

The focus of this guidance document is to outline tools and approaches that can be used by licence holders to produce high quality natural health products (NHPs). The licence holder is responsible for ensuring that:

- a) Product specifications are established in accordance with the requirements described in this guidance document.
- b) All quality information is documented, maintained, relevant, accurate and sufficient to support the quality of their NHPs.
- c) The most recent version of the finished product specifications is submitted to the Natural and Non-prescription Health Products Directorate (NNHPD).

The NNHPD will employ a risk-based approach that focuses on those elements of an application that most directly relate to safety and efficacy and may request additional documentation as necessary.

The licence holder is ultimately responsible for product quality. This guidance document describes the requirements for producing high quality NHPs; however, it allows for flexibility in how these requirements are met. Licence holders can substitute, modify or exclude any requirements specified in this guidance, provided that scientific rationales are documented and maintained. These rationales should be based on Good Manufacturing Practices (GMP), scientific principles and product history and experience. For example, NHPs that are produced in licensed facilities in countries with mutual recognition agreements with Canada would not necessarily have to be re-tested upon import.

Licence holders are expected to update product specifications within the sooner of 12 months or next lot/batch in order to comply with changes to quality requirements resulting from this guidance document.

Please note the following procedural changes that relate to the new approach to quality:

- 1) All applications are expected to include Finished Product Specifications (FPS) or attest to meeting the sample specifications included in this guide.
- 2) When referencing NNHPD monographs, deviations from monograph specific specifications must follow the principles outlined in this guidance document.
- 3) NNHPD will acknowledge receipt of quality amendments. However, it remains the responsibility of the licence holder to ensure that all quality changes meet the principles outlined in this guidance document.

Quality of Natural Health Products Guide

Natural and Non-prescription 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 governing statutes and regulations. They also serve 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 natural health products (NHPs).

This document should be read in conjunction with the [Natural Health Product Regulations](#), the [Good Manufacturing Practices](#) guidance document, the [Pathway for Licensing Natural Health Products Making Modern Health Claims](#) and the [Pathway for Licensing Natural Health Products Used as Traditional Medicines](#), as well as relevant sections of any other applicable guidance. Where applicable, links between requirements for product testing and good manufacturing practices (GMP) requirements have been clarified.

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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, while promoting a timely and efficient application review process.

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 high quality NHPs as the end result. Reference has been made to a number of

Did you know that alternate approaches can be used as long as they result in high quality NHPs?

national and international sources of standards, such as the *United States Pharmacopeia (USP)*, *European Pharmacopoeia (Ph. Eur.)*, and *Therapeutic Goods Administration of Australia (TGA)*. These sources should be consulted to meet product quality expectations. The expectation is that the product licence holder has all pertinent information to ensure regulatory requirements are met, and that the information submitted or attested to at the time of application for a licence is subsequently maintained following product licensing.

1.2 Background

Based on valuable feedback received from stakeholders through consultations and information sessions, as well as experience gained by scientific reviewers/assessment officers and submission coordinators at the Natural and Non-prescription Health Products Directorate (NNHPD), the *Evidence for Quality of Finished Natural Health Products Guidance Document* has been revised and replaced with the *Quality of Natural Health Products Guide*.

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 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

Product licence holders are ultimately responsible for ensuring the quality of their licensed NHPs, and for the establishment of the product specifications, as per section 44 of the NHPR. Although good manufacturing practice (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 good manufacturing practices (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 product licence application (PLA)) that the product will be manufactured, packaged, labelled, imported distributed and stored in accordance with 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 relies on a third party to provide this information. This also includes situations where the information is not shared directly with the product licence holder (i.e. proprietary information that could be provided to the NNHPD as a master file). 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 a valid quality technical agreement between the manufacturer/ importer and/or the contracted third party or product licence holder that is signed and dated by the parties involved. It should also clearly state 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

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 NNHPD, 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) 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 (GMPs).

Finished product specifications, testing activities and their documentation may also be required as a component of site licensing and GMP assessment activities of the NNHPD. For example, 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 Ingredient specific requirements

Where an NNHPD monograph exists for an ingredient or product, the specification section of the monograph should be consulted to determine whether or not specific outcomes for the ingredient or the finished product have been indicated. [The Natural Health Products Ingredients Database \(NHPID\)](#) also lists additional specifications for various ingredients. This information should be considered when establishing product specifications.

1.5.2 NNHPD finished product specification form

NNHPD'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 NNHPD website.

The NHPID and NNHPD monographs contain additional ingredient specific quality information that can help establish product specifications.

1.5.3 Specifications

A specification is defined as a list of tests, references to analytical or physical procedures, and appropriate tolerance 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 as 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 tolerance limits for each test. Chapters 2, 3, and 4 of this document describe the test parameters, analytical procedures and tolerance limits 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 pharmacopoeias

Licence holders may choose to follow other pharmacopoeias than those identified above that may be more appropriate for specific ingredients or products.

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 product specifications do not include tests and tolerance limits as per the pharmacopoeial monograph, there should be justification as to why the testing is not

The following pharmacopoeias and international standards are currently considered acceptable in their entirety by the NNHPD:

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)

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.

If licence holders attest to meeting one of these pharmacopoeias, then the monograph to which the licence holder is attesting should be clearly identified. Any additional testing that must be performed should be clarified or the scientific justification as to why the additional testing is not required must be documented.

In general, the NNHPD 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 NNHPD considers the limits prescribed in any one of the above pharmacopoeias to be acceptable. Licence holders 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 NNHPD, 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 NNHPD accepts the use of alternate methods that meet 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 \(NHPID\)](#). The NHPID also contains descriptions and information regarding specific test methods that are acceptable for the criteria specified.

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 Natural and Non-Prescription Health Products Directorate (NNHPD) 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 natural health product (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 in the References Section 5 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.
- Characterization of live microorganisms includes culture conditions such as strain viability, specific media used for growth, growth temperatures, growth times, cell collection, etc.

b. Process characterization for highly processed ingredients

- Characterization should include a full description of how the materials were processed.
- 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 NNHPD 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 contributes 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 serves solely for analytical purposes and does not contribute to therapeutic activity, to which the product is adjusted to achieve a reproducible composition.

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.

If a marker is used for quality control purposes only, then specifications which include a lower tolerance 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.

Did you know that the NNHPD refers to a product as 'standardized', if it is manufactured to consistently meet a predetermined concentration of a specific marker or set of markers?

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.

Licence holders 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](#)". 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.

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

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.

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

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 flora 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.

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.).

Chemical identification: These techniques include methods such as chromatography, spectrometry, gravimetry, capillary electrophoresis, DNA fingerprinting, Fourier Transform Infrared spectroscopy, or Near-Infrared spectroscopy. Genomic, proteomic, and metabolomic studies, combined with statistical techniques such as Principal Components Analysis, can be very useful to distinguish even minor differences including origin 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 \(Int. J. Syst. Bacteriol, 1980,30:225-420\)](#). 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 a High Performance Liquid Chromatography (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 to 80% to 120% of the label amount.

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 that is used to standardize a product, or for 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 product licence application (PLA) under the column entitled 'potency'. When a marker compound is declared on the PLA and the label tolerance limits for quantification should be set such that there is an upper and a lower limit.

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. Tolerance limits for the quantity of vitamins and minerals should be as per USP limits for the individual vitamins and minerals. In the absence of a pharmacopoeial standard, licence holders 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% of the label claim to ensure an appropriate amount of the medicinal ingredient at the expiry date. Potency of vitamins and minerals can be declared where appropriate.

Tolerance limits above 120% may be used if scientifically justified. Safety of higher limits and degradation products should always be considered.

Overage is used to compensate for the loss of vitamins and minerals during manufacture of the NHPs or loss/degradation of vitamins and minerals 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, tolerance limits of 80 to 120% of the label claim are generally appropriate. The safety

of degradation products should be taken into account when considering the expansion of tolerance limits.

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 microorganisms it is acceptable to list the total CFU count as the quantity and list the strains as sources of the medicinal ingredient.

Licence holders should ensure that all products meet a minimum of 80% of the label claim for viable organisms at the end of the shelf-life. Upper limits for total CFU's should be established according to GMPs. The licence holder should have evidence of the stability of that culture under the recommended storage conditions to the end of the products shelf-life, available upon request.

2.3.1.5 Enzymes

The quantity per dosage unit must include the activity of the enzyme. Tolerance limits for the activity of enzymes should be 80% to 150% of the label amount. The activity is measured according to the reaction catalyzed by individual enzymes (substrate specificity). Methods and units (e.g., FCC Lipase Units, FCC Lactase Units) specified in the *Food Chemicals Codex* (FCC) should be used. 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 licence holder to ensure that all products meet a minimum of 80% of the label claim for potency/activity at the end of the shelf-life.

2.3.2 Quantification by input

Quantification by input means that the active ingredients are not assayed at the finished product stage. 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. 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. It is the responsibility of the licence holder to ensure that quantification by input is appropriate for the ingredient.

Quantification by input may be appropriate when the active ingredient is a whole herb or a complex extract. In the case of medicinal ingredients where the formulation of the NHP is of such complexity that a validated assay method for the quantity of an 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" may be 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). In this case the product licence holder uses controls other than assay for some of the ingredients present, and assays critical ingredients.

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% 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 exist and be available to the NNHPD 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 Natural Health Product Regulations (NHPR), the finished product specifications shall contain detailed information regarding the purity of the natural health product (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 Natural and Non-prescription Health Products Directorate (NNHPD) monograph exists for an ingredient, the specification section of the monograph should be consulted to determine whether the NNHPD requires specific tests for the ingredient or the finished product. The [NHPID](#) should also be consulted for additional specifications for ingredients.

If the licence holder tests for contaminants at the raw material stage or when ingredients conform to an acceptable pharmacopoeial grade, no testing for the contaminant is required at the finished product stage as long as appropriate Good Manufacturing Practices (GMPs) are in place to assure that the finished product is free from any additional contamination. Raw materials that meet pharmacopoeial standards should not require further chemical purity testing. 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.

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 licence holder should maintain scientific rationales justifying exemption of these tests.

The NNHPD generally 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.), World Health Organization (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., *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.

Tolerance limits should comply with those set out in appropriate pharmacopoeias (e.g. USP, BP, Ph. Eur.).

3.1.1 Microbial contamination requirements for specific products and routes of administration

3.1.1.1 Multi-component products

For products with multiple ingredients, each with different tolerance limits, the tolerance limit 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.

Refer to Appendix 4 for additional information on microbial contaminant tolerance limits.

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 *Enterobacter* (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.

3.1.1.2 Products in liquid dosage form

Pseudomonas aeruginosa testing is generally required for non-probiotic liquid products unless alcohol is present at a concentration greater than 50%.

3.1.1.3 Sterile products

Sterile products (e.g. Ophthalmic products) should comply with the criteria as defined in Ph.Eur. 2.6.1 Sterility.

3.2 Chemical contaminants

Chemical contaminant testing should be considered for all products. However, it is generally 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 the acceptable test methods in the NHPID, Pharmacopoeial or any other internationally accepted methods for individual elements.

Chemical contaminant testing at the raw material stage or for ingredients conforming to an acceptable pharmacopoeial grade does not require re-testing for contaminants at the finished product stage.

Finished product testing is not required if testing was conducted on the raw materials or if the ingredients meet an appropriate pharmacopoeial grade.

Table 1: 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	< 0.09 µg/kg b.w./day
Lead	< 10.0 µg/day	< 0.14 µg/kg b.w./day
Total	< 20.0	< 0.29 µg/kg

Appendix 1, Table 6 contains reference body weights that should be used to calculate appropriate limits for sub-populations based on age.

mercury	µg/day	b.w./day
Methyl mercury	< 2.0 µg/day ¹	< 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 tolerance limits 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.

When tolerance limits for individual metals on specifications are defined in ppm or another concentration unit of measure, 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 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 licence holder is required to conduct additional testing with arsenic speciation to demonstrate that the dose of inorganic arsenic does not exceed 0.03 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 NNHPD 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

Testing for Chromium VI should be performed if a concern for Chromium contamination is identified. A tolerance limit of 0.29 µg/kg b.w./day or limits from an appropriate pharmacopeia should be applied.

3.2.1.3 USP <231> total heavy metals

The USP <231> and Ph.Eur 2.4.8 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 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 if it can demonstrate based on testing of representative batches of the product that no individual heavy metals approach the NNHPD 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 should meet the following limits:

Table 2: 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	1 ppm
Antimony	5 ppm

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

3.3 Other impurities

It is the licence holders 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 NNHPD monographs should be consulted when establishing specifications.

The USP, Ph. Eur., B.P. and FCC monographs are examples of some 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 or 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 NNHPD has set tolerance limits 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 NNHPD 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.

Licence holders should test other cyanobacterial products for microcystins if there is a history of contamination.

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 it is used 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 gas chromatography (GC) and high-performance liquid chromatography (HPLC) techniques. Tolerance limits 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 a tolerance limit of not more than 0.5% is considered acceptable to test for solvent residues.

If manufacturers have ascertained through a cumulative procedure, according to USP <467>, that the level of residual solvents is acceptable and below the acceptable limit, residual solvent testing is not required.

3.3.4 Hormone testing of animal materials

Non-human animal materials used in NHPs, such as ovaries, hypothalamus, prostate gland, mammary gland, pituitary gland, adrenal gland, and orchic gland, must not contain sex hormones, which are regulated as prescription drugs under the [Food and Drug Regulations](#) or as controlled substances as set out in Schedule IV to the [Controlled Drugs and Substances Act](#), and thus are excluded from NHPs by the [Natural Health Products Regulations](#). The main sex hormones of concern are progesterone, estrogens (Estradiol + Estrone), testosterone, and DHEA. Hormone testing is only required for those animal materials used in NHPs that are known to contain hormones regulated in Canada as prescription drugs or as controlled substances.

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 NNHPD.

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 tested using an appropriate method.

Pesticide testing may not be required for some products. For example, products with a certified organic content of $\geq 95\%$ or topical products using pharmacopeial grade ingredients that do not have pesticide residue limits may not require pesticide testing.

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 in the [List of Maximum Residue Limits Regulated Under the Pest Control Products Act](#).

3.3.8 Contaminants in marine oils

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 (Ph. Eur: EPA 2008; EPA 1994). Licence holders 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 3: Acceptable limits of dioxins and dioxin-like polychlorinated biphenyls in oils from marine sources

Dioxin and dioxin-like polychlorinated biphenyl contaminants	Maximum level ¹
Sum of PCDDs and PCDFs	2.0 pg TEQ TEF/g oil
Sum of PCDDs and PCDFs and Dioxin-like PCBs ²	10.0 pg TEQ TEF/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-nitrofurans 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 nitrofurans metabolites/residues from Furazolidone, Furaladone, Nitrofurantoin, and Nitrofurazone are of concern. Further information on analysis can be found in several articles, e.g.: 'Determination and confirmation of nitrofurans residues in honey using LC-MS/MS' JOURNAL-OF-AGRICULTURAL-AND-FOOD-CHEMISTRY. FEB 21 2007; 55 (4): 1103-1108, Lopez-MI; Feldlauer-MF; Williams-AD; Chu-PS. Licence holders are required to test for the presence 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, tolerance limits 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.

Tolerance limits 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 tolerance limits 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 4: Acceptable limits for oxidative stability parameters in marine oils

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

Did you know that diethylene glycol has been an adulterant in glycerin & toothpaste? Melamine has been an adulterant in milk derived products? And that erectile dysfunction, sleep aid and weight loss products have been adulterated with prescription drugs?

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 licence holder should develop product specific limits that ensure stability of the oil in the finished product.

3.3.12 Potential adulterants in natural health products

It is the responsibility of the product licence holder to ensure that the finished product is free from adulteration. The potential risk that undeclared ingredients are present should be considered along the entire supply chain.

Adulterations can occur as a result of poor quality control practises or it can be purposeful in order to use cheaper alternatives or improve product efficacy.

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

It is the responsibility of product licence holders to ensure that all products are free from TSE and BSE causing agents. Product licence holders are encouraged to consult the [Food and Drug Regulations B.01.047.1](#) for information on restrictions for “specified risk materials”.

Additionally the NNHPD strongly advises product licence holders not to 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 NNHPD recommends using alternatives 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. Additional tests and criteria

4.1 General indicators for quality

[Additional information can be found in the following documents: European Agency for the Evaluation of Medicinal Products \(EMA\): Note for Guidance on Quality of Herbal Medicinal Products \(CPMP/QWP/2819/00\) and Note for Guidance on Specification: Test Procedures for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products \(CPMP/QWP/2820/00\).](#)

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

This test is important in determining the amount of inorganic impurities in the form of extraneous (non-biological) materials that are present in plant, algal or fungal materials.

4.1.3 Water content

This test is required where the material is known to be hygroscopic. Tolerance limits 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 holder 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

A summary of physical test requirements for certain dosage forms is summarized in **Appendix 2**.

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 other pharmacopoeial methods. Tolerance limits 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 and dissolution 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-point testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms.

Did you know that disintegration testing is not required if dissolution testing is performed?

For extended-release NHPs, *in vitro* or *in vivo* correlation may be used to establish limits 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 limits 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. Tolerance limits 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 specification criteria as outlined in these publications.

4.3 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 can be found in the [Evidence for Homeopathic Medicines Guidance Document](#).

4.4 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 for 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 as “allergen free” are truthful.

4.5 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 licence holder to ensure that any reduced testing will not compromise the safety of the product and is supported by a scientific rationale.

Did you know that the Good Manufacturing Practices guidance document provides more detailed information on stability and reduced testing?

4.6 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 tolerance limits 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.

4.7 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 NNHPD may request stability information as a component of the site licensing process. For more information on stability please see the [Good Manufacturing Practices](#) guidance document.

Section 5. References

5.1 Health Canada documents and databases:

[Natural Health Products Ingredients Database](#) [Accessed 2013-02-19]

[The Natural Health Products Regulations](#) [Accessed 2013-02-19]

[Food and Drug Regulations](#) [Accessed 2013-02-19]

[Good Manufacturing Practices Guidance Document](#) [Accessed 2013-02-19]

[Site Licensing Guidance Document](#) [Accessed 2013-02-19]

Product Master Files. Therapeutic Products Directorate guidance. Available by writing to dmf.enquiries@hc-sc.gc.ca

[Product Licensing Guidance Document](#) [Accessed 2013-02-19] [Accessed 2012-06-19]

[Clinical Trials for Natural Health Products Guidance Document](#) [Accessed 2013-02-19]
[Accessed 2012-06-19]

[Compendium of Monographs](#) [Accessed 2013-02-19] [Accessed 2012-06-19]

[Master File Procedures](#) [Accessed 2013-02-19]

[Official method DO-25](#) [Accessed 2013-02-19]

[Canadian Guidelines for the Management of Naturally Occurring Radioactive Materials \(NORM\)](#)
[Accessed 2013-02-19]

[List of Maximum Residue Limits Regulated Under the Pest Control Products Act](#) [Accessed
2013-02-19]

5.2 International documents

AHPA (2003): *AHPA-AHP Standardization of Botanical Products: White Paper*, American Herbal Products Association, Silver Spring (MD)

[AHPA \(2006\): AHPA-AHP Good Agricultural And Collection Practice For Herbal Raw Materials, American Herbal Products Association, Silver Spring \(MD\)](#) [Accessed 2013-09-18]

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

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

[AOAC \(2002\) AOAC Guidelines for Single Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals](#) [Accessed 2013-02-19]

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[EMA \(2006\): Note for Guidance on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products, European Agency for the Evaluation of Medicinal Products \(CPMP/QWP/2819/00, 30/03/2006\)](#) [Accessed 2013-09-18]

[EMA \(2006\): Note for Guidance on Specification: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products, European Agency for the Evaluation of Medicinal Products \(CPMP/QWP/2820/00, 30/03/2006\)](#). [Accessed 2013-09-18]

EMA (2001). European Agency for the Evaluation of Medicinal Products. *Note for Guidance on Quality of Herbal Medicinal Products* (CPMP/QWP/2819/00, 26/7/2001).

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Section 6. Glossary

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’. [Accessed 2013-02-19]

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. Tolerance limits 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.

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.

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 tolerance limits which are numerical limits, ranges or other criteria for the tests

described. Specifications establish the criteria to which a finished product should conform 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.

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 NNHPD limit of <0.14 µg/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 should be used as per the table below.

Table 5: 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](#) [Accessed 2013-02-19] and the [Centres for Disease Control and prevention \(CDC\) growth charts](#) [Accessed 2013-02-19]. 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 6: 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 NNHPD standards.						

Appendix 2: 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	Number of discharges/ container	Delivered dose uniformity
Tablet, caplet, capsule, etc. ²	X	X		X						
Tablet, rapid dissolving	X		X	X						
Tablet or capsule, sustained release ³	X		X	X	X					
Tablet or capsule, delayed release ⁴	X	X		X						
Oral solutions and suspensions	X					X				
Topical preparations	X					X				
Transdermal patches	X				X		X	X		

Metered dosage forms									X	X
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- 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 Delayed release dosage forms include enteric coated tablets and capsules.

Appendix 3: General finished product specifications for natural health products

Test parameter		Tolerance limits
Identity testing		
Physical description of the finished product		Color, Shape, other tolerance limits as appropriate.
Identity of each Medicinal ingredient (raw material or finished product stage)		As appropriate to identify medicinal ingredient.
Microbial impurity testing (finished product stage) This testing should be performed as per USP, BP or Eur. Pharmacopeia and should be specific to the medicinal ingredient in the product as well as its dosage form.		
Total viable aerobic plate count		USP, BP or Eur. Pharm. limits.
Contaminating fungi (yeast and mould)		USP, BP or Eur. Pharm. limits.
<i>Salmonella spp.</i>		USP, BP or Eur. Pharm. limits.
<i>Escherichia coli</i>		USP, BP or Eur. Pharm. limits.
<i>Staphylococcus aureus</i>		USP, BP or Eur. Pharm. limits.
<i>Pseudomonas aeruginosa</i>		USP, BP or Eur. Pharm. limits.
Other microbial impurity testing as required by USP, BP or Eur. Pharm.		USP, BP or Eur. Pharm. limits.
Chemical contaminants (finished product or raw material stage for applicable ingredients)		
Elemental impurities	Arsenic - Inorganic arsenic - Organic arsenic	Oral: <0.14 µg/kg b.w./day <0.03 µg/ kg b.w./day <20 µg/ kg b.w./day Topical: 3 ppm
	Cadmium	Oral: < 0.09 µg/ kg b.w./day Topical: 3 ppm
	Lead	Oral: < 0.14 µg/ kg b.w./day Topical: 10 ppm
	Total mercury - methylmercury	Oral: < 0.29 µg/ kg b.w./day < 0.029 µg/ kg b.w./day Topical: 1 ppm
	Chromium IV (if applicable)	Oral: < 0.29 µg/ kg b.w./day Topical: 5 ppm
Solvent residues		ICH or USP limits
Pesticides		USP limits

Ingredient specific test parameters		
Mycotoxins (e.g. aflatoxin)		< 20 µg/kg (ppb) for aflatoxins (B1+B2+G1+G2) <5 µg/kg (ppb) for aflatoxin B1
Cyanobacterial toxins		0.02 µg MC-LR/kg b.w./day
Hormones (animal materials)		Absent
Marine oil contaminants	Sum of PCDDs and PCDFs	2.0 pg TEQ TEF/g oil
	Sum of PCDDs, PCDFs and Dioxin-like PCBs	10.0 pg TEQ TEF/g oil
Oxidative stability in oils	Non-marine oils	Pharmacopoeial limits.
	Marine oils - PV - AV - TOTOX Value (2X PV + AV)	NMT 5 mEq/kg NMT 20 mEq/kg NMT 26 mEq/kg
Antibiotic residues in bee products		Absent
Radioactivity		600 Becquerels/kg of substance.
Ash contents (for plant materials such as herbs)		Pharmacopoeial limits.
Loss on drying (for plant materials such as herbs)		Pharmacopoeial limits.
Incidental impurities (specify)		Pharmacopoeial limits if available.
Process impurities (specify)		Pharmacopoeial limits if available.
Ingredient specific impurities (specify)		Pharmacopoeial limits if available.
Related substances (specify)		Pharmacopoeial limits if available.
Potential adulterants (specify)		Pharmacopoeial limits if available.
Degradants (specify)		Pharmacopoeial limits if available.
Quantity (finished product stage)		
Quantity specified by assay for each medicinal ingredient		Conforms to Pharmacopoeial limits or 80-120 % of label claim. Conforms to 100% of label claim.
Quantity specified by input for each medicinal ingredient		
Performance tests*		
Disintegration or dissolution testing		≤ 45 min (uncoated) ≤ 60 min (plain coated) Dissolution profile must be established for controlled-release products. Enteric coated tablet limits should be in accordance with the pharmacopoeia (USP or Ph. Eur.).
Weight variation or uniformity of dosage units		Pharmacopoeial limits.

Antimicrobial effectiveness testing (for products containing a preservative)	Pharmacopoeial limits.
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*Refer to Appendix 2 for additional tests required for specific dosage forms.

Test methods used must be Pharmacopoeial or other internationally recognized methods

Appendix 4: General finished product specifications for products containing live microorganisms

Test parameter		Test method	Tolerance limits
Identity testing			
Physical description of the finished product		Color, shape, other tolerance limits as appropriate.	
Identity of each medicinal ingredient (raw material stage)	Phenotyping	Biochemical testing to enable visible observation of characteristics specific to the species.	A set of testing for sufficient confirmation of observable traits of the species, which can include but are not limited to the following: <ul style="list-style-type: none"> • Gram-staining • API sugar fermentation • Enzymatic activity • Fatty acid profile • Proteome profile
	Genotyping	Species identification by comparison to identical and non-identical type strains obtained from an internationally recognized culture collection (e.g. ATCC; NCTC).	Genome sampling/sequencing through a method that is adequate for the species, demonstrating a minimum homology of 97% to an identical type strain, and below 95% to non-identical ones.
		Strain characterization through complete genome sequencing.	Whole genome <i>in-vitro</i> sampling/sequencing through a method that is adequate for the species, to allow independent confirmation (e.g. RAPD-PCR; PFGE; ERIC-PCR; rep-PCR).
Microbial impurity testing (finished product stage)			
Total aerobic plate count ¹		Pharmacopoeial or other internationally recognized test methods.	10 ⁴ CFU/g or mL
Total yeast and mould count (fungi) ²			10 ² CFU/g or mL
<i>Enterobacteriaceae</i> and bile tolerant Gram-negative bacteria ³			10 ² CFU/g or mL
<i>Salmonella spp.</i>			Absent (10g or 10mL)

<i>Escherichia coli</i>			Absent (1g or 1mL)
<i>Staphylococcus aureus</i>			Absent (1g or 1mL)
<i>Pseudomonas aeruginosa</i> ⁴			Absent (1g or 1mL)
Chemical contaminants (finished product or raw material stage)			
Elemental impurities	Arsenic - Inorganic arsenic - Organic arsenic	Pharmacopoeial or other internationally recognized test methods.	<0.14 µg/kg b.w./day <0.03 µg/ kg b.w./day <20 µg/ kg b.w./day
	Cadmium		< 0.09 µg/ kg b.w./day
	Lead		< 0.14 µg/ kg b.w./day
	Total mercury - methylmercury		< 0.29 µg/ kg b.w./day < 0.029 µg/ kg b.w./day
	Chromium IV (if applicable)		< 0.29 µg/ kg b.w./day
Related impurities			Conforms to Pharmacopoeial limits if available.
Other			Conforms to Pharmacopoeial limits if available.
Quantity (finished product stage)			
Total viable count in colony forming units (CFU)		Internationally recognized methods.	At least 80% of label claim at the end of shelf life.
Performance tests (finished product stage) ⁵			
Disintegration or dissolution testing		Pharmacopoeial or other internationally recognized methods.	≤ 45 min (uncoated) ≤ 60 min (plain coated) Dissolution profile must be established for controlled-release products. Enteric coated tablet limits should be in accordance with the pharmacopoeia (USP or Ph. Eur.).
Virulence tests (raw material stage)			
Antibiotic/antifungal resistance		Broth microdilution or other equivalent non-clinical method.	Minimal inhibitory concentrations (MIC) below species limits, as published by an internationally recognized panel (e.g. EFSA).

Ingredient specific test parameters		
Virulence factor production	PCR/southern blot comparison with a closely related virulent strain (positive control).	Absence of the genetic elements responsible for the production of virulence factors characteristic to the species.
Toxigenic activity	Confirmatory published <i>in-vitro</i> method adequate for the species, or other internationally recognized methods.	Absence of toxin production known to the species (e.g. enteric, emetic).

PCR: Polymerase chain reaction

rep: Repetitive sequence-based

RAPD: Random amplification of polymorphic DNA

PFGE: Pulse field gel electrophoresis

ATCC: American type culture collection

NCTC: The national collection of type cultures

ERIC: Enterobacterial repetitive intergenic consensus

EFSA: European food safety authority

¹ Not required for products containing facultative anaerobic microorganisms (that can live and grow with or without molecular oxygen).

² Not required for products containing fungal microorganisms.

³ Could exceed the 10² CFU/g or mL limit for products containing non-microbial ingredients that have not undergone or have been subject to minimal processing such as an extraction – in which case a higher limit (OR complete exclusion of testing) in line with an appropriate pharmacopeia (e.g. USP, BP or Ph. Eur), would be considered acceptable.

⁴ Testing required for liquid preparations only.

⁵ Refer to Appendix 2 for additional tests required for specific dosage forms.