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COMPENDIUM OF MONOGRAPHS

NATURAL HEALTH PRODUCTS DIRECTORATE

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Canada

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

Health Canada

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

Natural Health Products Directorate

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INTRODUCTION

A monograph is a written description of particular elements on an identified topic. The Compendium is a compilation of monographs based on natural health product (NHP) ingredients.

The Natural Health Products Directorate (NHPD) developed the *Compendium of Monographs* as a tool for the timely and efficient review of the safety and efficacy of many commonly used NHPs.

The NHPD allows applicants to reference a NHPD monograph in support of the safety and efficacy of the NHP as part of their product licence application. This process is efficient for both applicants and Health Canada, since there is no need to evaluate the safety and efficacy of NHP ingredients that are already known to be safe and efficacious when used under the conditions specified in the NHPD monograph.

The Compendium consists of single and combination medicinal ingredient monographs, product category monographs and applicable quality specifications. All monographs appertain to adults, unless otherwise specified. Furthermore, the only acceptable non-medicinal ingredients are those listed in the *NHPD List of Acceptable Non-medicinal Ingredients*, unless otherwise specified. All other aspects of manufacturing and preparing the product for sale, for example good manufacturing practices and labelling, must comply with the *Natural Health Product Regulations* (the Regulations). For more information, see the *Evidence for Quality of Finished Natural Health Products* guidance document, the *Labelling Guidance Document*, the *Good Manufacturing Practices Guidance Document* and the relevant sections of the *Product Licensing Guidance Document*.

For a list of NHPD Single Ingredient Monographs, see the list of published Single Ingredient Monographs at http://hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_list_e.html

For a list of NHPD Product Monographs, see the list of published Product Monographs at http://hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/product_mono_produit_e.html

For a list of acceptable non-medicinal ingredients, see the *NHPD List of Acceptable Non-medicinal Ingredients* at http://hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/nmi-imn_list1_e.html

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6. (1) Subject to subsection (2), the Minister shall dispose of an application submitted under section 5 within 60 days after the day on which it is submitted if, in support of the application, the only information submitted by the applicant under paragraph 5(g) is that which is

a. in the case of an application respecting a natural health product that has only one medicinal ingredient, contained in a monograph for that medicinal ingredient in the Compendium; and

b. in the case of an application respecting a natural health product that has more than one medicinal ingredient, contained in a monograph for that combination of medicinal ingredients in the Compendium.

(2) If the Minister requests that additional information or samples be submitted under section 15, the 60-day period referred to in subsection (1) does not include the number of days beginning on the day on which the request is made and ending on the day on which the additional information or samples are received.

(3) For the purposes of this section, the Minister disposes of an application on the earlier of the day on which

a. the licence is issued in accordance with section 7; and

b. the applicant is sent a notice under subsection 9(1).

A compendial application cites a NHPD monograph in the Compendium to support the safety and efficacy of medicinal ingredient(s) in the NHP. When it does so, under the 60-day disposition described in section 6 of the Regulations, Health Canada must assess that application within 60 days of receipt.

For compendial applications, the only non-medicinal ingredients that may be used in association with that ingredient are those listed in the *NHPD List of Acceptable Non-medicinal Ingredients* unless otherwise specified. Requirements for non-medicinal ingredients are outlined in the *Evidence for Safety and Efficacy of Finished Natural Health Products*. The minimum requirements for the specifications of each type of ingredient will be found in **chapter 3**.

The 60-day disposition does not apply to irradiated products. See the *Evidence for Quality of Finished Natural Health Products* guidance document for more details.

1.2 NHPD Monograph Format

Each NHPD monograph contains the following elements:

- proper name;
- common name;
- source material;
- route of administration;
- dosage form;
- use or purpose;
- dose;
- duration of use;
- risk information;
- specifications; and
- non-medicinal Ingredients.

The interpretation of each element of the monograph can be found in **chapter 2** of the Compendium. Additional examples are located in the *Product Licensing Guidance Document.*

1.3 References Used in NHPD Monograph Development

The Compendium is comprised of monographs based on information obtained from scientific and traditional sources with regard to the safety and efficacy associated with the use of NHPs.

The NHPD considers the following when making the initial selection of NHP ingredients for which monographs may be developed:

- historical use, prior marketing experience or clinical research that does not raise concerns about the safety of the product and supports the efficacy of the product for its intended purpose and use;
- sales statistics from Canadian manufacturing associations have determined the product is commonly used in Canada, or an assessment of the product in accordance with the *Food and Drug Regulations* has determined it to be safe and effective;
- suggestions from the NHPD's Expert Advisory Committee; and
- suggestions from stakeholders.

Developing the monographs involves considering information gathered from sources such as:

- published compendia such as those of the World Health Organization, European Scientific Cooperative on Phytotherapy and the German Commission E;
- articles published in peer-reviewed journals;
- information published in national pharmacopoeias such as the *United States Pharmacopeia*, *British Herbal Pharmacopoeia* and the *Pharmacopoeia of the People's Republic of China*;
- other published expert committee reports such as the Dietary Reference Intakes (1997-2006) and the U.S. Agency for Health Care Research and Quality (ongoing); and

- Health Canada publications such the Therapeutic Products Directorate's *Category IV Monographs* and *Labelling Standards*.

1.4 Revising Monographs

The monograph revision process is currently being reviewed by the NHPD. Once the process for revising NHPD monographs is finalized it will be communicated in the NHPD Monthly Communiqué. The monograph revision process will be added to the *Compendium of Monographs* during the next guidance document revision process.

1.5 Adding Monographs

The NHPD may develop and add new monographs to the Compendium, when the available body of evidence for a NHP ingredient supports its inclusion in the Compendium.

Suggestions for ingredients that should be the subject of a monograph and included in the Compendium can be submitted to NHPD, along with the rationale and supporting data for consideration. Please send suggestions and comments to:

Natural Health Products Directorate
Bureau of Research, Outreach and Programs
Qualicum Building, Tower A
2936 Baseline Rd
Ottawa, ON
K1A 0K9

General inquiries may be made using the coordinates below:

E-mail: NHPD_DPSN@hc-sc.gc.ca
Phone: 1-888-774-5555

1.6 Combinations

Multiple NHP Ingredients

A Product Licence Application with multiple medicinal ingredients listed in a single NHPD monograph is considered a compendial application. If a Product Licence Application contains multiple medicinal ingredients that are monographed individually, they do not fall within the 60-day disposition clause, as the rationale for that combination will require evaluation. However, individual NHPD monographs can be used to support the safety and efficacy of individual ingredients for a non-compendial Product Licence Application.

Product Monographs

Ingredients outlined in the Therapeutic Products Directorate's (TPD's) *Category IV Monographs* and *Labelling Standards* are classified as either a drug or a NHP. A product with a single NHP

ingredient or a combination thereof will be governed by the Regulations. The NHPD is currently adapting relevant *Category IV Monographs* and *Labelling Standards* information into NHPD product monographs, to be incorporated in the NHPD *Compendium of Monographs*. Once incorporated in the Compendium, all requirements for a compendial submission will apply to these NHP ingredients.

A product monograph differs from those monographs describing a single NHP ingredient in that it outlines the conditions of use based on a product category (e.g. anti-perspirant, anti-fungal etc) and not the NHP ingredient. As such, a single NHP ingredient may appear on several product monographs. Therefore, the conditions of use for that NHP ingredient, such as dose, including directions of use, recommended use or purpose and risk information, will differ depending on the product category. Product monographs will include all acceptable combinations of NHP ingredients within a product category.

For more information on ingredient classification, see *A Summary of NHP/Drug Classification of TPD Category IV Labelling Standards Ingredients*. http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/list_mono4_e.html

For more information on combination products, see Chapter 9.0, Combination of Medicinal Ingredients, of the *Evidence for Safety and Efficacy of Finished Natural Health Products guidance document*.

2.0 ELEMENTS OF A MONOGRAPH

When submitting a compendial application, several items on the Product Licence Application form must parallel the monograph content exactly, including the proper name, common name, source material, recommended route of administration and recommended dose. The remaining sections of the monograph - use or purpose and risk information - may use a "statement to the effect of." This allows applicants to alter the wording, but not the intent, of the monograph elements. An NHPD assessment officer will evaluate the suggested wording to determine whether it has the same intent as the monograph. When the information provided in the Product Licence Application form does not convey the same intent, the applicant will be given the option of rewording the claim to reflect the monograph or of having the Product Licence Application form removed from the 60-day disposition and transferred to the non-compendial assessment stream.

The following are the parameters for the use of a NHPD monograph under the 60-day disposition:

- **Proper name.** The proper name must be identical to the way it appears on the monograph.
- **Common name.** The common name must be chosen from one of the common names from the options provided in the monograph.
- **Source material.** The source material must be chosen from the options provided in the monograph. More than one source material is acceptable, providing that all source materials listed in the Product Licence Application form reflect the same dose and/or use or purpose on the referenced monograph.
- **Route of administration.** The route of administration must be chosen from the options provided in the monograph. Please see Appendix 8 of the *Product Licensing Guidance Document* for a list of acceptable routes of administration.
- **Dosage form.** The dosage form must reflect the route of administration noted in the monograph and must be chosen from the list of recognized dosage forms. Please see Appendix 7 of the *Product Licensing Guidance Document* for a list of acceptable dosage forms. A number of dosage forms are unsuitable for compendial applications as they require quality assessment. See **Appendix 1** of this document for a list of unacceptable dosage forms.
- **Use or purpose.** The uses have been identified for each monographed ingredient based on NHPD's evaluation of the safety and efficacy data. Applicants may choose from one or more claims provided in the monograph or create an alternative using a "statement to the effect of."
- **Dose.** The total daily dose must be either equal to that noted in the monograph, or, when a range is specified, fall within the range indicated in the monograph. Furthermore, to make a traditional use claim, the method of preparation must be one that was traditionally used. Please see the *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document* for a list of traditional methods of preparation. The dose indicated on the monograph may include:

- **Subpopulation.** All monographs appertain to adults unless otherwise specified.
- **Potency.** Only when the monograph includes a potency, can a potency be included in the Product Licence Application form.
- **Frequency.** The frequency must be the same as the frequency on the monograph when specified. When the monograph specifies a divided dose the frequency must be more than once daily. If no frequency is specified, the applicant may select an appropriate frequency.
- **Directions of use.** Where specified, all directions of use must be included in the Product Licence Application form. The directions of use may be identical to that on the monograph or the applicant may choose to write a "statement to the effect of."

- **Duration of use.** When the monograph includes duration of use, it must be included on the Product Licence Application form.
- **Risk information.** All risk information contained in the monograph must be included in the Product Licence Application form. The risk information may be identical to that on the monograph, or the applicant may choose to write a "statement to the effect of."
- **Specifications.** The specifications must meet the minimum requirements outlined in **Chapter 3** of the Compendium. Please note that certain monographs will include additional specifications relevant to that ingredient or product.
- **Non-medicinal ingredients**. Only non-medical ingredients listed on the *NHPD List of Acceptable Non-medicinal Ingredients* may be used unless otherwise specified.

3.0 SPECIFICATIONS

Applicants should consult the product specifications herein in conjunction with the Guidance Document *Evidence for the Quality of Finished Natural Health Products* and any NHPD monthly communiqués relevant to quality issues.

By submitting a compendial application, applicants attest to the specifications in the Compendium and are not required to submit product specifications in their application package. Please note, however, that the Compendium sets out *minimum* specifications for products, and therefore applicants should also include in their specifications any additional tests or study results which are specific to their product and are not indicated in the compendial specifications.

Specifications for product quantity and purity (where relevant) should be applicable for the duration of the product's shelf life.

Applicants not attesting to the compendial specifications for their products who submit specifications which do not meet with those of the Compendium will have their applications removed from the compendial review stream to allow for a review of product quality. If tests are to be performed on raw materials rather than the finished product, this should be clearly stated on the finished product specifications. Additional documentation to support quality should also be submitted where applicable (e.g. documentation to support the claim that gelatin is free from risk of transmission of TSE).

Table 1: Finished product specifications template for a product containing a plant, plant material, alga, fungus or bacterium and/or their extracts or isolates +

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Macroscopic/organoleptic (not applicable to extracts and isolates)	Pharmacopoeial or other internationally recognized methods	Conforms to herbarium reference material
	Microscopic (not applicable to extracts and isolates)	Any microscopy method	Conforms to herbarium reference material
	Chemical identity (for extracts and isolates)	TLC, HPLC or other internationally recognized methods	Characteristic of the material
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	$< 1 \times 10^4$ cfu/g or ml
	Total viable aerobic count	Pharmacopoeial or other internationally recognized methods	$< 1 \times 10^5$ cfu/g or ml

Purity (Chemical)	*Escherichia coli*	Pharmacopoeial or other internationally recognized methods	< 1 X10^1 cfu/g for all internal use except for teas, decoctions, or topical dosage forms: < 1 X 10^2 cfu/g
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	For plant, plant material, alga, fungus or bacterium: < 1 X 10^2 cfu/ g or ml for all internal uses except for teas, decoctions, or topical dosage forms: < 1 X 10^4 cfu/g or ml For extracts: Not detectable per g or ml
	Pseudomonas aeruginosa (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Aflatoxins (for nuts and ginseng or their extracts and isolates or any substances derived from these) Cyanobacterial toxins (for algal materials)	Pharmacopoeial or other internationally recognized methods Internationally recognized methods	Aflatoxins < 20 µg/kg (ppb) of substance Limits based on available toxicity data
	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Pesticides	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial limits
	Solvent residues (for extracts and isolates)	Pharmacopoeial or ICH	Conforms to pharmacopoeial or ICH limits

	Other impurities (for extracts and isolates) **	Pharmacopoeial	Conforms to pharmacopoeial limits
	Radioactivity (if suspected)	International Atomic Energy Agency	600 Becquerel/Kg of substance
Quantity/potency	Quantity tests	GC, HPLC or other internationally recognized methods	80 -120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

Table 2: Finished product specifications template for a product containing a non-human animal material and/or their extracts or isolates +

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Macroscopic/organoleptic (not applicable to extracts and isolates)	Pharmacopoeial or other internationally recognized methods	Conforms to reference material
	Microscopic (not applicable to extracts and isolates)	Any microscopy method	Conforms to reference material
	Chemical identity (for extracts and isolates)	TLC, HPLC or other internationally recognized methods	Characteristic of the material
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 1 X 10^4 cfu/g or ml
	Total viable aerobic count	Pharmacopoeial or other internationally recognized methods	< 1 X 10^5 cfu/g or ml
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Pseudomonas aeruginosa (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
Purity (Chemical)	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Pesticides	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial limits
	Solvent residues (for extracts and isolates)	Pharmacopoeial or ICH	Conforms to

			pharmacopoeial or ICH limits
	Other impurities (for extracts and isolates) **	Pharmacopoeial	Conforms to pharmacopoeial limits
	Specific contaminants (PCDDs, PCDFs and PCBs in marine animal materials only)	As per CRN monograph****	As per CRN monograph****
	Radioactivity (if suspected)	International Atomic Energy Agency	600 Becquerel/Kg of substance
Quantity/potency	Quantity tests	GC, HPLC or other internationally recognized methods .	80 -120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

****Council for Responsible Nutrition's Monograph at: http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf

Table 3: Finished product specifications template for a product containing enzymes +

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Physical description Chemical identity	Any appropriate method HPLC, MS, gel electrophoresis, spectrophotometric methods, substrate specific or other appropriate assays.	Not applicable Appropriate to identify Medicinal Ingredients
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 1 X 10^4 cfu/g or ml
	Total viable aerobic count	Pharmacopoeial or other internationally recognized methods	< 1 X 10^5 cfu/g or mL
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Pseudomonas aeruginosa (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Enterobacteriaceae	Pharmacopoeial or other internationally recognized methods	< 1 X 10^2 cfu/g or ml
Purity (Chemical)	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other	< 0.29 µg/kg b.w./day

		internationally recognized methods	
	Antibiotic activity (for microbially derived enzymes)	FAO/WHO or other internationally recognized methods	Not detectable
	Solvent residues	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial or ICH limits
	Related impurities**	Pharmacopoeial	Conforms to pharmacopoeial limits
Quantity	Enzyme activity assay	Assay (substrate specific), HPLC or other internationally recognized methods	80%-150% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

Table 4: Finished product specifications template for a product containing vitamins +

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Physical description Chemical identity	Any appropriate method Pharmacopoeial or other internationally recognized methods	Not applicable Conforms to pharmacopoeial standard(if applicable) Appropriate to identify MI
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 3 X 10^2 cfu/g or mL
	Total viable aerobic Count	Pharmacopoeial or other internationally recognized methods	< 3 X 10^3 cfu/g or mL
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Pseudomonas aeruginosa (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
Purity (Chemical)	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Solvent residues	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial or ICH limits
	Related impurities**	Pharmacopoeial	Conforms to pharmacopoeial limits

Quantity/Potency	Quantity tests	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial limits or, in their absence, 80 -120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

Table 5: Finished product specifications template for a product containing amino acids +

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Physical description Chemical identity	Any appropriate method Pharmacopoeial other internationally recognized methods	Not applicable Conforms to pharmacopoeial standard(if applicable) Appropriate to identify MI
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 3 X 10^2 cfu/g mL
	Total viable aerobic count	Pharmacopoeial or other internationally recognized methods	< 3 X 10^3 cfu/g or mL
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
Purity (Chemical)	*Pseudomonas aeruginosa* (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Solvent residues	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial or ICH limits
	Other impurities **	Pharmacopoeial or other internationally	Conforms to pharmacopoeial limits

		recognized methods	
Quantity/Potency	Quantity tests	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial limits or 80 -120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

Table 6: Finished product specifications template for a product containing essential fatty acids+

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Physical description Chemical identity	Any appropriate method Pharmacopoeial or other internationally recognized methods	Not applicable Characteristic of the material Appropriate to identify MI
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 1 X 10^4 cfu/g or mL
	Total viable aerobic count	Pharmacopoeial or other internationally recognized methods	< 1 X 10^5 cfu/g or mL
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Pseudomonas aeruginosa (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
Purity (Chemical)	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Solvent residues	Pharmacopoeial or other internationally recognized methods	Conforms to Pharmacopoeial or ICH limits
	Specific contaminants (PCDDs, PCDFs and PCBs if oils are of marine animal origin)	As per CRN monograph****	As per CRN monograph****

	Other impurities**	Pharmacopoeial or other internationally recognized methods	Conforms to pharmacopoeial limits
Quantity	Quantity tests	Internationally recognized methods (GC, HPLC etc)	80%-120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

****Council for Responsible Nutrition's Monograph at:
http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf

Table 7: Finished product specifications template for a product containing synthetic duplicates+

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Physical description Chemical identity	Any appropriate method Pharmacopoeial other internationally recognized methods	Not applicable Appropriate to identify MI
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 3 X 10^2 cfu/g or mL
	Total viable aerobic count	Pharmacopoeial or other internationally recognized methods	< 3 X 10^3 cfu/g or mL
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Pseudomonas aeruginosa (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
Purity (Chemical)	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Solvent residues	Pharmacopoeial or other internationally recognized methods	Conforms to Pharmacopoeial or ICH limits
	Other impurities**	Pharmacopoeial or other internationally	Conforms to pharmacopoeial limits

		recognized methods	
Quantity	Quantity tests	Internationally recognized methods (GC, HPLC etc)	80%-120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

Table 8: Finished product specifications template for a product containing minerals+

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Physical description Chemical identity	Any appropriate method Pharmacopoeial other internationally recognized methods	Not applicable Appropriate to identify MI
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 3 X 10^2 cfu/g or mL
	Total viable aerobic count	Pharmacopoeial or other internationally recognized methods	< 3 X 10^3 cfu/g or mL
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Pseudomonas aeruginosa (for liquids with < 50% alcohol)	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
Purity (Chemical)	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Solvent residues	Pharmacopoeial or other internationally recognized methods	Conforms to Pharmacopoeial or ICH limits
	Related impurities**	Pharmacopoeial	Conforms to pharmacopoeial limits

Quantity	Quantity tests	Pharmacopoeial or other internationally recognized methods	Conforms to Pharmacopoeial limits or, in their absence, 80 -120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for disintegration)	Pharmacopoeial or other internationally recognized methods	NMT 45 min (uncoated tablet) NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

Table 9: Finished product specifications template for a product containing probiotics+

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity (Genus, epithet, strain) *May be performed on raw material if no appropriate test is available for MI in finished product	Physical description	Any appropriate method	Not applicable
	Phenotyping	Microscopy or Gram stain reactions, or biochemical tests or culturing and growth conditions and strain number	Characteristic for genus/epithet/strain. Database comparison (e.g. API strips). Specify strain-specific culturing and growth conditions
	Genotyping (optional)	PCR/sequence analysis and restriction fragment length polymorphism (RFLP)	Characteristic of the bacterial strain
Purity (microbial)	Contaminating fungus (yeast and mould)	Pharmacopoeial or other internationally recognized methods	< 1 X 10^4 cfu/g or ml
	Enterobacteriaceae	Pharmacopoeial or other internationally recognized methods	< 1 X 10^2 cfu/g or ml
	Escherichia coli	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Salmonella spp.	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
	Staphylococcus aureus	Pharmacopoeial or other internationally recognized methods	Not detectable per g or ml
Purity (Chemical)	Arsenic	Pharmacopoeial or other internationally recognized methods	< 0.14 µg/kg b.w./day
	Cadmium	Pharmacopoeial or other internationally recognized methods	< 0.09 µg/kg b.w./day
	Lead	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Total mercury	Pharmacopoeial or other internationally recognized methods	< 0.29 µg/kg b.w./day
	Related impurities**	Pharmacopoeial	Conforms to pharmacopoeial limits
Quantity	Total viable count	Internationally recognized methods	80%-300% of label claim
Performance tests (where	Disintegration (for tablets and capsules)	Pharmacopoeial or other internationally	NMT 45 min (uncoated tablet)

applicable)	(Dissolution may be substituted for disintegration)	recognized methods	NMT 60 min (coated tablet)

+- The tolerance limits specified are applicable to products containing single or multi ingredients from this category

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

Table 10: Specifications template for finished products containing synthetic duplicates for topical use

Test Parameters	Test	Method(s)	Tolerances
Physical description of finished product	Organoleptic	Visual, olfactory	Color, shape
Identity of medicinal ingredients *May be performed on raw material if no appropriate test is available for MI in finished product	Physical: specific rotation, refractive index (for a liquid), solubility in common solvents (e.g., water, alcohols), specific gravity, residue on ignition Chemical: molecular weight, MS, infrared absorption (IR), NMR, HPLC, GC, AA and/or any other appropriate identification tests.	Pharmacopoeial	Conforms to pharmacopoeial standard (if applicable) Appropriate to identify MI
Physical description of finished product	Organoleptic (such as colour, form, etc)	Appropriate method(s)	n/a
Purity (microbial)	Total Viable Aerobic Count*	Pharmacopoeial	< 3 X 10^3 microorganisms per g or per mL
	Contaminating fungus*	Pharmacopoeial	< 3 X 10^2 microorganisms per g or per mL
	Escherichia coli*	Pharmacopoeial	Not detectable per g or mL
	Salmonella*	Pharmacopoeial	Not detectable per g or mL
	*Staphylococcus aureus**	Pharmacopoeial	Not detectable per g or mL
	*Pseudomonas aeruginosa** (for liquids with < 50% alcohol)	Pharmacopoeial	Not detectable per g or mL
Purity (Chemical)	Total Heavy Metals**	Pharmacopoeial (e.g. USP <231>)	≤10 ppm (as Pb)
	Solvent residues**	Pharmacopoeial or other internationally recognized methods	Conforms to Pharmacopoeial or ICH limits
	Related impurities**	Pharmacopoeial	Conforms to pharmacopoeial limits
Quantity/potency	Quantitative tests	HPLC, GC etc. or other internationally recognized methods	conforms to relevant pharmacopoeial standard or in its absence, default of 80-120% of label claim
Performance tests (where applicable)	Disintegration (for tablets and capsules) (Dissolution may be substituted for	Pharmacopoeial or other	NMT 45 min (uncoated tablet)

	disintegration)	internationally recognized methods	NMT 60 min (plain coated tablet)
	Antimicrobial Effectiveness***	USP <51>, Ph. Eur. 5.1.3 or equivalent	Meets pharmacopoeial requirement

* May be tested in accordance with USP General Chapter <1112>
n/a- not applicable

** Not required if impurities are tested in raw materials and the impurity is not a degradation product.

*** Required for products containing preservatives, performed at the end of shelf-life (test on development batches). Not required on every batch.

APPENDIX 1: LIST OF UNSUITABLE DOSAGE FORMS*:

A number of dosage forms are unsuitable for compendial applications as they require quality assessment.

Categories of dosage forms that are unsuitable for compendial applications:

- metered;
- combined, extended or delayed release;
- patch, systemic release; or
- liposomal formation

Specific dosage forms that are unsuitable for compendial applications:

- aerosol, metered-dose;
- capsule, combined release;
- capsule, delayed release;
- capsule, extended release;
- cream, liposomal;
- gel, extended release;
- granule, delayed release;
- patch, extended release;
- powder, delayed release;
- powder for suspension, extended release;
- powder, metered dose;
- spray, metered dose;
- suppository, extended release;
- suspension, liposomal;
- syrup, extended-release;
- tablet, combined release;
- tablet, delayed release;
- tablet, extended release; and
- enteric coated dosage forms

*Please note that this list is not exhaustive.