

As part of the Natural Health Products Directorate's (NHPD's) ongoing commitment to continuous improvement, the previously published guidance document titled "Evidence for Quality of Finished Natural Health Products" is being replaced with the proposed "Quality of Natural Health Products Guide". The focus of this new guide is to point to tools and approaches that can be leveraged by applicants to achieve a compliant outcome. It is the responsibility of the product licence applicant to ensure that finished product specifications will be established in accordance with the requirements described in the guidance document and attest to ensure that all information is documented, maintained, relevant, accurate and sufficient to support the quality of their NHP(s). Any documentation that is not requested at the time of review could be requested by NHPD at any time.

This guide is to be read in conjunction with all other documents that outline requirements for good manufacturing practices of NHPs.

DRAFT: QUALITY OF NATURAL HEALTH PRODUCTS GUIDE

Natural Health Products Directorate

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“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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Contact the Natural Health Products Directorate

Natural Health Products Directorate
Health Canada
2936 Baseline Rd., Tower A
Ottawa, Ontario
K1A 0K9

www.healthcanada.gc.ca/nhp

Fax: (613) 948-6810

Email: pla.info.dlmm@hc-sc.gc.ca

FOREWORD

This guide has been developed with a goal of providing assistance to industry and health care professionals on how they can assure high quality natural health products (NHPs) through the application of key policies, processes and regulatory requirements. It also serves to provide guidance to Health Canada employees, thereby ensuring transparency, fairness, and consistency in how quality standards are assessed.

Guidance documents are tools to assist stakeholders and do not have the force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document will be acceptable if they support an equivalent outcome resulting in high quality NHPs.

This guide also attempts to clarify expectations of regulated parties and to highlight potential approaches to assist regulated parties in meeting pertinent requirements to assure the quality of NHPs in Canada. The approaches and methods outlined in this document are to provide a clear pathway for the quality components of the product licence application, and are not intended to be seen as the only way to meet those requirements. By providing information to Health Canada regarding the quality of NHPs, product licence applicants are attesting to the truthfulness, accuracy and effectiveness of that information. This information may be reviewed utilizing a risk-based approach that ensures that core components of the application are reviewed that relate to safety, while promoting a timely and efficient application review process. Where applicable, links between requirements for product testing and good manufacturing practices (GMP) requirements have been clarified.

This document should be read in conjunction with the relevant sections of other applicable guidance, including the Pathway for Licensing Natural Health Products Making Modern Health Claims and the Pathway for Licensing Natural Health Products Used as Traditional Medicines, including any relevant annexes.

SECTION 1. INTRODUCTION	5
1.1 Purpose	5
1.2 Background	5
1.3 Scope	5
1.4 Roles and Responsibilities	6
1.5 General Overview - The Product Licence Application (PLA)	7
1.5.1 Products Referencing NHPD Monographs	7
1.5.2 NHPD Finished Product Specification Form	7
1.5.3 Specifications	8
1.5.4 Acceptable Pharmacopoeia	8
1.6 Natural Health Products Ingredients Database	9
SECTION 2. CHARACTERIZATION, IDENTIFICATION AND QUANTIFICATION STANDARDS	9
2.1 Characterization	9
2.1.1 Chemicals	9
2.1.2 Processed Ingredients	9
2.1.3 Extracts	10
2.1.3.1. Standardized Extracts	10
2.1.3.2. Fortified Extracts	11
2.2 Identification Tests	11
2.2.1 Appropriate Identification of Botanical Products	11
2.2.1.1 Techniques for Identification of Botanical Products	12
2.2.2 Appropriate Identification of Specific Medicinal Ingredients	13
2.2.3 Identity Testing on the Finished Product	13
2.3 Quantity	13
2.3.1 Quantification by Assay	14
2.3.1.1 Botanical Ingredients Including Extracts	14
2.3.1.2 Vitamins and Minerals	14
2.3.1.3 Isolates and Synthetic duplicates	14
2.3.1.4 Live Microorganisms	15
2.3.1.5 Enzymes	15
2.3.2 Quantification by Input	15
SECTION 3. PURITY STANDARDS	16
3.1 Microbial Contaminants	16
3.1.1 Microbial Contamination Requirements for Specific Products and Routes of Administration	17
3.1.1.1 Plants, Algae, Fungi or Animal Materials in Oral Dry Dosage Form	17
3.1.1.2 Products Containing Live Microorganisms in Dry Oral Dosage Form	17
3.1.1.3 Products in Liquid Dosage Form	18

3.1.1.4 Sterile Products	18
3.2 Chemical Contaminants	18
3.2.1 Elemental Impurities	18
3.2.1.1 Arsenic	19
3.2.1.2 Chromium VI	19
3.2.1.3 USP <231> Total Heavy Metals	20
3.2.2 Topical Products.....	20
3.3 Other Impurities	21
3.3.1 Mycotoxins (e.g., Aflatoxins)	21
3.3.2 Cyanobacterial Toxins (e.g. Microcystins)	21
3.3.3 Solvent Residues	21
3.3.4 Hormone Testing of Animal Materials	22
3.3.5 Enzyme Preparations	22
3.3.6 Incidental Impurities, Related Substances and Process Impurities	22
3.3.7 Pesticide Residues.....	22
3.3.8 Contaminants in Oils of Animal Origin.....	23
3.3.9 Antibiotic Residues in Bee Products.....	23
3.3.10 Radioactivity	24
3.3.11 Oxidative Stability in Oils	24
3.3.12 Probiotics	24
3.3.13 Potential Adulterants in Natural Health Products.....	25
3.3.14 Ingredients sourced from tissues that are susceptible to transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE).....	25
SECTION 4. SPECIFIC TESTS AND CRITERIA FOR FINISHED PRODUCTS	25
4.1 General Indicators for Quality	26
4.1.1 Foreign Matter	26
4.1.2 Determination of Acid Insoluble Ash.....	26
4.1.3 Water Content	26
4.1.4 Non-Medicinal Ingredients.....	26
4.2 Performance Tests.....	26
4.2.1 Disintegration	26
4.2.2 Dissolution.....	27
4.2.3 Uniformity of Dosage Units.....	27
4.3 Standards for Specific Finished Products	27
4.4 Standards for Homeopathic Medicines	27
4.5 Analytical Testing and Requirements to Support Label Claims.....	28
4.5.1 Organic Products	28
4.6 Reduced Testing Schedules that are Captured on Specifications	28

4.7	Antimicrobial Effectiveness Testing	28
4.8	Stability Testing.....	28
SECTION 5. REFERENCES.....		30
5.1	Health Canada Documents and Databases:	30
5.2	International Documents	30
SECTION 6. GLOSSARY		34
APPENDIX 1. CALCULATIONS.....		38
APPENDIX 2. PHYSICAL TESTS REQUIRED FOR DIFFERENT DOSAGE FORMS		40

SECTION 1. INTRODUCTION

1.1 Purpose

This guidance document is intended to provide direction to support stakeholders in assuring that natural health products (NHPs) are produced in a high quality manner, and to set out how an applicant or licensee can establish an acceptable level of compliance to the *Natural Health Products Regulations* (NHPR), as it relates to the quality requirements for NHPs.

The quality component of a product licence application is primarily founded on the expectation of industry to provide all pertinent information, and to attest to the truthfulness, accuracy and sufficiency of that information, as to how its product(s) meet the quality requirements found in the NHPR. The review of this information may employ a risk-based approach that focuses on those elements of the application that most directly relate to safety, and to assure an application review process that meets its published performance standards (see Application Management Policy).

This document provides examples of appropriate approaches to ensure quality NHPs through following applicable requirements. Alternate approaches to the principles and practices described in this document, or any other approaches to comply with expectations outlined in this guidance may be acceptable provided they support quality NHPs as the end result. The expectation is that the product licence holder has all pertinent information to ensure regulatory requirements are met, that they are submitted or attested to (as the case may be) at the time of application for a licence and subsequently maintained following product licensing.

1.2 Background

As a result of consultations and experience gained by scientific reviewers/assessment officers and submission coordinators at the NHPD, the Evidence for Quality of Finished Natural Health Products Guidance Document has been revised and replaced with the Quality of NHPs Guidance Document. This guide outlines expectations and approaches to assure the quality of NHPs authorized for sale in Canada. The approaches and methods outlined in this document are intended to provide a clear pathway for the quality components of the product licence application, and are not intended to be seen as the only way to meet requirements. Alternate approaches and methods can be utilized if the outcome remains a high quality NHP. Following the guidance document provides the surest pathway to meeting quality requirements for NHPs. Where applicable, links between requirements for product testing and Good Manufacturing Practices (GMP) requirements have been clarified.

1.3 Scope

Unless otherwise stated, the quality expectations outlined in this document apply to all types of NHPs that fall under the purview of the Regulations, including applications made through the compendial review stream. This document should be read in conjunction with other NHPD guidance documents, in particular the Pathway to Modern NHPs, the Pathway to Traditional NHPs (and their annexes), Site Licensing Guidance Document, Good Manufacturing Practices Guidance Document, Evidence for Homeopathic Medicines, and any other applicable guidance,

to ensure the expectations for product quality are understood and applied. Further, reference has been made to a number of national and international sources of standards, such as the United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.), and Therapeutic Goods Administration of Australia (TGA). It is recommended that these sources be consulted to meet product quality expectations.

Requirements and standards relating to specific ingredients, products and/or dosage forms have also been included where they differ from or are additional to the general standards. While exemptions for testing of NHPs are not the rule, they may be appropriate in some circumstances if supported by an alternative method supporting an equivalent outcome.

This document can be utilized as a starting point for products being manufactured for use in clinical trials, though applicants seeking authorization for a clinical trial should also consult the guidance document “Clinical Trials for Natural Health Products”.

1.4 Roles and Responsibilities

The product licence holder is ultimately responsible for ensuring the quality of their licenced NHP, and for the establishment of the product specifications, as per section 44 of the NHPR. Although GMP Requirements under Part 3 of the NHPR do not specifically refer to product licence holder responsibilities, section 43 does indicate that no person shall sell an NHP unless it is manufactured, packaged, labelled, imported, distributed or stored in accordance to GMPs. As per section 5(j) of the NHPR, the product licence applicant is required to confirm this responsibility by providing an attestation (in the PLA) that the product will be manufactured, packaged, labelled, imported distributed and stored in accordance to GMPs. It is the responsibility of the product licence holder to ensure that the product is handled in such a way as to ensure the product's stability to the end of its shelf- life.

It is recognized that the product licence holder may rely on another party to produce the NHP, including establishment of the specification and testing the product for release and stability. As such, clear roles and responsibilities for developing and maintaining data and records should be established when the product licence holder or applicant relies on a third party to provide this information. Documentation should be kept by the product licence holder that clearly defines the responsibilities between themselves and the contracted third parties. Such documentation may include the following:

1. A valid quality technical agreement (excluding any financial information) between the manufacturer/ importer and/or the contracted third party or product licence holder that is signed and dated by the parties involved, and clearly states who is responsible for developing and maintaining the appropriate information/data, and/or performing any key functions for the regulatory compliance of the product that have been delegated by the product licence holder to another party.

Data (e.g. specifications, testing, studies or standard operating procedures) should be available to Health Canada upon request, but may be made available through a master file from the originator of the documentation (manufacturer, contractor, product licence holder, etc.)

1.5 General Overview - The Product Licence Application (PLA)

In accordance with Part 1, s. 4, 5 and 7 of the NHPR, a product licence is required to sell a NHP. To obtain a product licence, an application must be submitted to the NHPD, and include information documenting that the NHP is safe, effective and of high quality. Information required to be submitted in support of the quality of the NHP includes, as per s. 5 (i), a copy of the specification to which the product will comply. The submission of a signed Product Licence Application (PLA) form will be regarded as an attestation acknowledging the licence holder's responsibility to meet the requirements set out in the NHPR and associated guidance documents relating to quality and Good Manufacturing Practices.

The quality component of a product licence application is primarily founded on the expectation of industry to provide all pertinent information, and to attest to the truthfulness, accuracy and sufficiency of that information, as to how its product(s) meet the quality requirements found in the NHPR.

When submitting a product license application, it is the applicant's responsibility to ensure that any alternative tests or adopted limits are scientifically justified and assures an equivalent or more stringent outcome.

After an application has been submitted and screened for completeness, the NHPD may assess the information provided by the applicant using a risk-based approach focusing on the components of the application that may impact the safety of the finished product.

Finished product specifications, testing activities and their documentation will be required as a component of site licensing and GMP assessment activities of the NHPD. In particular, the site licence component may assess the application of appropriate processes and methodologies and documented outcomes of these tests, such as for microbial and heavy metal testing, to ensure the high quality attested to in the product licence application.

1.5.1 Products Referencing NHPD Monographs

Where an NHPD monograph exists for an ingredient, the specification section of the monograph should be consulted to determine whether or not specific tests for the ingredient or the finished product are required. The Natural Health Products Ingredients Database (NHPID) also lists specific requirements for ingredients when the NHPD has determined additional requirements are necessary. These test parameters and acceptance criteria should be applied to the specifications, unless alternative methods have been provided with a justification to ensure the same outcome.

1.5.2 NHPD Finished Product Specification Form

NHPD's Finished Product Specifications (FPS) form was developed as a tool to help applicants comply with the quality requirements set out in Section 44 of the NHPR. The FPS form and user guide are available for download from the Guidance Document section and the Forms and Templates section of the NHPD website.

1.5.3 Specifications

A specification is defined as a list of tests, references to analytical or physical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a NHP should conform to be considered acceptable for its intended use. Specifications are critical quality standards that are provided in the PLA and are part of the conditions of market authorization. Conformity of product lots with these specifications should be assessed by the person responsible for Quality Assurance, who signs and dates the lot release.

In accordance with section 44 (2) of the Regulations, the product specification shall contain tests describing the identity and quantity of each medicinal ingredient in the NHP, the purity of the NHP, the potency (if applicable), as well as the associated acceptance criteria for each test. Chapters 2, 3, and 4 of this document describe the test parameters, analytical procedures and acceptance criteria that the finished product specifications should contain in order to meet an acceptable level of compliance with the specifications requirement (i.e. the quality standards that NHPs are expected to meet).

1.5.4 Acceptable Pharmacopoeia

The following pharmacopoeias and international standards are currently considered acceptable by the NHPD:

- United States Pharmacopeia (USP)
- British Pharmacopoeia (BP)
- European Pharmacopoeia (Ph. Eur.)
- Pharmacopée française (Ph.f.)
- Pharmacopoeia Internationalis (Ph.I.)
- Japanese Pharmacopoeia (JP)
- Food Chemicals Codex (FCC)

Product Licence Holders should consult the Evidence for Homeopathic Medicines Guidance Document for acceptable pharmacopoeias for homeopathic medicines.

It is expected that if a monograph is published in one of these pharmacopoeias, the pharmacopoeial monograph specifications should be considered as minimum specifications used for testing of the medicinal ingredient and finished product. If the specifications do not include tests and acceptance criteria as per the monograph, there should be justification as to why the testing is not necessary. The current official version of the pharmacopoeia should be used in all cases. In order to comply with pharmacopoeial monographs, the monograph in its entirety should be applied, including all other pharmacopoeial requirements. It is not acceptable to apply requirements from different pharmacopoeial monographs unless the monographs are harmonized or there is a suitable rationale for the mixing of pharmacopoeial standards. The product should also meet all definitions in the pharmacopoeia and general chapter being used to determine criteria.

It should be noted that the European Pharmacopoeia only includes monographs for raw materials. If applicants attest to meeting one of these pharmacopoeias, then the monograph to which the applicant is attesting to should be clearly identified and any additional testing that

must be performed should be clarified or the applicant should have documented the scientific justification as to why the additional testing is not required.

In general, the NHPD supports leveraging published specifications, test methods and acceptable limits from the above international pharmacopoeias. When this document does not include differentiated specifications for a particular test, the NHPD considers the limits prescribed in any one of the above pharmacopoeias to be acceptable. Applicants are advised to consult these pharmacopoeias for details about test methods and acceptable limits. If pharmacopoeial limits are less stringent from those specified by the NHPD, the applicant should choose the standard that is most suitable for supporting a high quality NHP. When proposing limits less stringent than those specified in this guidance, they should be scientifically accurate and justifiable.

The NHPD accepts the use of alternate methods that meet with pharmacopoeial requirements. When alternate methods are used for testing to meet pharmacopoeial specifications, the relevant pharmacopoeia should be consulted for information on whether or not the alternate methods are considered suitable.

1.6 Natural Health Products Ingredients Database

Additional guidance for medical and non-medicinal ingredients can be found in the Natural Health Products Ingredients Database (NHPID) <http://webprod.hc-sc.gc.ca/nhp-id-bdipsn/search-rechercheReq.do> [Accessed 2012-06-28].

SECTION 2. CHARACTERIZATION, IDENTIFICATION AND QUANTIFICATION STANDARDS

2.1 Characterization

Characterization is the determination of distinguishing features and special qualities of a medicinal ingredient using a variety of physical and/or chemical techniques. The NHPD requires information on the characterization of medicinal ingredients in order to adequately evaluate the evidence for their identity and the safety and efficacy of the NHP.

2.1.1 Chemicals

Highly purified ingredients, such as isolates and synthetic duplicates, should be described by the chemical name of the entire ingredient, e.g. the name should include the salt or hydrated moieties and not just the name of the active moiety.

2.1.2 Processed Ingredients

For ingredients such as extracts, characterization can be defined by the methods and controls used to process the ingredient. There should be adequate quality control measures put in place at all stages of the manufacturing process in order to ensure batch-to-batch consistency.

a. Process characterization of crude materials

- Crude materials can be characterized by how they were obtained as well as how the materials were harvested and cleaned. For further details see the Good Agricultural and Collection Practices (GACP) guidelines cited below.
- Additional characterization can be defined by the processing after harvesting/purifying (i.e. - whether the materials were dried or kept fresh, whether the materials were kept whole, cut or powdered.)
- Characterization of identity, purity and stability of the crude material is of considerable importance especially when crude materials are added to finished products directly, without further processing.

b. Process characterization for highly processed ingredients

- Characterization should include a full description of how the materials were processed.
- Characterization of probiotics includes culture conditions such as strain viability, specific media used for growth, growth temperatures, growth times, cell collection, etc.
- Substances that are processed or chemically modified after purification of the active ingredient(s) are considered different medicinal ingredients from the original extract. For example, processes such as fermentation, esterification to decrease acid lability, hydrolyzation to increase solubility or bioactivity, or stabilization by conversion to a salt form all result in the production of a different ingredient.

2.1.3 Extracts

The NHPD requires manufacturers to adopt processes that serve to optimize the batch-to-batch consistency of a raw material, ingredient, or product.

2.1.3.1. Standardized Extracts

In some cases, the process may involve identifying specific chemicals (also known as markers) that can be used to help manufacture a consistent product. Markers are chemically defined constituents or groups of constituents that can be used to control batch-to-batch consistency of the finished product whether or not they have any therapeutic activity. They are classified as follows:

- **Active constituent marker:** A known and generally accepted constituent or group(s) of constituents that contribute to therapeutic activity. The product can be adjusted by standardization to a level of active constituent marker that is reproducible – either to a level that is naturally found in the plant or to a more concentrated level in an extract.
- **Analytical marker:** A constituent or group(s) of constituents that serve solely for analytical purposes and do not contribute to therapeutic activity, to which the product is adjusted to achieve a reproducible composition.

NHPD refers to a product as ‘standardized’ if it is manufactured to consistently meet a predetermined concentration of a specific marker or set of markers.

Specifications for standardized products should include identity, quantity of declared components (if applicable) and impurities (e.g. degradation products) and testing for likely contaminants (e.g. incidental compounds, residual solvents).

An extract can be partially characterized by its specifications and the ratio of the quantity crude equivalent of the whole herb to the quantity of the extract. For a liquid extract, a ratio of 1:5 means that 1 g of crude material was used to prepare 5 mL of extract and for a solid extract a ratio of 5:1

means that 5 g of crude material was used to prepare 1 g of extract, i.e. the first number in the ratio is always the proportion of crude material and the second number is always the proportion of extract.

When a marker compound is being quantified, NHPD assumes for the purpose of setting finished product and raw material specifications that the marker is an active or a co-active, and therefore acceptance criteria for quantification should be set such that there is an upper and a lower limit. NHPD accepts limits of 80.0 - 120.0% to allow for natural variation. If wider limits are proposed, adequate documentation should be provided to support wider limits which are tied to the natural variation of the marker and scientific knowledge about the effect on safety and efficacy of variation in the marker.

If there is evidence that the marker is used for quality control purposes only, then specifications which include a lower acceptance limit only would be acceptable. However, the content of the marker should not appear on the product label under these circumstances as this is considered misleading to the public. This information should be made available on request.

2.1.3.2. Fortified Extracts

Fortified extracts are acceptable when the amount of component that is added to the extract is declared as a separate medicinal ingredient.

Applicants can learn more about extract types in documents published by other regulatory authorities such as the EMA document "Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products" (March 11, 2010). Note that terminology varies among these documents.

2.2 Identification Tests

The approach to and amount of identity testing required is dependent on the type of ingredient. The tests employed should be specific enough to distinguish the correct ingredient/plant species and plant part(s) from likely adulterants. Testing techniques should be specific for the substance and based on unique aspects of the ingredient and may be performed at the raw material or finished product stage.

It is necessary to implement controls at all stages of the production process (i.e. growth, harvest and processing) in the following cases:

- A medicinal ingredient where the constituents responsible for the biological activity are unknown.
- A chromatographic fingerprint cannot be established.
- Due to the complex nature of the finished product.

GACP and Good Manufacturing Practices (GMP) should be applied to the supply chain to ensure adequate identification, quality control and batch-to-batch consistency.

2.2.1 Appropriate Identification of Botanical Products

In order to identify botanicals unambiguously, manufacturers should follow GACP for plant identification. Several principles which should be followed by growers and collectors of plant materials to ensure plant identification and authentication are included in several detailed

documents. Refer to “Good practices for plant identification”, “World Health Organization Good Agricultural and Collection Practices Guidelines” and “American Herbal Products Association-American Herbal Pharmacopoeia Good Agricultural and Collection Practice for Herbal Raw Materials” for details. Full citations for these documents are included in the reference section. The recommended identification procedures for botanical ingredients are dependent on the form of the plant and the stage of manufacture.

With respect to extracts, valid chemical assay analytical methods such as those set out in pharmacopoeial monographs in comparison with reference standards are relevant as identification techniques when there is a complete lack of morphological characteristics. An extract of a plant is not the same as the whole plant material; rather it is derived from the plant and defined by the nature of the solvent used and the physical conditions under which the extraction is performed. Therefore complete identification of extracts should include details of the manufacturing process. Extracts should also have consistent batch-to-batch organoleptic characteristics.

2.2.1.1 Techniques for Identification of Botanical Products

1. **Macroscopic/Organoleptic techniques:** These techniques include defined morphological and anatomical characteristics of the whole plant or plant part; colour, fracture, smell, taste, etc.. References to floras and field guides and comparison to voucher specimens can be used if flowering plant specimens can be obtained. These characteristics are determined at the raw material stage, before the original form of the material is changed during the production process; therefore qualification of suppliers is necessary to ensure control of the supply chain.
2. **Microscopic techniques:** Use of high magnification and special light or staining techniques are required to examine for characteristics established for the ingredient. These examinations should be compared to authenticated or in-house reference materials and/or authoritative technical descriptions (e.g. Ph.Eur.).
3. **Chemical identification:** These techniques include methods such as chromatography, spectrometric, gravimetric, capillary electrophoresis, DNA fingerprinting, Fourier Transform InfraRed spectroscopy, or Near-InfraRed spectroscopy. Methods can be validated using chemical reference materials. Genomic, proteomic, and metabolomic studies combined with statistical techniques such as Principal Components Analysis can be very useful to distinguish even minor differences including provenance of the raw material.

The combination of botanical characteristics and chemical identification tests should be chosen to eliminate misidentification of the botanical, e.g., to detect substitution of a different species, such as the supply of cactus in place of Hoodia).

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. Extracts can also be identified by active constituent or analytical markers.

2.2.2 Appropriate Identification of Specific Medicinal Ingredients

Isolates and synthetic duplicates of materials of natural origin (e.g., flavonoids such as rutin and vitamins) should be identified at the raw material stage by physical description (e.g., colour, crystalline form, melting point or boiling point, optical rotation, etc.) and appropriate chemical identification tests such as Infrared spectroscopy should also be performed. For example, fish oils can be characterized by the fatty acid composition of the oil, acid value, anisidine value, peroxide value, total oxidation value, specific peak retention times from chromatography compared to a reference standard and/or any other appropriate identification tests.

If the medicinal ingredient is an enzyme, characterization includes details of the source organism. Additional details such as gel electrophoresis, substrate specificity, isoelectric point, specific activity should also be documented. Testing can be done according to pharmacopoeial methods or methods approved by the International Enzyme Commission.

For micro-organisms where strain identification is necessary (e.g. probiotics), a qualitative description of the probiotic culture should be provided. This includes identity parameters such as Latin binomial name (e.g., *Bifidobacterium longum*) which is on an approved list of bacterial names (Int. J. Syst. Bacteriol, 1980,30:225-420, <http://www.bacterio.cict.fr/>) [Accessed 2012-06-19]. The identity of probiotic strains should be determined unambiguously using the most current valid methodology, preferably by using a combination of phenotypic and genotypic methods. Strain identity should be verified routinely. Identification should ensure the absence of non-product bacteria at the raw material stage.

2.2.3 Identity Testing on the Finished Product

Generally it is only possible to test for a specific medicinal ingredient in the finished product if the ingredient is a single chemical entity, and the ease of testing is determined by the complexity of the matrix.

Additionally, the description of the final dosage form should be documented as part of the identification of the finished product. Tests for identification of the finished product might include tests such as organoleptic evaluation (sensory characteristics e.g., taste, odour, feel, appearance such as 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.

A physical description of the finished product should always be included on the finished product specifications (e.g. clear colourless liquid, size 0 capsule red upper, blue lower).

2.3 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. Some exceptions are enumerated below.

2.3.1 Quantification by Assay

Quantification by assay is a method for determining the presence or quantity of a component or ingredient. In the case of medicinal ingredients that are single chemical entities, those that contain a constituent which is used to standardize a product, or those who have a known biological activity, quantitative assay tests can be done at the finished product stage according to appropriate analytical methods described in the pharmacopoeias (e.g., USP, Ph. Eur.).

2.3.1.1 Botanical Ingredients Including Extracts

Specific marker compounds may be assayed in whole herbs and extracts of botanical ingredients. If no pharmacopoeial standard is available for assaying the marker, then it is the product licence holder's responsibility to determine appropriate limits for the marker based on data on safety and efficacy of the product and natural variability of the marker.

Quantitative tests for a particular component in an extract can be done at either the finished product stage or at the extract ingredient stage using appropriate analytical methods. If the evidence supporting a claim is based on the quantity of a particular active component, then quantification of that component should be performed at the finished product stage. The quantification of a component of any extract can be recorded in the PLA form under the column entitled 'potency'.

When the component that is analysed is found in several ingredients in the product, e.g. caffeine in green tea and guarana, then the total amount of the component should be reflected on the label and specifications should be set to reflect the total amount from all sources.

2.3.1.2 Vitamins and Minerals

For vitamins, quantitative tests should be done on the finished product according to appropriate analytical methods described in an acceptable pharmacopoeia or other internationally accepted methods. Acceptance criteria for the quantity of vitamins and minerals should be as per United States Pharmacopeia limits for the individual vitamins and minerals. In the absence of a pharmacopoeial standard, applicants should have a scientific rationale for quantities that are outside the general tolerance limits of 80-120%. It is recommended that the lower limit for the assay be set at 90.0% of the label claim to ensure an appropriate amount of the medicinal ingredient at the expiry date. Potency of vitamins can be declared where appropriate.

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.

2.3.1.3 Isolates and Synthetic duplicates

When ingredients are isolates or synthetic duplicates and no pharmacopoeial standard is available, acceptance criteria of 80 to 120% of the label claim are generally appropriate. If the safety of degradation products is unknown, then expansion of these limits may not be acceptable.

2.3.1.4 Live Microorganisms

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

In the case where the medicinal ingredient is a blend of microorganism it is acceptable to list the total CFU count as the quantity and list the strains as sources of the medicinal ingredient.

Acceptance criteria for the quantity of live microorganisms should be 80% to 300% of the label claim. If the applicant proposes test limits for quantities that are outside these tolerance limits, they should be scientifically justified and documented test limits.

Where a viable count for a culture is included on the labelling of the product, the applicant should have evidence of the stability of that culture under the labelled storage conditions available upon request. Applicants should ensure that all products should meet 80% of the label claim for viable organisms at the end of the shelf-life.

2.3.1.5 Enzymes

Acceptance criteria for the quantity of enzymes should be 80% to 150% of the label amount. Additionally, 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). Validated methods and units should be used such as *Food Chemicals Codex* (FCC) units (e.g., FCC Lipase Units, FCC Lactase Units). Quantitative tests for a particular component in an extract can be done at either the finished product stage or at the extract ingredient stage using appropriate analytical methods. If the quantity of an enzyme is declared by weight, the activity should be declared as a potency. It is the responsibility of the applicant to ensure that all products meet 80% of the label claim for viable organisms at the end of the shelf-life.

2.3.2 Quantification by Input

Quantification by input means that the active ingredient in the finished product is not assayed. The objective evidence that the quantity of a medicinal ingredient (e.g., a plant material) has been added to the finished product is calculated using the manufacturing batch record controlled by appropriate application of GMPs and in-process controls.

Quantification by input is appropriate when the active ingredient is a whole herb or a complex extract and no claims are being made regarding the presence of markers or other biological activity. In the case of medicinal ingredients where the formulation of the NHP is of such complexity that a validated assay method for the ingredient is unavailable or difficult to achieve (e.g. there is no published method of analysis for the medicinal ingredient, or the non-medicinal ingredients interfere with analysis), quantification by “input” is considered to be acceptable.

It may also be acceptable to quantify an ingredient by input for a multi-ingredient product (e.g. multi-vitamin mineral products) when the ingredient is not critical to the claims being made and is more stable than other ingredients present in the formulation. In this case the product licence holder uses controls other than assay for some of the ingredients present, and assays critical ingredients. Quantification by input is also appropriate when the quantity represents less than 10% of the known active amount of an ingredient.

Generally, the quantity of a medicinal ingredient is expressed as the targeted weight (e.g., mg) of the processed substance in each unit of the dosage form.

Raw material specifications for the medicinal ingredient(s) to be quantified by input should be comprehensive to ensure that adequate control of the medicinal ingredient(s) occurs and should be available upon request. Standard operating procedures (SOPs) and batch records should clearly document the controls that are in place during manufacturing to ensure an adequate amount of medicinal ingredient is added to the mix during processing to achieve the labelled quantity per dosage unit. These documents should indicate the target quantity for the medicinal ingredient (i.e., 100.0% of the label claim) and include controls on weight variation during tableting or encapsulation. Generally a 5.0% variation in weight for individual dosages is acceptable. A description of how batch homogeneity will be controlled should also exist and be available to the NHPD on request if more than one medicinal ingredient is mixed, or if the medicinal ingredient is mixed with non-medicinal ingredients.

SECTION 3. PURITY STANDARDS

As required by section 44 (2) (a) of the NHPR, the finished product specifications shall contain detailed information regarding the purity of the NHP, including statements indicating its purity tolerances. Product licence holders are responsible for ensuring that all possible efforts are made to understand the potential for contamination and the impact on the population consuming the NHP in order to minimize the presence of contaminants in NHPs. The finished product specifications should include tests and methods and tolerance limits for the microbial and chemical contaminants as outlined in the following sections on **Microbial Contaminants** and **Chemical Contaminants**.

Product licence holders should also consider appropriate testing for contaminants not listed here which may be necessary for their product (e.g., aflatoxin testing if the presence of aflatoxins is likely (e.g. ginseng, peanuts)). Where an NHPD monograph exists for an ingredient, the specification section of the monograph should be consulted to determine whether the NHPD requires specific tests for the ingredient or the finished product. The NHPID also lists specific requirements for ingredients when the NHPD has determined additional requirements are necessary.

If the applicant tests for contaminants and adulterants at the raw material stage, no testing for the contaminant/adulterant is required at the finished product stage as long as a scientific rationale is provided assuring that the finished product is free from any additional contamination or adulteration during the manufacturing process. For example, testing for arsenic in all raw materials is sufficient as there is not likely to be any opportunity for contamination with arsenic during manufacturing, but testing for microbial contamination at only the raw material stage is not acceptable as microbial contamination can occur at any stage of the manufacturing process.

3.1 Microbial Contaminants

Good Agricultural and Collection Practices and GMPs are necessary to ensure low levels of microbial contamination. Routine microbial reduction techniques should not be used as a replacement for GMP or to ensure that the finished product will meet specifications for microbial contamination.

Testing for microbial contamination should be performed at the finished product stage. If testing for microbiological contamination is not performed on the finished product, the applicant should provide a scientific rationale justifying exemption of these tests.

The NHPD applies limits to the following organisms:

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

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

Product licence holders are responsible for determining appropriate microbial test requirements for their product. If cases of contamination of the particular product with a specific micro-organism are known or suspected or if another organism is considered a more appropriate indicator organism (e.g., *S. aureus*, *Bacillus*, *Enterococcus*, *Campylobacter*, *Clostridium*, *Shigella* or *Listeria* species), it is the responsibility of the product licence holder to ensure that the product is free of known indicator organisms.

Acceptance criteria should comply with those set out in one of the acceptable pharmacopoeias (e.g. USP, BP, Ph. Eur.).

3.1.1 Microbial Contamination Requirements for Specific Products and Routes of Administration

3.1.1.1 Plants, Algae, Fungi or Animal Materials in Oral Dry Dosage Form

For a multi-component product, the acceptance criteria for the finished product would generally be based on the least stringent limit; however limits should be reduced if warranted by routine analysis showing lower levels of contamination.

3.1.1.2 Products Containing Live Microorganisms in Dry Oral Dosage Form

Testing should be performed as per the European Pharmacopoeia chapters 2.6.12 and 2.6.13 or equivalent methodology. The interpretation of abbreviations used in the table below and interpretation of test results to show compliance with the limits listed below should be consistent with this publication.

Table 1: Specification for products containing live microorganisms

Ingredient	Total Aerobic Microbial Count (CFU/g or mL)	Total Yeast and Mould Count (CFU/g or mL)	Bile tolerant Gram negative bacteria	<i>E. coli</i>	<i>Salmonella</i> spp.
Probiotics and		10 ² Maximum	10 ²	Absent	Absent (25

live microorganism		acceptable count: 200		(1 g)	g)
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For products containing live microorganisms, 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 Enterobacteriaceae". Note that selective testing for coliforms or only for members of the genus *Enterobacteria* (i.e. a subset of the family Enterobacteriaceae) is not considered sufficient as it may potentially fail to screen for other gram negative facultative rods that belong to the same family of Enterobacteriaceae and are also known pathogens such as members of the genera *Klebsiella*, *Shigella*, etc.

3.1.1.3 Products in Liquid Dosage Form

Pseudomonas aeruginosa testing is required for liquid products unless alcohol is present at a concentration of greater than 50%.

3.1.1.4 Sterile Products

Products should comply with the criteria as defined in Ph.Eur. 2.6.1 Sterility. If sterile products are intended for ophthalmic use additional pH testing is required.

3.2 Chemical Contaminants

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

3.2.1 Elemental Impurities

Elemental impurities include catalysts and environmental contaminants that may be present in raw materials or finished products. These impurities may occur naturally, be added intentionally as part of the manufacturing process, or be introduced inadvertently (e.g., through interactions with processing equipment). Elemental impurities may 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 for individual elements.

Table 2: Acceptable limits for elemental impurities

Element	Adult Limit per day	Limit per day per kg body weight
Total Arsenic OR Inorganic Arsenic Organic Arsenic	< 10.0 µg/ day < 2.1 µg/ day < 1.4 mg/ day	< 0.14 µg/kg b.w./day < 0.03 µg/kg b.w./day < 20 µg/kg b.w./day
Cadmium	<6 .0 µg/ day	< 0.090 µg/kg b.w./day

Lead	<10.0 µg/ day	<0.14 µg/kg b.w./day
Total mercury (Methyl mercury)	<20.0 µg/day (< 2.0 µg/day) ¹	<0.29 µg/kg b.w./day (< 0.029 µg/kg b.w./day) ¹

¹Methyl mercury determination is not necessary when the content for total mercury is less than the limit for methylmercury.

The acceptance criteria for arsenic, cadmium, lead and total mercury are consistent with relevant international standards. Studies clearly document adverse health effects at blood lead levels between 1 and 10 µg/dL, including developmental neurotoxicity, neurodegenerative, cardiovascular, renal and reproductive effects. Further to this, current information indicates that there is insufficient weight-of-evidence to conclude that there is a threshold below which health effects would not be seen. Therefore, the risk management objective for lead is to reduce exposure to lead, and hence associated risks, to the greatest extent practicable. Please refer to the table in Appendix 1 to calculate appropriate limits for sub-populations other than adults.

When acceptance criteria for individual metals on specifications are defined in ppm or another concentration based specification, the daily exposure for the most vulnerable labelled subpopulation should not be exceeded. Please refer to the example of calculations given in Appendix 1. The maximum daily intake should be documented in the rationale on the Finished Product Specifications Form and used to justify the proposed limit.

When testing is performed at the raw material stage, calculation of the total daily exposure in the finished product should be performed. This calculation is based on the quantity of each ingredient present in the product, the maximum potential contamination given the proposed limits for each raw material and the daily dose of the product. Examples of this type of calculation can be found in the proposed USP general chapter <2232> Elemental Contaminants in Dietary Supplements, published in the Pharmacopeial Forum 36(1).

3.2.1.1 Arsenic

If total arsenic content in the finished product exceeds the current tolerance limit of 0.14 µg/kg b.w./day (taking into account dosage and subpopulation), the applicant is required to conduct additional testing with arsenic speciation to demonstrate that the dose of inorganic arsenic does not exceed 0.030 µg/kg b.w./day and the dose of organic arsenic does not exceed 20.0 µg/kg b.w./day.

The method used in the Arsenic Limit Test set out in the most recent Food Chemicals Codex (FCC, 6th or subsequent edition) is suitable for the determination of inorganic versus organic arsenic in botanical, algal or other biological ingredients. The NHPD recommends either the use of HPLC coupled with ICP-MS or ICP-AES or the FCC method (colorimetry) for analysis of arsenic compounds in finished NHPs.

3.2.1.2 Chromium VI

Chromium VI levels are seen to be technically avoidable when they exceed the limit of <0.29 µg/kg b.w./day.

3.2.1.3 USP <231> Total Heavy Metals

Testing for total heavy metals expressed as lead as per methods USP <231> or Ph.Eur. 2.4.8 is generally not considered an acceptable replacement for methods that detect arsenic, cadmium, mercury and lead separately.

In addition to intake from dietary sources, a person's intake of elemental impurities will vary significantly depending on the quantity of an NHP consumed. The USP Heavy metal test is not considered equally sensitive for all toxic metal impurities which react with Thioacetamide. There is no known Tolerable Daily Intake (TDI) or Tolerable Daily Amount (TDA) value established by any scientific expert committee or working group for total heavy metals. For these reasons, setting a tolerance limit of not more than 10 ppm for total heavy metals at the finished product stage will not necessarily provide adequate protection to consumers. Unsafe exposure could occur from a product with a large daily dosage or with a high level of one heavy metal contaminant exceeding its tolerance limit even though the 10 ppm total limit is met due to low levels of the other heavy metals. In the case of an ingredient which is known to selectively accumulate heavy metals, the product should be tested for individual heavy metals (e.g. cadmium in certain plants, arsenic in certain algae, or mercury in marine oils).

A Total Heavy Metals test result of not more than 10 ppm will be acceptable only under the following circumstances.

1. The USP <231> test should be shown to be appropriate for the matrix tested.
2. The USP <231> test with a limit of not more than 10 ppm will be acceptable where the applicant can demonstrate based on testing of representative batches of the product that no individual heavy metals approach the NHPD tolerance limits.
3. If the product fails the USP <231> test it must be tested for the individual heavy metals using an appropriate quantitative test.

3.2 .2 Topical Products

Dermal exposure is the most significant route of exposure for topical products. Heavy metal concentrations in topical products are seen to be technically avoidable when they exceed the following limits:

Table 3: Acceptable limits for heavy metals in topical products

Element	Limit in parts per million (ppm)
Arsenic	3 ppm
Cadmium	3 ppm
Lead	10 ppm
Total mercury	3 ppm
Antimony	5 ppm

It is the applicant's responsibility to ensure that the finished product contains as little heavy metal contamination as possible.

3.3 Other Impurities

It is the applicant's responsibility to ensure that all raw materials used in the manufacture of NHPs have appropriate specifications and testing is in compliance with sections 5 and 44 of the NHPR. The specifications section of the NHPD monographs and the tables in the "Finished Product Specifications Form User Guide" include criteria for individual ingredients that are to be met in conjunction with these requirements.

The USP, Ph. Eur., B.P. and FCC monographs are considered appropriate monographs for control of the quality of an ingredient or finished NHP.

3.3.1 Mycotoxins (e.g., Aflatoxins)

Testing is required for products containing ginseng and peanuts or any substance derived from these sources as they may be contaminated with aflatoxins due to poor agricultural practices and storage conditions. 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 is required if a medicinal ingredient has documented cases of fungal contamination or if fungal contamination is considered likely.

The NHPD has set acceptance criteria of < 20 µg/kg (ppb) for aflatoxins (B1+B2+G1+G2), and <5 µg/kg (ppb) for aflatoxin B1. While aflatoxins are a common mycotoxin contaminant, other mycotoxins may be of concern (e.g. ochratoxin A). It is the product licence holder's responsibility to determine which mycotoxins may present a risk to health, and to determine test methods and tolerance limits for those mycotoxins of concern.

3.3.2 Cyanobacterial Toxins (e.g. Microcystins)

NHPs containing the cyanobacterium (blue-green alga, BGA), *Aphanizomenon flos-aquae*, have a history of contamination with a group of hepatotoxic compounds called microcystins (MCs) so testing for microcystins is necessary.

The NHPD has adopted a finished product tolerance limit of 0.02 µg MC-LR/kg b.w./day or a raw material tolerance limit of 1 ppm, provided that the total consumption per day remains less than 0.02 µg MC-LR/kg b.w. when calculated for the finished product.

Applicants should test other cyanobacterial products for microcystins if there is a history of contamination. Health Canada tests for microcystins on a significant number of marketed *Spirulina* products have not detected such contamination so microcystin testing for *Spirulina* products is usually not necessary.

3.3.3 Solvent Residues

Solvents known to cause unacceptable toxicities (ICH Class I) are not considered appropriate for NHPs. If Class I solvents cannot be avoided, then confirmation of acceptability of the solvent is required before its use on the raw material. Use of solvents associated with less severe toxicity (ICH Class II) should be limited in order to protect consumers from potential adverse

effects. Wherever possible, the least toxic solvents (ICH Class III) should be used. These class lists are available in the ICH 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. Acceptance criteria for solvent residues should conform to ICH or pharmacopoeial limits.

If only ICH Class III solvents are used in the manufacture of the NHP, a test for loss on drying with acceptance criteria of not more than 0.5% loss on drying is considered acceptable to test for solvent residues.

3.3.4 Hormone Testing of Animal Materials

Hormone testing is only required for those animal materials used in NHPs that contain significant amounts of hormones regulated in Canada as prescription drugs or as controlled substances. These glands include ovaries, hypothalamus, prostate, mammary, pituitary, adrenal and orchic (testes) glands.

A copy of a certificate of analysis or any other equivalent document confirming the absence of prescription or controlled sex hormones in the raw materials or finished product using a method with an acceptable limit of detection should be included.

3.3.5 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.

3.3.6 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, catalysts and degradation products) in the product. 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 and be available upon request.

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 should be submitted to the NHPD.

3.3.7 Pesticide Residues

Testing for pesticides in plant or plant materials, algae, fungi, non-human animal materials, or extracts derived thereof, should be done according to the multi-residue method and limits outlined in the Ph.Eur., United States Food and Drug Administration's Pesticide Analytical

Manual 1 or WHO Methods for Pesticide Screening I. 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 should be routinely tested for using an appropriate method.

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.

Testing of chemical residues in accordance with the *Food and Drug Regulations* is acceptable if the ingredients are also used as foods. Pesticide limits for specific food commodities are found at http://www.hc-sc.gc.ca/cps-spc/alt_formats/pdf/pest/part/protect-proteger/food-nourriture/mrl-lmr-eng.pdf [Accessed 2012-08-17]

3.3.8 Contaminants in Oils of Animal Origin

Polychlorinated dibenzo-para-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and dioxin-like polychlorinated biphenyls (dioxin-like PCBs) are contaminants in certain products, particularly oils from fish and other marine sources.

When testing for PCDDs, PCDFs and dioxin-like PCBs is necessary, the testing should be performed using appropriate analytical methods, such as method No. 1613 revision B of the Environmental Protection Agency for PCDDs and PCDFs and method No. 1668B of the Environmental Protection Agency for chlorinated biphenyl congeners (USP 32; EPA 2008; EPA 1994). Applicants are advised to consult the Commission of the European Communities documents on dioxins and dioxin-like PCB contaminants in marine oil for further information (EU 2006a.b; EU 2001). The table below provides the limits for these specified chemical contaminants in marine oils:

Table 4: Acceptable limits of dioxins and dioxin-like polychlorinated biphenyls in oils from marine sources (USP 32; EU 2006)

Dioxin and dioxin-like polychlorinated biphenyl contaminants	Maximum level ¹
Sum of PCDDs and PCDFs	2.0 pg TEQ /g oil
Sum of PCDDs and PCDFs and Dioxin-like PCBs ²	10.0 pg TEQ /g oil

¹ Expressed in World Health Organization (WHO) toxic equivalents using WHO-toxic equivalent factors (TEFs). Analytical results relating to 17 individual dioxin congeners of toxicological concern are expressed in a single quantifiable unit: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxic equivalent concentration or TEQ (EU 2006).

² The dioxin-like PCBs that can be determined by Method 1668B are the 12 PCBs designated as toxic by WHO: congeners 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189 (EPA 2008; EU 2006).

3.3.9 Antibiotic Residues in Bee Products

Consistent with the prohibition on chloramphenicol and 5-nitrofurantoin compounds as contaminating substances in food products such as honey according to the *Food and Drug Regulations*, C.01.610.1, NHPs should not contain any of these antibiotics or their residues. In particular nitrofurantoin metabolites/residues from Furazolidone, Furaltadone, Nitrofurantoin, and Nitrofurazone in particular are of concern. Further information on analysis can be found in several articles, e.g.: '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-nitrofurans residues and chloramphenicol in honey and royal jelly. Alternatively a justification for why the testing is not required must be documented, scientifically sound and available upon request.

3.3.10 Radioactivity

In specific circumstances where there is a risk of radioactive contamination, it may be necessary to test for radioactivity. If radioactivity is suspected, acceptance criteria should be set as follows: 600 Bq/kg of substance if irradiation has been used to reduce microbiological load, 300 Bq/kg of substance if naturally occurring radioactive materials are likely to be present.

Acceptance criteria for radioactivity have been adapted from the European Commission Directive (Recommendation 2003/120/EC) when irradiation has been used to reduce microbiological load and the Canadian Guidelines for the Management of Naturally Occurring Radioactive Materials (NORM), Unconditional Derived Release Limits to the public for Diffuse NORM Sources, adapted to ensure consumption of the material will not exceed a maximum effective dose of 0.3 mSv/year.

3.3.11 Oxidative Stability in Oils

Oxidative stability testing is applicable to all oils that have a high degree of unsaturation to ensure stability. Where oxidative stability tests are required by pharmacopoeial monographs, the acceptance criteria as per the appropriate monograph may be used. Testing should be done according to AOAC and/or Pharmacopoeial analytical methods for peroxide, anisidine, and total oxidation (TOTOX) values of marine oils or omega-3 fatty acids derived from marine oils to ensure their oxidative stability.

Table 5: Acceptable Limits for Oxidative Stability Parameters in Marine Oils

Peroxide value (PV)	NMT 5 mEq/Kg
Anisidine value (AV)	NMT 20
TOTOX value	NMT 26 Calculated as 2 x PV + AV

The above limits are appropriate for the raw materials, but may not be appropriate for the finished product if non-medicinal ingredients interfere with the testing. In these cases the applicant should develop product specific limits that ensure stability of the oil in the finished product.

3.3.12 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 recommended storage conditions to the end of the product's shelf life.

3.3.13 Potential Adulterants in Natural Health Products

Manufacturers are responsible for ensuring that raw materials are free of potential adulterants by using GMPs for sourcing and testing raw materials. When raw materials are known to have a history of adulteration with undeclared ingredients, the finished product manufacturer should consider the need for specific testing for the adulterant in the raw material or the finished product unless they have evidence that the product has been tested by the manufacturer and the raw material suppliers have been audited. The potential risk that undeclared ingredients are present should be considered along the entire supply chain. The NHPD may at any time request testing that demonstrates that the product is free from adulteration.

Examples of recent cases of adulteration include diethylene glycol in glycerin (raw material) or in toothpaste (finished product), melamine in milk derived products, and addition of undeclared prescription drugs to male erectile dysfunction, sleep aid and weight loss products. It is the responsibility of the product licence holder to ensure that the product is free from adulteration.

3.3.14 Ingredients sourced from tissues that are susceptible to transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE).

It is the responsibility of the product license applicants to ensure that all products are free from TSE and BSE. Product License holders are encouraged to consult the *Food and Drug Regulations* B.01.047 for information on restrictions for “specified risk materials” http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/page-21.html?term=bovine#s-B.01.047.1 [Accessed 2012-06-28].

Additionally the NHPD strongly advises product license applicants to not use tissues that are susceptible to TSE including bones (other than vertebral column or skull) of cattle, sheep, goat, deer or elk velvet antlers. The NHPD recommends using alternative such as plant materials (e.g. vegicaps), gelatin made of materials from animals that are not susceptible to TSEs (e.g. pig), or gelatin made from skin and hides of any animal.

SECTION 4. 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. The procedures used to conduct such tests should be based on pharmacopoeial or scientific literature and international standards. 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 for certain dosage forms is summarized in **Appendix 2**.

Additional information can be found in the following documents: 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).

4.1 General Indicators for Quality

4.1.1 Foreign Matter

This test is important to ensure that the plant, algal or fungal material is entirely free from visible signs of contamination such as sand, glass and metal. Testing should be done according to pharmacopoeial methods.

4.1.2 Determination of Acid Insoluble Ash

Acid insoluble ash is important to determine the amount of inorganic impurities in the form of extraneous (non-biological) materials in a plant, algal or fungal material.

4.1.3 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.

4.1.4 Non-Medicinal Ingredients

It is the responsibility of the Product Licence Applicant to ensure that all non-medicinal ingredients (NMIs) adhere to any restrictions outlined in the NHPID and that NMIs are used in quantities sufficient to support the intended purpose.

4.2 Performance Tests

4.2.1 Disintegration

In accordance with section 103 of the NHPR, specifications are required for disintegration times for solid oral NHPs intended to be swallowed whole, such as uncoated tablets, plain coated tablets or hard or soft gelatin capsules. Disintegration times should be tested using the official method DO-25 or pharmacopoeial methods. Acceptance criteria for disintegration should be based on the routine disintegration times for the product, but not more than 45 minutes for uncoated tablets or 60 minutes for plain-coated tablets.

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 by dissolution testing. The disintegration test is not required when the product is to be chewed.

4.2.2 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, and generally is a more robust quality control test than disintegration.

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.

4.2.3 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. Tests for uniformity of dosage units should be performed as described in the USP or Ph. Eur and should meet the acceptance criteria as outlined in these publications.

4.3 Standards for Specific Finished Products

Specific tests are required for transdermal patches including adhesive strength and peel force. **Appendix 2** shows examples of specific testing requirements for various dosage forms.

4.4 Standards for Homeopathic Medicines

Specific standards for homeopathic products including determination of identity, expression of quantity and homeopathic potency, requirements for sterilization of nosodes and exemptions from testing and can be found in Evidence for Homeopathic Medicines Guidance Document (<http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/ehmg-nprh-eng.php>) [Accessed 2012-06-19].

4.5 Analytical Testing and Requirements to Support Label Claims

Routine tests should appear on the Finished Product Specifications to support label claims such as “gluten free” or “sulphite free”. Health Canada has established a limit of 20 ppm of gluten and 20 ppm for sulphites for finished NHPs labelled as “gluten-free” and “sulphite free”. It is the responsibility of the product licence holder to ensure that all label claims such “allergen free” are truthful.

4.5.1 Organic Products

The NHPD does not certify or verify products as organic. Food ingredients should comply with the Organic Products Regulations, 2009. If an applicant is making a label claim, the product should be certified by an accredited agency.

4.6 Reduced Testing Schedules that are Captured on Specifications

The Finished Product Specifications should clearly indicate the testing schedule, and SOPs should be available for what procedures are in place in the case where a product fails a test. The implementation of the reduced testing program may be reviewed and verified during the life cycle of the site licencing process. It is the responsibility of the applicant to ensure that any reduced testing will not compromise the safety of the product.

4.7 Antimicrobial Effectiveness Testing

Antimicrobial preservatives are ingredients added to dosage forms to protect them from microbiological growth and associated degradation. Where antimicrobial preservatives are added to a product, tests must be utilized that 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.

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.

4.8 Stability Testing

Stability testing of NHPs is required by Section 52 of the NHPR. The purpose of stability studies is to assess the impact of environmental factors (temperature, humidity, light, etc.), the packaging material (the container closure system), and intrinsic factors (ingredient interactions, degradation, natural spoilage etc.) on the quality, safety and efficacy of the product, and to establish a shelf-life for the NHP. The product licence holder is ultimately responsible for product quality, and as such, product stability. If these obligations are delegated to a third-party a clear understanding of roles and responsibilities must be established to ensure that compliance is achieved. The expectation on applicants is that any pertinent information that is necessary to show safety or efficacy will be included as a component of the information

package submitted under 5(j) of the NHPRs. For more information on stability please see additional guidance related to establishing Good Manufacturing Practices.

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SECTION 6. GLOSSARY

Acceptance Criteria: The numerical limits, ranges, or other criteria corresponding to the tests listed. The acceptance criteria establish the set of criteria to which the natural health product should conform to be considered acceptable for its intended use.

Adulterants: Section 30. (1) (a) of the *Food and Drugs Act* defines “any food or drug or class of food or drugs is adulterated if any prescribed substance or class of substances is present therein or has been added thereto or extracted or omitted therefrom”. In this context “prescribed” means as set out by guidance or policy or regulation. In this guidance document, the term ‘adulterant’ is used specifically to mean an undeclared substance, i.e. drugs or other substances that are added to increase the perceived potency or inexpensive substances that are added to increase the weight or decrease cost. As such, adulterant is distinguished separately from the term ‘contaminant’. Reference: http://www.hc-sc.gc.ca/dhp-mps/pubs/complement/bq-qhm_doc-02-02/index-eng.php

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.

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.

Assay. A method for determining the presence or quantity of a component

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.

Batch or lot: A batch is a definite quantity of a raw material or finished product produced under the same series of consistent conditions. A lot may be comprised of one or more batches and is received or released for further use.

Batch-to-batch consistency: The application of product knowledge, good agricultural or wildcrafting practices, and GMPs to minimize inherent variations in the composition of natural substances in order to ensure a consistent product from one batch to the next.

Botanical ingredient (botanical): An ingredient consisting of, or derived from a plant. (NSF/ANSI 173-2010)

Chemical name. The unambiguous name of a chemical substance cited in the International Union of Pure and Applied Chemistry Nomenclature or other scientific literature.

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. A protein that acts as an organic catalyst, increasing the rate at which a specific biochemical reaction occurs. Enzymes may be derived from a plant, algal, bacterial, a fungal, or non-human animal material.

Extract. A substance prepared by treating a plant, algal, bacterial, fungal, or non-human animal material with solvents or other means (e.g. crushing) to selectively obtain a subset of the raw material's 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.

Identity validation terms:

Sensitivity: the ability of a method to detect a botanical in the presence of carriers and/or adulterants.

Selectivity: "Selectivity of a method refers to the extent to which it can determine particular analyte(s) in a complex mixture without interference from other components in the mixture" or ability to yield a negative result for known contaminants/adulterants (IUPAC 2001)

Specificity: Specificity is sometimes used in place of selectivity, however this term should be used only for methods which are truly specific

Selectivity rate: the probability that a method will classify a true negative result as negative

False positive rate: the probability a method will yield a positive result for a botanical when the material is a known contaminant or adulterant.

False negative rate: the probability a method will yield a negative result for a material known to contain the botanical.

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.

kg b.w./day: Abbreviation for kilogram body weight per day. Acceptance criteria in this document are frequently set based on toxicological data which indicates an acceptable daily exposure based on body weight.

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 derivatives may be acceptable as more stable, bioavailable or safer sources for the mineral.

Moiety(ies). a part or functional group of a molecule.

Native extract: An ingredient that consists only of components present in the original plant, algal, bacterial, fungal or animal material obtained during the extraction process (e.g. extractable herbal matter). It excludes any excipients or other added substances. The term may refer to liquid extracts or semi-solid extracts from which the added solvent has been removed, or may refer to a dry extract.

NMT: Abbreviation of 'Not more than'

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 should be listed in one of the homeopathic pharmacopoeias specified in the Evidence for Homeopathic Medicines guidance document.

Organic. An internationally recognized standard denoting a material certified to have been produced in accordance with the production, processing, packaging, storage and distribution provisions of the organic product standards.

Overage. Planned extra quantity added to the batch during manufacturing to ensure the correct target quantity of the ingredient in the finished product to the end of the product's shelf life.

Plant. A member of the biological kingdom Plantae, consisting of complex multicellular eukaryotes with a cell wall composed primarily of cellulose. Plants usually 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 should be provided only when a potency claim appears on the product label and when the literature supports a specific product with that standardized component. For homeopathic products potency refers to the degree of dilution of a homeopathic medicine.

Primary molecular structure. The chemical structure of a substance isolated from a natural 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 holder. An individual with legal ownership of and responsibility for the NHP. The product licence holder may be located in or outside of Canada. Product licence holders who are located outside of Canada must identify a Canadian representative.

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.

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

Specifications. Quality standards which include tests, references to analytical procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described. Specifications establish the criteria to which a finished product should conform in order to be considered acceptable for its intended use.

Stability testing terminology:

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a medicinal ingredient by using extreme storage conditions

Long term or real-time studies: Stability studies under the recommended storage conditions for the expected or approved shelf-life.

On-going stability studies: Studies to monitor the product during its shelf life and ensure that it remains within its specifications under labelled storage conditions.

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, most of the vitamin C in products marketed in Canada is a synthetic duplicate of the ascorbic acid that occurs naturally in plants and animals.

Validation. The action taken to demonstrate, and to provide documented evidence that a process will, with a high degree of assurance, consistently achieve the desired and intended results.

Vitamin. One of a group of naturally occurring organic substances required in small amounts by the body to maintain health; insufficient amounts may cause deficiency diseases.

APPENDIX 1. CALCULATIONS

Chemical Contaminants

(a) 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
Total daily intake of product:	1500 mg
Amount of lead in the product:	2 ppm (0.002 mg Pb/g of product)
Amount of Pb consumed per day:	0.003 mg (3 µg)

Amount of Pb consumed per day per kg body weight:	0.043 µg/kg b.w/day (i.e. meets NHPD acceptance criteria of <0.14 µg/kg b.w/day)
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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 should be used as per the table below.

Table 6: Reference Body Weight by Sub-population

Subpopulation by age	Reference Weight (kg)
Infants, 0 months	3.4
Infants, 1 month	4.2
Infants, 2-6 months	6
Infants, 7–12 months	9
Toddlers, 1-3 years	12
Early Childhood, 4-8 years	20
Puberty, 9–13 years	36
Adolescents, 14-18 years	54
Adults, 19+ years	70

The above table was developed from Health Canada body reference weights (<http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index-eng.php#rhw>) and the Centres for Disease Control and prevention (CDC) growth charts (<http://www.cdc.gov/growthcharts>). The above weights should be used when performing calculations for chemical contaminants (e.g. heavy metals, solvent residues). From age 9 there is a divergence in body weight between males and females in the tables used to determine reference weights. The smallest body weight of the two subpopulations is used for ages 9-18.

Table 7: Worksheet – Conversion of analysis of elemental impurity concentration to daily intake of impurity (Adapted from AHPA (2008) Background on California Proposition 65: Issues related to heavy metals and herbal products)

Elemental impurity	Adult daily maximum intake	(1) TOTAL intake of product (in grams/day)	Multiply	(2) Concentration of heavy metal in product (in ppm)	Equals	(3) TOTAL daily intake of heavy metal (in µg/day)
Total arsenic	10 µg		x		=	
Arsenic (inorganic oxides)	2.1 µg		x		=	
Arsenic (organic derivatives)	1.4 mg		x		=	
Cadmium	6 µg		x		=	
Lead	10 µg		x		=	
Total mercury	20 µg		x		=	
Methyl mercury	2 µg		x		=	
If TOTAL daily intake (column 3) in any of the seven rows above is greater than the stated “daily max” for that row, then the product quality does not meet with NHPD standards.						

APPENDIX 2. PHYSICAL TESTS REQUIRED FOR DIFFERENT DOSAGE FORMS

Table 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 ¹	Adhesive Strength	Peel Force
Tablet, Caplet, Capsule, etc. ²	X	X		X	X				
Tablet, rapid dissolving	X		X	X	X				
Tablet or Capsule, sustained ³ release	X		X	X	X	X			
Tablet or Capsule, delayed ⁴ release	X	X		X	X				
Oral solutions and suspensions	X						X		
Topical Preparations	X						X		
Transdermal Patches	X					X		X	X

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

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

³ Sustained release dosage forms include extended release, combined release, timed release dosage forms.

⁴ Extended release dosage forms include enteric coated tablets and capsules.