ppm for the total heavy metals at the finished product stage is not uniformly applicable to all NHPs, since the intake of heavy metals would vary significantly depending on the quantity of natural health products consumed. The USP Heavy metal test is not considered equally sensitive for all heavy metals which react with Thioacetamide, hence the sum of the NHPD tolerances for individual heavy metals is not considered valid for determining the Tolerable Daily Intake (TDI) or Tolerable Daily Amount (TDA) that would signify the toxicological impact. There is no known TDI value established by any scientific expert committee or working group for total heavy metals.

However, since the method is based on comparison with a lead standard, the limit of not more than 10 ppm will be acceptable provided that the permitted daily exposure is less than 20.3  $\mu\text{g}/\text{day}$  (dose of approximately 2 g of the dosage form per day) and that the following caveats are also noted.

1. The USP <231> test should be shown to be appropriate for the matrix tested.
2. If the exposure level is greater than 20.3  $\mu\text{g}/\text{day}$ , calculated as lead equivalents, the USP <231> test with a limit of not more than 10 ppm may be acceptable where the applicant can demonstrate based on testing of representative batches of the product that no individual metals approach the NHPD tolerance limits.
3. For traditional medicines, individual heavy metal limits should be tested using a quantitative method, due to known incidences of contamination, particularly with Arsenic and Mercury.
4. In the case of plants and algae which are known to selectively absorb and accumulate heavy metals, the product should be tested for individual heavy metals, or additional justification why the USP <231> test is valid should be provided.

5. A commitment from the applicant that, if the product fails the USP <231> test, the product will be tested for the individual heavy metals using an appropriate quantitative test.

If the USP <231> test is not considered appropriate (e.g., in the case of fish oils where testing of total Mercury is required due to known issues of contamination), NHPD will continue to ask for individual heavy metal testing.

**Mycotoxins (e.g., aflatoxins):** Testing is required for products containing ginseng and peanuts or any substance derived from these sources. Ginseng and peanuts may be contaminated with aflatoxins due to poor agricultural practices and storage conditions. Testing should be done according to internationally accepted methods. Appropriate measures should be taken at the raw material stage in order to ensure that the finished products do not contain such toxins. Other products where mycotoxin testing may be required are Evening Primrose Oil, Sugar Cane and Sugar Beets, Cottonseed and Corn-derived products. The need for mycotoxin testing will be evaluated on a case-by-case basis during the product assessment. Justification will be requested if a product has documented cases of fungal contamination.

**Cyanobacterial Toxins (where applicable), Microcystin:** Testing is required for algal products (e.g., blue green algae). The methods used and their limits should be provided.

**Solvents:** Solvents known to cause unacceptable toxicities (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Class I)) should be avoided in production unless their use can be strongly justified in a risk-benefit assessment report showing adequate supporting data for safe use. Solvents associated with less severe toxicity (ICH Class II) should be limited in order to protect consumers from potential adverse effects. Wherever possible, less toxic solvents (ICH Class III) should be used. This class list is available in *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidelines for Residual Solvents, harmonized tripartite guidelines*.

Testing for solvents should be done according to Pharmacopoeial (USP, Ph.Eur.) methods using GC and HPLC techniques. Tolerance limits for solvent residues should conform to ICH or pharmacopoeial limits.

**Incidental Impurities, Related Substances and Process Impurities:** Processing or purification steps may introduce organic or inorganic impurities (e.g., intermediates, other isomers, racemic compounds, reagents and catalysts) in the product. As well, other related substances (e.g., degradation products) may be present. All known impurities present in the raw material at significant levels should be listed on the raw material specifications with their associated tests and tolerance limits.



When conformance to an acceptable standard is declared, (e.g., USP, BP), manufacturers should be aware that the potential impurities declared on the monograph may not be the same as those found in the medicinal ingredient due to differences in the manufacturing process. Where differences in the impurity profile exist, the applicant should provide additional testing for impurities where applicable.

If the impurity profile of an isolated or synthetic medicinal ingredient is altered due to a change in the source material or manufacturing process, revised specifications with the new tolerance limits for the impurities must be submitted to NHPD.

**Pesticide Residues:** Testing for pesticides in plant or plant materials, algae, fungi, or non-human animal materials (e.g., **fish and marine mammals (e.g., seal)**) or extracts derived thereof, should be done according to the multi-residue method outlined in the European Pharmacopoeia, United States Food and Drug Administration's *Pesticide Analytical Manual 1* or WHO methods for pesticide screening I. Multi-residue pesticide screening is preferential. The pesticide residues that are routinely tested should be those pesticides which were used in treatment of the plant or any pesticides where residues are suspected and may carry over to the final dosage form.

Pesticide testing is not required for products with a certified organic content of 95% or more as long as certification from an accredited certification body is provided.

The limits specified in USP, Ph. Eur., or WHO for pesticide residues are considered to be acceptable.

### 2.4.3.3 Additional Tests

**Foreign matter:** This test is important to ensure that the plant/plant material, alga or fungus is entirely free from visible signs of contamination such as sand, glass and metal. Testing should be done according to internationally recognized methods.

Tolerance limits for foreign matter should be as specified in International standards such as WHO.

**Determination of acid insoluble ash:** Acid insoluble ash is important to determine the amount of inorganic impurities in the form of extraneous (non-physiological) materials in a plant/plant material. Testing and tolerance limits for acid insoluble ash should be as specified in International standards.

**Water Content:** This test is required where the material is known to be hygroscopic. Acceptance criteria should be justified by data on the effects of moisture absorption on the product (e.g., potency and stability). A 'loss on drying' procedure may be adequate, but in some cases (e.g., plants containing essential oils), specific tests such as the Karl Fischer method may be required.

**Contaminants in oils of animal origin:** Testing for polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls

(PCBs) in products isolated from fish and marine mammals (e.g., seals) is required where bioaccumulation of these products exists in fatty tissues. Tolerance limits for PCBs, PCDDs and PCDFs were developed from Canadian food residue levels that are set by the Food Directorate, Health Canada. Testing should be performed using appropriate analytical methods. Applicants are advised to consult the Council for Responsible Nutrition (CRN) monograph on fish oils for further information.

**Antibiotic residues in honey and royal jelly:** Since chloramphenicol and 5-nitrofurantoin compounds are prohibited substances in honey products according to the *Food and Drugs Act and Regulations*, C.01.610.1, NHPs should not contain any of these antibiotics or their residues. Nitrofurantoin metabolites/residues from Furazolidone, Furaltidone, Nitrofurantoin, and Nitrofurazone in particular are of concern. Further information on analysis can be found in several articles, the most recent being: 'Determination and confirmation of nitrofurantoin residues in honey using LC-MS/MS' JOURNAL-OF-AGRICULTURAL-AND-FOOD-CHEMISTRY. FEB 21 2007; 55 (4): 1103-1108, Lopez-MI; Feldlaufer-MF; Williams-AD; Chu-PS. Applicants will be requested to provide a test for the detection of 5-nitrofurantoin residues and chloramphenicol in honey and royal jelly. Alternatively a justification for why the testing is not required may be submitted.

**Organic products:** An application for finished products containing organic ingredients must be accompanied by a proof of certification. Organic ingredients should comply with the *Organic Products Regulations of Canada*, December 2006. Certification of the plant/plant material or fungi (e.g., organic mushrooms) by accredited agencies is considered to be acceptable.

Note: Organic products must not contain the same ingredients in both organic and non-organic forms. Ingredients that do not meet the organic requirement may be used only when they make up less than 5% of the total ingredients and when the following information is supplied: a description of efforts made in good faith to locate or develop a source of the certified organic form of the ingredient, and progress made over the years to eliminate non-organic material.

**Radioactivity:** In specific circumstances where there is a risk of radioactive contamination, it may be necessary to test for radioactivity. Tolerance limits for radioactivity (if irradiation has been used to reduce microbiological load) have been adapted from European Commission Directive (Recommendation 2003/120/EC).

**Enzyme preparations:** Enzyme preparation and testing should be done in compliance with the joint Food and Agriculture Organization (FAO) and WHO Expert Committee on Food Additives publication *General Specifications for Enzyme Preparations Used in Food Processing*. Enzymes derived from microbial sources should be tested for antimicrobial activity at the raw material stage. Antimicrobial activity should be absent. Established methods for screening for microbial activity or USP <81> showing negative results can be used where appropriate.

## 2.5 Quantity

Under section 44 (2) (b) (c) of the Regulations, the finished product specifications shall contain detailed information for each medicinal ingredient respecting its quantity per dosage unit.

The tolerance limits for the quantity of medicinal ingredients should conform to the relevant pharmacopoeial standard or in its absence to 80% to 120% of the label amount. The exceptions are enumerated below. If “quantification by input” is used as described below, then this limit does not apply; rather the amount of medicinal ingredient added is controlled as described in the section “quantification by input”. If the applicant provides test limits for quantities that are outside the tolerance limits, a scientific rationale is required justifying these test limits.

### 2.5.1 Quantification by Assay

In the case of medicinal ingredients with constituents of known biological activity, quantitative assay tests can be done at the finished product stage according to appropriate analytical methods.

For most isolates, (e.g., amino acids and essential fatty acids) and synthetic duplicates, quantitative tests at the finished product stage should be conducted according to appropriate analytical methods described in the pharmacopoeia (e.g., USP, Ph. Eur.). The quantity is expressed as the weight (e.g., mg) of the medicinal ingredient.

All quantitative and potency tests for a standardized extract should be done at the finished product stage according to appropriate analytical methods. When the active constituents or markers are known and measurable, the amount in which they are present (potency) should be declared in the specifications.

### 2.5.2 Quantification by Input

In the case of medicinal ingredients where there is no known method of analysis of the medicinal ingredient, or the non-medicinal ingredients interfere with analysis, quantification by “input” is considered to be acceptable. In this case the active ingredient in the finished product is not assayed. The objective evidence that a quantity of a medicinal ingredient (e.g., a plant material) has been added to the finished product is calculated from a manufacturing batch record and controlled by appropriate application of GMP and in-process controls. Generally, the quantity of medicinal ingredient is expressed as the theoretical weight (e.g., mg) of the processed substance in each unit of the dosage form. Other tests on the finished product as required by this guidance are still to be performed (e.g., microbial testing).

Whenever quantification by input rather than assay is used, justification should be provided in the PLA. Justification should include a survey of methods which could be

used to assay the medicinal ingredient and an assessment of the risk not assaying the compound.

Certificates of analysis or raw material specifications for the medicinal ingredient(s) to be quantified by input are required to indicate that adequate control of the medicinal ingredient is in place.

A batch record or a description of controls that are in place during manufacturing to ensure the labelled amount of medicinal ingredient should be provided in the product licence application. These documents should indicate the target quantity for the medicinal ingredient (i.e., 100% of the label claim) and include controls on weight variation during tableting or encapsulation. Generally a 5% variation in weight for individual dosages is acceptable. A description of how batch homogeneity will be controlled should also be provided if more than one medicinal ingredient is mixed, or if the medicinal ingredient is mixed with non-medicinal ingredients.

### **Vitamins and minerals**

For vitamins, quantitative tests should be done on the finished product according to appropriate analytical methods described in an acceptable pharmacopoeia (USP, Ph.Eur.). The quantity of vitamins should be expressed as follows: Biotin (mg), Folate (mcg), Pantothenic acid (mg), Niacin (mg), Vitamin A (mg and IU), Thiamine (mg), Riboflavin (mg), Vitamin B<sub>6</sub> (mg), Vitamin B<sub>12</sub> (mcg), Vitamin C (mg), Vitamin D (mcg and IU), Vitamin E (mg and IU) and Vitamin K (mcg).

Tolerance limits for the quantity of vitamins and minerals should be as per United States Pharmacopoeia limits for the individual vitamins and minerals. If the applicant provides test limits for quantity that are outside the tolerance limits, a scientific rationale is required justifying the test limits.

Overage is used to compensate for the loss of vitamins during manufacture of the NHPs or loss/degradation of vitamins during shelf-life of the finished product. Applicants should provide justification when overages are used for vitamins, in formulating the NHPs. For example, when an applicant uses a 50% overage of Vitamin C (in comparison to the label claim) in the product to compensate for the loss due to heat treatment of the product, this fact should be clearly stated in the application and the results to justify the overage should be provided. The acceptance limits for overages should not be greater than the upper limit for content as per the pharmacopoeial standards.

### **Bacteria and Probiotics**

Enumeration of probiotic cultures should be performed using selective culture methods at the raw material and also at the finished product stage. The total count of the cells should be expressed as colony forming units (CFU) per gram.

Tolerance limits for the quantity of bacteria and probiotic cultures should be 80% to 300% (excluding cyanobacteria for which the limit is 80%-120%). If “quantification by input” is used as described in the previous section, then this limit will not apply. If the applicant provides test limits for quantity that are outside the tolerance limits, a scientific rationale justifying these test limits is required.

For bacteria, quantification by input is considered to be acceptable only in the case of cyanobacteria. If the bacterium does not grow in readily visible colonies, enumeration of the bacteria should be performed using selective culture methods at the raw material and the finished product stage. The total count of the cells should be expressed as colony forming units (CFU) per gram or mL.

## **Enzymes**

Tolerance limits for quantity of enzymes should be 80% to 150% of the label amount. For enzymes, the quantity per dosage unit should include the activity of the enzyme. The activity is measured according to the reaction catalyzed by individual enzymes (substrate specificity). For digestive enzymes the activity is expressed in the *Food Chemicals Codex* (FCC) units (e.g., FCC Lipase Units, FCC Lactase Units). Other enzymes should be indicated as International units (IU), or activity units (U). Tests using High Pressure Liquid Chromatography or other appropriate analytical methods are necessary to determine compliance with the declared representations of enzyme activity.

## **2.6 Stability Testing**

Stability testing of natural health products is required by Section 52 of the Regulations. Applicants should provide a description of the tests which have been completed or will be performed in order to determine the shelf-life (i.e., the post-approval stability protocol for the product). These tests should be listed in the finished product specifications. If tests are only performed during stability testing, and not for release of the finished product, then the tests should be marked as such, or a separate specification for stability testing can be used.

Typical tests used to demonstrate that a product is stable include chemical assays of medicinal ingredients, fingerprint chromatograms showing that the proportional content of the product does not change with time, organoleptic tests, tests for specific degradation products, microbial tests or other applicable tests. The appropriate use of tests to demonstrate stability should be justified by the applicant.

A commitment to perform all tests listed in the stability protocol after storage as labelled on the finished product and to meet the specifications for the finished product at the end of the shelf-life should be provided. The conclusions of the testing and the justification of the expiry period and storage conditions should be kept on file by the applicant and may be requested by NHPD.

**Oxidative stability in oils:** Testing should be done according to AOAC and/or Pharmacopoeial analytical methods for peroxide, anisidine, and totox values of **fish/seal** oils or omega-3 fatty acids derived from fish/seal oils to ensure the oxidative stability of the fish oils/omega-3 fatty acids. This requirement is applicable to all oils that have a high degree of unsaturation to ensure stability.

#### Oxidative Stability Parameters for Fish/Seal oils

Peroxide value (PV)	max. 5 mEq/Kg
Anisidine value (AV)	max. 20
Totox value	max. 26 Calculated as $2 \times PV + AV$

Where oxidative stability tests are required by pharmacopoeial monographs, the acceptance criteria as per the appropriate monograph may be used.

**Probiotics:** Where a viable count for the probiotic culture is included on the labelling of the product, the applicant should have evidence of the stability of that culture under the storage conditions.

## SECTION 3. SPECIFIC TESTS AND CRITERIA FOR FINISHED PRODUCTS

Tests other than those listed in the aforementioned chapters of this document may be needed in specific situations or as new information becomes available. Specific tests may be applicable on a case-by-case basis and must be conducted when these tests affect the quality of the products. The procedures used to conduct such tests should be pharmacopoeial, if possible, when no method exists for the testing, or when improved technology allows for a more accurate and precise method, an alternative method may be used as long as it is specific and reproducible. A summary of physical test requirements or certain dosage forms is summarized in **Appendix 8**.

The information provided below was incorporated from Evaluation of Medicinal Products (EMA): *Note for Guidance on Quality of Herbal Medicinal Products* (CPMP/QWP/2819/00, 26/7/2001) and *Note for Guidance on Specification: Test Procedures for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products* (CPMP/QWP/2820/00, 26/7/2001).

### 3.1 Disintegration

Under section 103 (and also section 15) of the Regulations, the tablet disintegration times should be provided for NHPs intended to be swallowed whole whether uncoated and plain coated tablets or hard and soft gelatin capsules. Applicants are required to comply with these tablet disintegration times as tested by the official method DO-25 or Pharmacopoeial methods.

For rapidly dissolving NHPs (dissolution > 80% in 15 minutes at pH 1.2, 4.0, 6.8) that are highly soluble throughout the physiological range (dose/solubility volume < 250 ml from pH 1.2 to 6.8), disintegration testing may be substituted for dissolution testing. The disintegration test is not required when the product is to be chewed or when it is a liquid extract. Oil-soluble vitamins (A, D, E, K) do not have to be subjected to disintegration or dissolution tests.

### 3.2 Dissolution

This test is used to measure the release of an active substance (usually a single ingredient) from solid oral dosage products i.e., tablet or capsule dosage forms.

Single-point measurements are normally considered suitable for immediate-release dosage forms. For modified-release dosage forms, appropriate sampling procedures should be followed under suitable test conditions. For example, multiple-point sampling should be performed for extended-release dosage forms, while two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms.

For extended-release NHPs, *in vitro* or *in vivo* correlation may be used to establish acceptance criteria when human bioavailability data are available for formulations exhibiting different release rates. When such data are not available, and release cannot be shown to be independent of *in vitro* test conditions, then acceptance criteria should be established on the basis of available batch data.

For products whose active constituents are not highly soluble throughout the physiological pH range, dissolution may not be always necessary but could be done as a periodic test. Applicants are expected to provide evidence to support the selection of dissolution versus disintegration testing.

### **3.3 Uniformity of Dosage Units**

Uniformity of dosage units refers to both the mass of the dosage form and the content of the active substance in the dosage form. The specifications should include one or the other, or both where the active constituent is less than 5% of the total weight. Acceptance criteria should be set for weight variation, fill volume or uniformity of fill. When appropriate, tests may be performed as in-process controls; however, the acceptance criteria should be included in the specifications.

A standard weight or volume measure is normally used. However, if the actual dosage unit a person takes is controlled, it may be either measured directly or calculated, based on the total measured weight or volume of the NHP, divided by the total number of doses expected. If dispensing equipment, such as a medicine dropper or bottle dropper tip is used, this equipment may be used to measure the dose. For inhalation and nasal products, the limits should be based on the target delivery amount of NHP per actuation, with corrections as necessary to convert from per-dose amounts to per-actuation amounts. For powders that are reconstituted, uniformity of mass testing is generally considered acceptable.

Note: The most commonly used dosage forms that are acceptable by the NHPD are listed in **Appendix 6**.

### **3.4 Sterilization**

The sterility of a product cannot be guaranteed by testing; it has to be assured by the application of valid method(s) of sterilization. NHPD requires the use of appropriate sterilization procedures only when the route of administration of the finished product is ophthalmic or when a finished product makes a sterile claim on the label.

The current United States Pharmacopoeia (USP <1211>) defines the methods of terminal sterilization. The choice of the appropriate method for a given finished dosage form requires a knowledge of the sterilization techniques and information concerning any effects of the process on the material being sterilized. Validation of the sterilization technique may be requested to support the application.



### 3.5 Antimicrobial Effectiveness Testing

Antimicrobial preservatives are ingredients added to dosage forms to protect them from microbiological growth or from microorganisms which may be introduced either:

- inadvertently during or subsequent to the manufacturing of the finished dosage form;  
or
- from repeatedly withdrawing individual doses.

Where antimicrobial preservatives are added to a product, NHPD is requesting that tests to demonstrate the effectiveness of antimicrobial protection are performed on the product. Test methods used and acceptance criteria should be as specified in an acceptable Pharmacopoeia (e.g., current USP <51>; Ph. Eur. 5.1.3), and should be performed on the final dosage form with suitable limits included. This test should be performed at a minimum at the end of the shelf life, but is usually performed at several stages during product development.

The concentration of the preservatives shown to be effective in the final dosage form should be below a level that may be toxic to human beings, and should be at the lowest concentration necessary to preserve the product.

## SECTION 4. HOMEOPATHIC MEDICINES

This chapter outlines the quality requirements for all homeopathic medicines. In order to complete a full submission package for a product licence, applicants for homeopathic medicines will also need to consult the following documents:

- *Evidence for Homeopathic Medicines Guidance Document*;
- *Good Manufacturing Practices Guidance Document*;
- *Evidence for the Safety and Efficacy of Finished Natural Health Products Guidance Document*;
- *Site Licence Guidance Document*.

### 4.1 Definition of a Homeopathic Medicine

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

1) Manufactured from, or contain as medicinal ingredients, only substances referenced in a homeopathic monograph in one of the following homeopathic pharmacopoeiae, as they are amended from time to time:

- *Homeopathic Pharmacopoeia of the United States* (HPUS);
- *Homöopathische Arzneibuch* (German Homeopathic Pharmacopoeia)(HAB);
- *Pharmacopée française* (French Pharmacopoeia) (PhF);
- *European Pharmacopoeia* (Eur. Pharm.);
- *British Homeopathic Pharmacopoeia* (BHP);
- *Indian Homeopathic Pharmacopoeia*.

2) Prepared in accordance with the methods outlined in one of the above-mentioned homeopathic pharmacopoeiae, as they are amended from time to time.

### 4.2 Overview of Quality Specifications for Homeopathic Medicines

The quality requirements for homeopathic medicines should include specifications for the following:

- Identity (prior to dilution);
- Microbial purity (at the finished product stage);
- Chemical purity (not required if the medicinal ingredients are diluted 2X or above).

Applicants are required to provide the specifications details at the raw material and/or at the finished product stage as outlined below.

#### 4.2.1 Manufacturing

GMPs must be followed during the manufacture of homeopathic medicines. (For more information on GMP requirements, please refer to the *Good Manufacturing Practices*

*Guidance Document*.) Applicants are not required to provide details of the manufacture of homeopathic medicines. However, NHPD reserves the right to request manufacturing details when it deems this information to be warranted.

## **4.2.2 Specifications**

### **4.2.2.1 Identification**

Identification of the medicinal ingredients should be conducted at the raw material stage as outlined in pharmacopoeial monographs. The medicinal ingredients used in the product should be identified at the raw material stage by identification tests such as chromatographic methods (High Performance Thin Layer Chromatography (HPTLC), HPLC, or GC), or spectroscopic methods and/or any other applicable chemical identification test. Physical identity of the medicinal ingredient (for example, organoleptic evaluation) is not required.

### **4.2.2.2 Purity**

Homeopathic medicines should be tested for microbiological contaminants at the finished product stage, as outlined in **chapter 2.4.3.1 above**. Each medicinal ingredient used in the product should also be tested for the chemical contaminants, as outlined above, at the raw material stage. If the applicant does not test the medicinal ingredients for the microbiological and chemical contaminants, then a rationale citing scientific evidence should be provided justifying the test exemption.

#### **4.2.2.2.1 Microbial Contaminants**

Microbial testing is required at the finished product stage. The requirements for specific testing and acceptance criteria are the same as for all NHPs as described in Section 2.4.3.1.

NHPD may allow skip-lot testing of microbial contaminants in the case of a few homeopathic products (such as pills that are not used for direct consumption). Applicants will be required to provide the details of the characteristics of the product, the history of the microbial contamination in the product and other relevant details to support the reduced testing regime.

### **4.2.2.3 Nosodes**

Nosodes are homeopathic preparations of pathological organs or tissues, causative agents such as bacteria, fungi, ova, parasites, virus particles and yeast as well as disease products, excretions and secretions. Because nosodes are, by nature, prone to microbiological contamination the NHPD requires assurance of their sterility at the raw material stage. Nosodes are only listed as monographs in the HPUS, and therefore, must comply with the sterility requirements as per the HPUS guidelines.

#### **4.2.2.4 Chemical Contaminants**

Testing of chemical contaminants is not required if the medicinal ingredient is diluted above 2X. Otherwise, testing of these should be performed as stated in Section 2.4.3.2.

Heavy metal tests are not required when the medicinal ingredient is a heavy metal itself. For example, if mercury is the medicinal ingredient, the raw material does not need to be tested for mercury.

## SECTION 5. REFERENCES

### 5.1 Health Canada documents

*Product Master Files*. Therapeutic Products Directorate guidance. Available by writing to [dmf\\_enquiries@hc-sc.gc.ca](mailto:dmf_enquiries@hc-sc.gc.ca)

*Product Licensing Guidance Document* available at [http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index_e.html)

*Master File Procedures* available at [http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index_e.html)

*Compendium of Monographs* available at [http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index_e.html)

*Official method DO-25* available at [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/tab\\_com\\_e.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/tab_com_e.pdf)

### 5.2 Related documents

American Herbal Pharmacopoeial and Therapeutic Compendium. American Herbal Pharmacopoeia, P.O. Box 66809, Scotts Valley, CA; (1997-2002).

Association of Analytical Chemists International. *Official Methods of Analysis*, 17th edition. Association of Analytical Chemists International, 481 Frederick Avenue, Suite 500, Gaithersburg, MD; 2000.

British Herbal Medicine Association. *British Pharmacopoeia*, P.O.Box 304, Bournemouth, Dorset, BH7 6JZ, England; 1996.

European Commission Recommendations. *On the protection and information of the public to exposure resulting from the continued radioactive caesium contamination of certain wild food products as a consequence of the accident at the Chernobyl nuclear power station*. Official Journal of the European Union (2003/120/EC).

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European Agency for the Evaluation of Medicinal Products. *Evaluation of Medicinal Products for Human Use. Note for Guidance on Specification: Test Procedures for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products* (CPMP/QWP/2820/00, 26/7/2001).

General Specifications for Enzyme Preparations Used in Food Processing JECFA Compendium of Food Additive Specifications, FAO Food and Nutrition Paper No. 52, Addendum 7. FAO, Rome, 1999.

International Atomic Energy Agency. *Assessment of doses to the public from ingested radionuclides*, Vienna, Austria; 2000.

International Union of Biochemistry and Molecular Biology. *Enzyme Nomenclature: Recommendations of the Nomenclature Committee of IUBMB*, Academic Press, NY; 1992.

International Conference on Harmonization. *Technical Requirements for Registration of Pharmaceuticals for Human Use. Guidelines for Residual Solvent*, harmonized tripartite guideline; 1997.

NSF International. *NSF International Standard/American National Standard on Dietary Supplements*, NSF/ANSI 173-2006. NSF-International, Ann Arbor, MI ; 2006.

Organization for Economic Co-operation and Development. *Principles on Principles of Good Laboratory Practices. Series on Principles of Principles of Good Laboratory Practices and Compliance Monitoring*. Env/MC/Chem (98)17, Paris, FR.; 1997.

United States Environmental Protection Agency. *Method 1613, Revision B. Tetra-Octa CDDs and CDFs by Isotope Dilution HRGC/HRMS*. EPA 821-B-94-005; USEPA, Washington, DC; 1994.

United States Environmental Protection Agency. *Methods for Determination of Metals in Environmental Samples*, Supplement 1-EPA/600/R-94-111; USEPA, Washington, DC; 1994.

United States Environmental Protection Agency. *Microwave-assisted Acid Digestion of Sediments, Sludges, Soils and Oils*, EPA Method 3510, USEPA, Washington, DC; 1994.

United States Food and Drug Administration. *Pesticides Analytical Manual 1 (PAM 1)*. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Rockville, MD; 1999.

United States Pharmacopeial Convention Inc. *United States Pharmacopeia USP 30-NF 25.*, United States Pharmacopeial Convention Inc., 121601 Twinbrook Parkway, Rockville, MD; 2007.

World Health Organization. *Quality Control Methods for Medicinal Plant Materials*, World Health Organization, Geneva, Switzerland; 1998.

## APPENDIX 1. GLOSSARY

**Alga.** A member of the biological kingdom Protista, consisting of unicellular, colonial or relatively simple multicellular eukaryotes that have a cell wall containing cellulose or silica, that usually produce their own food by photosynthesis using various chlorophylls and accessory pigments (some may also be heterotrophic under appropriate conditions), that are essentially aquatic and that lack multicellular dependent embryos.

**Animal.** A member of the biological kingdom Animalia, consisting of complex multicellular eukaryotes whose cells have a membrane but no wall, that have muscle and nervous tissue in most members, that are heterotrophs that mostly ingest food into a specialized cavity where it is digested, and that reproduce sexually by means of motile sperm and larger, nonmotile eggs (in some animals there is also asexual reproduction).

**Amino acid.** An organic molecule containing amino and carboxylic groups attached to same carbon atom. Amino acids are building blocks of proteins (chief constituents) found in a plant or a plant material, an alga, a bacterium, a fungus, or a non-human animal material.

**Bacterium.** A member of the biological kingdom Bacteria, one of the three domains of life, consisting of usually unicellular (sometimes aggregated, colonial or simple multicellular) prokaryotes whose cells lack nuclei or other internal compartmentalization. Most species have a cell wall external to the plasma membrane, composed primarily of peptidoglycan. Bacteria have diverse means of nutrition; the group consists mostly of chemoheterotrophs, but there are also chemoautotrophs, photoautotrophs and photoheterotrophs. They reproduce by binary fission.

**Chemical name.** The name an ingredient is referred to in the International Union of Pure and Applied Chemistry Nomenclature.

**Common name.** For any medicinal or non-medicinal ingredient contained in a NHP, the name by which it is commonly known and is designated in a scientific or technical reference.

**Dosage form.** The final physical form of the NHP which may be used by the consumer without requiring any further manufacturing.

**Enzyme.** An organic catalyst, usually a protein, increasing the rate at which a specific biochemical reaction occurs. Enzymes may be derived from a plant or a plant material, an alga, a bacterium, a fungus, or a non-human animal material.

**Essential amino acid.** An amino acid that cannot be synthesized in the body and has to be supplied through the diet or a supplement to meet human needs. Current knowledge indicates that there are eight amino acids that are regarded as essential for humans: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine.

**Essential fatty acid.** A fatty acid that cannot be synthesized in the body and has to be supplied through the diet or a supplement. Current knowledge indicates that there are only two essential fatty acids: linoleic acid and alpha-linolenic acid.

**Extract.** A substance prepared by treating a plant or a plant material, an alga, a bacterium, a fungus, or non-human animal material with solvents to remove any constituents.

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

**Fungus.** A member of the biological kingdom Fungi, consisting mostly of complex multicellular eukaryotes with a cell wall, usually composed primarily of chitin. Fungi are heterotrophs that absorb nutrients from their surroundings after decomposing organic material. They reproduce by unicellular spores produced sexually and/or asexually.

**Isolate.** A purified constituent of a defined molecular structure obtained from a plant or a plant material, an alga, a bacterium, a fungus or a non-human animal material.

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

**Marker compound.** A constituent that occurs naturally in the material and that is selected for special attention (e.g., for identification or standardization purposes) by a researcher or manufacturer. Marker compounds are not necessarily pharmacologically active.

**Mineral.** Natural minerals are naturally occurring solid, inorganic substances with a definite and predictable chemical composition and physical properties. Synthetic minerals are produced by synthesis.

**Non-human animal material.** A body part or secretion obtained from an animal other than humans that is used to prepare a NHP, including attenuations used in homeopathic medicine. For homeopathic medicines, non-human animal materials must be listed in one of the homeopathic pharmacopoeias of the United States, France, Germany or Europe.

**Organic.** A labelling and advertising term denoting a plant or plant material, alga, fungus or non-human animal material certified to have been produced in accordance with the production, processing, packaging, storage and distribution provisions of the National Standard of Canada for Organic Agriculture. Certification according to other organic standards is also acceptable. Products not within the scope of agricultural standards (e.g., aquatic non-human animal material, alga, cyanobacteria (“blue algae”))



must be certified to have been produced in accordance with an aquacultural or other applicable organic standard.

**Plant.** A member of the biological kingdom Plantae, consisting of complex multicellular eukaryotes with a cell wall composed primarily of cellulose. Plants produce their own food by photosynthesis using chlorophylls a and b (secondarily lost in parasites), are mostly terrestrial and have multicellular reproductive structures producing dependent embryos.

**Potency.** The amount per dosage unit of the standardized component(s), which helps characterize the quantity of the ingredient. It must be provided only when a potency claim appears on the product label or when the literature supports a specific product with that standardized component.

**Primary molecular structure.** The chemical structure of a substance isolated from a plant or a plant material, an alga, a bacterium, a fungus, or non-human animal material, obtained in its original, unaltered form.

**Probiotic.** A monoculture or mixed culture of live microorganisms, which when administered in adequate amounts, confers a health benefit in humans.

**Product licence applicant.** An individual with legal ownership of and responsibility for the NHP. The product licence applicant may be located in or outside of Canada. Applicants who are located outside of Canada must identify a Canadian representative.

**Proper name.** In respect of an ingredient of a NHP, one of the following:

(a) if the ingredient is a vitamin, the name for that vitamin set out in item 3 of Schedule 1 (*Natural Health Products Regulations*, 2003);

(b) if the ingredient is a plant or a plant material, an alga, a bacterium, a fungus, a non-human animal material or a probiotic, the Latin nomenclature of its genus and, if any, its specific epithet; and

(c) if the ingredient is other than one described in paragraphs (a) or (b), the chemical name of the ingredient.

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

**Specifications.** Quality standards referred to in the proposed Regulations and which describe tests and methods (analytical and biological), tolerances and/or acceptance criteria which are numerical limits, ranges or other criteria for the tests described. Specifications establish the criteria to which a finished product must conform in order to be considered acceptable for its intended use.

**Standardization.** The application of product knowledge, good agricultural or wildcrafting practices, and good manufacturing practices to minimize inherent variations in the composition of natural substances in order to ensure a consistent product from one batch to the next.

**Synthetic duplicate.** A substance that shares an identical chemical structure and pharmacological properties with its natural counterpart. “Natural” means a product that is isolated or comes from a natural source (e.g., plant or mineral). “Synthetic” means a product that is chemically produced. For example Epinephrine is a synthetic duplicate of the epinephrine produced by the human body.

**Vitamin.** Naturally occurring organic substances required in small amounts by the body to maintain health.

## APPENDIX 2. SCHEDULE 1 OF THE NATURAL HEALTH PRODUCTS REGULATIONS

Schedule 1 (*Subsection 1(1)*)

Includes Natural Health Product Substances

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

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<sup>1</sup> Vitamin K (K1 & K2) has been recently added to the list of acceptable vitamins with a maximum permissible limit of 120 µg.

## APPENDIX 3. QUALITY REQUIREMENTS OF MEDICINAL INGREDIENTS USED IN HOMEOPATHIC MEDICINE

Test Parameters	Test	Method(s)	Tolerances Limits
Identity (raw material)	Chemical fingerprinting	TLC, HPTLC or HPLC or GC, and/or spectroscopic	Characteristic for the item
Purity Microbial contaminants (Finished product)	Contaminating fungus (yeast and mould)**	Pharmacopoeial or WHO	< 1 X 10 <sup>4</sup> CFU/g or mL
	Total Aerobic Count**	Pharmacopoeial or WHO	< 1 X 10 <sup>5</sup> CFU/g or mL
	<i>Escherichia coli</i> **	Pharmacopoeial or WHO	Absent
	<i>Salmonella</i> spp.**	Pharmacopoeial or WHO	Absent
	<i>Staphylococcus aureus</i> **	Pharmacopoeial or WHO	Absent
	<i>Pseudomonas aeruginosa</i> **	Pharmacopoeial or WHO	Absent
Purity Chemical contaminants (Raw material/Finished product)	Arsenic	Pharmacopoeial or WHO	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or WHO	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or WHO	<0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or WHO	<0.29 µg/kg b.w./day
	Pesticides	Pharmacopoeial or WHO	
	Mycotoxins	AOAC-International (Association of Analytical Chemists)	Aflatoxins < 20 ppb

\*\* Microbial tests are not required when the finished product is available in a solvent containing equal to or greater than 50% ethanol.

*Pseudomonas aeruginosa* test is only required for the finished products in liquid form.

Preservative efficacy should be demonstrated at the end of the shelf-life for homeopathic products in liquid form unless they are sterile products and packaged in a single-dose format.

## APPENDIX 4. ACCEPTABLE LIMITS FOR MICROBIAL AND CHEMICAL CONTAMINANTS

Table 1. Acceptable limits for microbial contaminants in finished products

Schedule 1 List Item	Contaminating Fungus	Total viable aerobic count	<i>E. coli</i>	<i>Salmonella</i> spp.	<i>S. aureus</i>	<i>Enterobacteriaceae</i>	<i>P. aeruginosa</i>
1	$< 1 \times 10^4$	$< 1 \times 10^5$ N/A** for bacteria	Absent for all internal use except for teas, decoctions or topical dosage form: $< 1 \times 10^2$	Absent	$< 1 \times 10^2$ for all internal use except for teas, decoctions or topical dosage forms: $< 1 \times 10^4$	N/A (except for bacteria: $< 1 \times 10^2$ )	N/A
2	$< 1 \times 10^4$	$< 1 \times 10^5$	Absent	Absent	Absent	N/A (except for enzymes $< 1 \times 10^2$ )	Absent
3	$< 3 \times 10^2$	$< 3 \times 10^3$	Absent	Absent	Absent	N/A	Absent
4	$< 3 \times 10^2$	$< 3 \times 10^3$	Absent	Absent	Absent	N/A	Absent
5	$< 1 \times 10^4$	$< 1 \times 10^5$	Absent	Absent	Absent	N/A	Absent
6	$< 3 \times 10^2$	$< 3 \times 10^3$	Absent	Absent	Absent	N/A	Absent
7	$< 3 \times 10^2$	$< 3 \times 10^3$	Absent	Absent	Absent	N/A	Absent
8	$< 1 \times 10^4$	N/A	Absent	Absent	Absent	$< 1 \times 10^2$	N/A

\*\* N/A: not applicable

### Notes:

- Units are in Colony Forming Units (CFU) per gram or per millilitre.
- Absent means  $< 1 \times 10^1$  CFU/g or CFU/mL for Total viable aerobic count, *Enterobacteriaceae* and Yeast and Mould count, not detected in 10 g or 10 mL for *Salmonella* spp. and not detected in 1 g or 1 mL for *E. coli*, *P. aeruginosa* and *S. aureus*
- For a multi-component product, the tolerance limits for the finished product would generally be based on the least stringent limit.

**Table 2. Acceptable limits for chemical contaminants**

Contaminants	Tolerance Limits
Arsenic	< 0.14 µg/kg b.w./day
Cadmium	< 0.09 µg/kg b.w./day
Lead	< 0.29 µg/kg b.w./day
Total mercury	< 0.29 µg/kg b.w./day
Mycotoxins (when applicable)	Aflatoxins: < 20 µg/kg (ppb) of substance
Solvent residues (when applicable)	ICH or Pharmacopoeial limits
Related substances and process impurities (when applicable)	No undeclared impurity, Pharmacopoeial limits (as per monograph for medicinal ingredient or finished product)
Pesticides (when applicable)	Pharmacopoeial limits
Specific toxins (when applicable)	PCDDs & PCDFs < 2 pg/kg b.w./day PCBs < 0.13 µg/kg b.w./day
Radioactivity (if suspected)	600 Becquerels/kg of substance
Antibacterial activity (for microbiologically- derived enzymes)	None

Oxidative Stability Tests for fish/seal oil	Peroxide Value (PV)	AOCS Official Method Cd 8-53	max. 5 mEq/kg
	<i>p</i> -Anisidine Value (AV)	AOCS Official Method Cd 18- 90	max. 20
	Totox Value		max. 26 (calculated as 2 x PV +AV)

# APPENDIX 5. CALCULATIONS

## (a) Chemical Contaminants

### Example of calculation for lead content of a finished NHP intended for adults:

Weight of Tablet: 250 mg

Recommended dosage: 2 tablets/ 3 times per day

Amount of lead in the product: 0.002 mg Pb/g (2 ppm) of product

Amount of Pb consumed per day: 0.003 mg or 3 mcg

Amount of Pb consumed per day based on body weight: 0.043 mcg/kg b.w/day (NHPD tolerance limit 0.29 mcg/kg b.w/day)

Notes: This calculation assumes a body weight of 70 kg for an average adult. If the dosage is intended for children, the appropriate body weight for the age of the child in the recommended use or purpose should be used.

## APPENDIX 6. LIST OF ACCEPTABLE DOSAGE FORMS

Aerosol	Powder for Solution
Aerosol, Metered-Dose	Powder for Suspension, Extended Release
Bar, Chewable	Powder for Suspension
Bulk / Loose	Powder, Metered Dose
Capsule	Shampoo
Capsule, Combined Release	Soap, Bar
Capsule, Delayed Release	Soap, Liquid
Capsule, Extended Release	Solution
Cream	Solution, Extended Release
Cream, Liposomal	Sponge
Compact	Spray
Concealer	Spray, Metered Dose
Dentifrice, Gel	Stick
Dentifrice, Paste	Strip
Douche	Succus
Dressing	Suppository
Elixir	Suppository, Extended Release
Emulsion	Suspension
Enema	Suspension, Liposomal
Floss	Syrup
Fluid Extract	Syrup, Extended-Release
Foundation	Tablet
Gel	Tablet, Chewable
Gel, Extended Release	Tablet, Combined Release
Globules	Tablet, Delayed Release
Granule	Tablet, Effervescent
Granule, Effervescent	Tablet, Extended Release
Granule, Delayed Release	Tablet, Rapid Dissolving
Gum, Chewing	Tea, Herbal
Jam	Tincture
Kit	Vapour from Liquid
Lotion	Vapour from Solid
Lozenge	Wafer
Makeup	Wipe
Mouthwash / Gargle	
Ointment	
Pad	
Paste	
Patch	
Patch, Extended-Release	
Pellet	
Pencil	
Piece, Chewable	
Plaster	
Powder	
Powder, Effervescent	
Powder, Delayed Release	
Powder for Gel	



## APPENDIX 7. FINISHED NATURAL HEALTH PRODUCT SPECIFICATION TEMPLATE

Name of the Finished Product: \_\_\_\_\_

Name of Manufacturer of Finished Product: \_\_\_\_\_

Assessment Criteria		Test	Test Method	NHPD's Accepted Tolerance Limits	
<b>Identity</b>		Physical Description (e.g., shape, colour)			
		Chemical identification of the medicinal ingredient (e.g., HPLC)		May be tested at the raw material stage if justified.	
<b>Performance tests</b>		Disintegration and/or Dissolution (when applicable)		$\leq 45$ min (uncoated) $\leq 60$ min (plain coated) Dissolution profile to be provided for controlled-release products Enteric coated tablets to be tested in accordance with the pharmacopoeia (USP or Ph.Eur.)	
		Particle Size Distribution, (if applicable, e.g., tea)			
<b>Purity</b>	Chemical Contaminants	Arsenic		$< 0.14 \mu\text{g} / \text{kg b.w./day}$	
		Cadmium		$< 0.09 \mu\text{g} / \text{kg b.w./day}$	
		Lead		$< 0.29 \mu\text{g} / \text{kg b.w./day}$	
		Total Mercury		$< 0.29 \mu\text{g} / \text{kg b.w./day}$	
		Specific tests for fish oil, when applicable	PCDDs, PCDFs		Dioxins $< 2 \mu\text{g}/\text{kg b.w./day}$ ; Pharmacopoeial
			PCBs		PCBs $< 0.13 \mu\text{g}/\text{kg b.w./day}$
		Oxidative Stability Tests for fish oil	Peroxide Value (PV)		$\leq 5 \text{ mEq}/\text{kg}$
			<i>p</i> -Anisidine Value (AVI)		$\leq 20$
			Totox Value		$\leq 26$ (calculated as $2 \times \text{PV} + \text{AVI}$ )

Assessment Criteria		Test	Test Method	NHPD's Accepted Tolerance Limits
		Pesticides (if applicable)		Pharmacopoeial or WHO
		Mycotoxins or aflotoxins when applicable		Aflatoxins: < 20 µg/kg (ppb) of substance
		Solvent Residues (when applicable)		ICH Q3C or pharmacopoeial
		Other impurities (Product and/or process related impurities, <i>if applicable</i> (e.g., co-extracted substances, inactive isomers, degradation product, intermediate product, reagents, catalysts)		Pharmacopoeial limits
		Loss on Drying (for plant materials, e.g., herbs as such and tea)		Pharmacopoeial limits
		Foreign Matter (for plant materials, e.g., herbs as such and tea)		Pharmacopoeial limits
		Ash Contents (for plant materials, e.g., herbs as such and tea)		Pharmacopoeial limits
	Microbial Contaminants	Total Viable Aerobic Count	Pharmacopoeial	as per Table 1, Appendix 3 of the Quality guidance document
		Contaminating fungus (Yeast & Mold)		
		<i>Escherichia coli</i>		
		<i>Salmonella spp.</i>		
		<i>Staphylococcus aureus</i>		
		<i>Enterobacteriaceae</i> (for enzymes and probiotics)		
<i>Pseudomonas aeruginosa</i> (if product is in liquid form and <50% aqueous)				

Assessment Criteria	Test	Test Method	NHPD's Accepted Tolerance Limits
	<i>ethanol</i> )		
	Other indicator organisms (when applicable)		
<b>Quantity/Potency</b>	Quantity (e.g., weight in mg) of each medicinal Ingredient per dosage unit		As per Section 2.5
	Tablet/Capsule weight variation		Pharmacopoeial limits

## APPENDIX 8. PHYSICAL TESTS REQUIRED FOR DIFFERENT DOSAGE FORMS

Dosage Form	Description	Disintegration or Dissolution	Dissolution	Weight Variation	Average Weight	Uniformity of Dosage Unit	Preservative Efficacy <sup>1</sup>	Adhesive Strength	Peel Force
Tablet, Caplet, Capsule, etc. <sup>2</sup>	X	X		X	X				
Tablet, rapid dissolving	X		X	X	X				
Tablet or Capsule, sustained <sup>3</sup> release	X		X	X	X	X			
Tablet or Capsule, delayed <sup>4</sup> release	X	X		X	X				
Oral solutions and suspensions	X						X		
Topical Preparations	X						X		
Transdermal Patches	X					X		X	X

<sup>1</sup> This test is not generally included in the routine specifications, but is tested during development and during stability studies.

<sup>2</sup> This includes all immediate release dosage forms except those which state or imply a rapid onset or rapid release of the medicinal ingredient.

<sup>3</sup> Sustained release dosage forms include extended release, combined release, timed release dosage forms.

<sup>4</sup> Extended release dosage forms include enteric coated tablets and capsules.