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Clinical Trials For Natural Health Products

The Natural Health Products Directorate (NHPD) has changed its name to the Natural and Non-prescription Health Products Directorate (NNHPD) subsequent to its recently expanded mandate to include the oversight of non-prescription and disinfectant drugs in addition to natural health products (NHPs). Please note that we are currently modifying documents to reflect this change.

Thank you for your patience and understanding.

About This Guidance Document

This guidance document is designed to assist organizations and individuals in applying for authorization to conduct a clinical trial for a natural health product (NHP) in Canada . The legal requirements for clinical trials for natural health products in Canada are found in Part 4 of the *Natural Health Products Regulations (NHP Regulations).* The Natural Health Products Directorate (NHPD) in the Health Products and Food

Branch of Health Canada administers the *NHP Regulations*.

Guidance documents do not have the force of law, but provide suggestions about how to meet the legal requirements. Alternate approaches that meet the legal requirements may be acceptable but should be discussed in advance with the NHPD to avoid failure to comply with statutory or regulatory requirements. The NHPD may ask for information, material or changes not indicated in this guidance document, but required as per the *NHP Regulations*.

The NHPD is the directorate of Health Canada responsible for authorizing or denying permission to conduct a clinical trial for a natural health product. Information from clinical trials is used in assuring the safety, efficacy and quality of natural health products. The process of applying for authorization to conduct a clinical trial is designed to ensure the safety and ethical treatment of human experimental subjects and other persons involved in the trial. Adequate protocols and procedures for each clinical trial are required to provide a reasonable expectation that the trial objectives will be met.

Not all clinical trials of natural health products require authorization from Health Canada . This guidance document includes information on which types of clinical trials of natural health products do not require authorization.

This *Clinical Trials for Natural Health Products Guidance Document* should be read in parallel with the *NHP Regulations*. The regulations were published in Canada Gazette, Part II, on June 18, 2003. An electronic version of the regulations is available on the internet. In this guidance document, references to relevant sections of the *NHP Regulations* are enclosed in square brackets.

This guidance document refers to other NHPD documents found on the internet. Documents of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) may be useful in preparing a Clinical Trial Application (CTA). These documents can be found on the ICH website.

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1.0 Clinical Trials for Natural Health Products

1.1 Regulatory Overview

According to section 1(1) of the NHP Regulations, a **natural health product** is:

"a substance set out in Schedule 1 or a combination of substances in which

all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans; (b) restoring or correcting organic function in humans; or (c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health."

However, an NHP does not include a substance set out in Schedule 2 of the *NHP Regulations*, any combination of substances that includes a substance set out in Schedule 2 or a traditional medicine that is or includes a substance set out in Schedule 2.

An NHP also does not include a substance that is listed or within any limitations specified in Part I or Part II of Prescription drug list (prescription drugs) to the *Food and Drug Regulations*, or a combination of substances or traditional medicine that contains an ingredient that is listed or within any limitations specified in Part I or Part II of Prescription drug list [Section 2(2) of the *NHP Regulations*] (Prescription drug list).

Consult the *Evidence for Homeopathic Medicines Guidance Document* for information on substances allowed in homeopathic medicines regulated by the NHPD.

For an overview of the *NHP Regulations*, please refer to *Overview of the NHP Regulations Guidance Document*. Part 4 of the *NHP Regulations* describes what is required for clinical trials using an NHP. The requirements of a **clinical trial** (CT) with an NHP are similar to the requirements for a CT of a conventional pharmaceutical as described in Division 5 of the *Food and Drug* Regulations, but Part 4 of the *NHP Regulations* takes into consideration the unique aspects of CTs for NHPs.

The scope of Part 4 of the NHP Regulations is to ensure:

- The safety, efficacy and quality of both the CT **protocol** and the investigational product(s) and **placebo/comparator** given during the study
- The safety of clinical trial subjects and other people
- Compliance with ICH, **Good Clinical Practice** (GCP) and federal and provincial laws. Information concerning GCPs can be found in section 74 of the *NHP Regulations* or in the ICH Guidance Document *Good Clinical Practice: Consolidated Guideline: ICH Topic E6*
- That people with suitable expertise conduct properly designed CTs

General requirements for CTs for NHPs are set out in Part 4 of the *NHP Regulations*:

- "...no person shall sell or import a natural health product for the purposes of a clinical trial unless the person is authorized under this part" [Section 65(a) of the *NHP Regulations*]. **"Sell" - means to "provide for use"**. The seller does not need to accept payment for the transaction. For example, in this case the manufacturer may be selling the NHP to the sponsor or principal investigator. In addition, a CT sponsor who provides study medication free of charge to trial subjects would also be considered to be selling that product under the definition Section 2 of the *Food and Drugs Act*.
- Before a **phase I**, **II**, or **III**, but not a phase **IV** clinical trial for an NHP takes place, it must be approved by the NHPD (see section 12 of this document). The sponsor shall notify the NHPD of the date on which the CT will commence at least 15 days in advance. Should the CT (Phase I-III) be discontinued, the sponsor shall notify the NHPD

within 15 days after the day of the discontinuance (see section 8 of this document).

- In order to obtain approval from the NHPD, a CTA must be submitted to the NHPD (see section 3 of this document). The NHPD will issue a Notice of Authorization if the NHP will not endanger the health of a CT subject or other person and there is a reasonable probability of achieving the CT objective.
- If the NHP is to be used in accordance with its approved **conditions of use**, then the trial is considered to be a phase IV CT and Health Canada authorization is not required but Research Ethics Board (REB) approval is required. The term "within approved conditions of use" means that the product is being used as per the product label approved by Health Canada. A label is considered to be approved by Health Canada if the product has a Natural Product Number (**NPN**), Drug Identification Number (**DIN**), or Drug Identification Number for Homeopathic Medicine (**DIN-HM**). If the product is used outside the parameters described on the approved label, then the trial would be considered to be a Phase I-III CT.
- If the product licence of an NHP being used in a phase IV clinical trial is suspended or cancelled [Sections 18-21 of the *NHP Regulations*], the sponsor must discontinue the CT and contact the NHPD for advice.

Parts of the NHP Regulations that do not apply to NHP CTs:

- NHPs must have a product licence to be sold or imported. NHPs used in CTs do not require a product licence because the safety, efficacy, and quality of the study substance is to be evaluated during the assessment of the CTA.

- A site licence is required for manufacturers, packagers, labellers and **importers** of NHPs to be marketed, but is not required for **CT sites** or sites where an NHP is being prepared for use in a CT.

1.2 When a CTA Should Be Submitted to the NHPD

1.2.1 Inadequate evidence to support safety and efficacy of an NHP in humans

A CT may be needed:

- If an NHP previously approved by Health Canada is being tested for a condition of use not captured on the product label.
- For NHPs that are not yet approved by Health Canada and for which additional efficacy and safety evidence is required before marketing can be authorized (see Evidence for Safety and Efficacy of Finished NHPs Guidance Document).
- For NHPs with no prior history of use in humans (e.g., new isolates or new extracts on their own or in combination with other medicinal ingredients proven to be safe).

Evidence requirements for combination products are described in section 12 of *the Evidence for Safety and Efficacy of Finished NHPs Guidance Document*.

Evidence requirements for traditional products are described in section 2.2.2 of the *Evidence for Safety and Efficacy of Finished NHPs Guidance Document*. A **traditional product** is (1) based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, or in the prevention, diagnosis, improvement or treatment of a physical or mental illness and (2) a product for which the traditional use extends back at least fifty years. CTs

may be required for traditional products that are not being used in a traditional manner, or any other NHP depending on the available evidence to support their safe and efficacious use.

Evidence requirements for homeopathic medicines are described in the *Evidence for Homeopathic Medicines Guidance Document*.

1.2.2 Comparative bioavailability

Comparative bioavailability studies evaluate the pharmacokinetics of two NHP formulations in healthy adult volunteers. This type of study is useful to determine the pharmacokinetic properties of an NHP and as a practical matter, is usually done with a single chemical entity. For example, a company has an NHP that is identical to another NHP currently on the market. A comparative test could be conducted for the two NHPs to determine if the new NHP has the same bioavailability as the existing NHP.

1.2.3 N-of-1 trials

An N-of-1 trial is a randomized multiple crossover trial in a single subject. Groups of individual subjects are included in the trial design. The subject undergoes pairs of treatment periods, one period with the active substance and one with the matched placebo. The key criteria for an N-of-1 trial are that:

- both the subject and the qualified investigator are blind to allocation
- the proposed treatment is useful for chronic and stable conditions
- the proposed treatment has a rapid onset of action and ceases to act soon after it is discontinued
- a minimum of two pairs of treatment periods is required for

statistical analysis; ideally three or more pairs should be used

For further information on N-of-1 trials, please refer to the following sources:

Guyatt G, Jaeschke R, McGinn T. *Therapy and validity:N-of-1 randomized controlled trials. User's guides to the medical literature: A manual for evidence based clinical practice.* Chicago, IL : American Medical Association, 2002: 275-290.

Guyatt G, Sackett D, Adachi J, Roberts R, Chong J, Rosenbloom D, et al. *A clinician's guide for conducting randomized trials in individual patients*. CMAJ 1988; 139: 497-503.

1.2.4 Clinical trials involving both an NHP and a conventional pharmaceutical

1.2.4.1 NHP to be used to treat side effects of a conventional pharmaceutical

The NHPD will authorize and monitor these types of CTs as long as the pharmaceutical is being used within its approved conditions of use. The term "within its approved conditions of use" means that the product is being used as per the product label/monograph approved by Health Canada. For pharmaceuticals, a product label/monograph is considered to be approved by Health Canada if the product has a DIN.

1.2.4.2 NHP versus conventional pharmaceutical taken by individuals in different arms of the trial

The NHPD will authorize and monitor CTs involving a trial comparing an NHP versus a **conventional pharmaceutical**, as long as the pharmaceutical arm of the trial is a phase IV trial (i.e., the pharmaceutical is being used within its approved conditions of use (see section 1.2.4.1)). A comparator treatment arm is not required for clinical trials testing an

indication of use of an NHP for which there is an established pharmaceutical treatment, unless it is unethical to use a placebo.

1.2.4.3 NHP to be used to increase efficacy of a conventional pharmaceutical

The NHPD will authorize and monitor these types of CTs as long as the pharmaceutical is being used according to its approved conditions of use. The Therapeutic Products Directorate (TPD) will be consulted if deemed necessary. For these types of clinical trials, the CTA should be submitted to the NHPD only. If a consultation with the TPD is required, the NHPD will make additional copies of the application and forward it to the TPD.

This type of CT may include a number of different arms. For example, a trial could investigate an NHP and a pharmaceutical versus a pharmaceutical, an NHP and pharmaceutical versus a placebo, or any combination of the above.

1.2.5 NHPs for conditions of use not appropriate for self care

The NHPD will authorize and monitor these types of CTs. Other directorates will be consulted if deemed necessary. For these types of clinical trials, the CTA should be submitted to the NHPD only. If a consultation with other directorates is required, the NHPD will make additional copies of the application and forward it to the appropriate directorate.

The Safety Factors found in section 9 of the Evidence for Safety and Efficacy of Finished NHPs Guidance Document can be used to determine if the NHP is suitable for self care.

According to section 3 of the *Food and Drugs Act*, the approved marketed label of an NHP cannot claim that the product is a treatment, prevention

or cure for any of the diseases, disorders or abnormal physical states referred to in Schedule A. However, an NHP can be used in a clinical trial to treat, prevent or cure any of the diseases, disorders or abnormal physical states referred to in Schedule A because the product will be used under the care of a physician or dentist as appropriate.

1.3 When a CTA Should Be Submitted to the Therapeutic Products Directorate and not the NHPD

1.3.1 NHP/pharmaceutical combinations

When the pharmaceutical is being used outside the conditions of use approved by Health Canada or is not approved for sale in Canada, the CT will be authorized and monitored by the TPD regardless of whether the NHP is being used to treat the side effects or to enhance the efficacy of the conventional pharmaceutical.

"Outside the conditions of use approved by Health Canada" means that the pharmaceutical is NOT being used as per the product label/monograph approved by Health Canada. For pharmaceuticals, a product label/monograph is considered to be approved by Health Canada if the product has a DIN.

1.3.2 NHP that contains a medicinal ingredient that requires a prescription

The TPD will authorize and monitor CTAs for which an NHP contains an ingredient that is listed on Part I or Part II of Prescription drug list of the *Food and Drug Regulations*. For example, a CT testing a multivitamin product that provides more than 10,000 IU of Vitamin A per day would need to be submitted to the TPD.

1.4 When a CTA Does Not Need to Be Submitted to Health Canada

1.4.1 Observational studies

These types of studies do not require authorization from Health Canada, but do require approval from a REB. An **observational study** is one where the investigators do not manipulate the use of, or deliver, an intervention (e.g. do not assign patients to treatment and control groups) nor collect samples from patients that are outside of routine care, but only observe patients who are (and sometimes patients who, as a basis of comparison, are not) exposed to the intervention, and interpret the outcomes. For example, a patient may approach a physician wanting to take a specific NHP. The role of the physician is to provide advice to the patient on whether or not the NHP is safe for use. The physician may want to conduct further analysis on information or on samples already collected from the patient as part of the patient's routine care. As this is within the scope of the physician's practice, this is not considered a CT. If additional samples (i.e. samples that are not part of routine care) are collected via invasive or non invasive procedures (e.g. blood or urine) from the patients to study the outcomes of the NHP, then the study would be considered a CT and would require authorization from Health Canada and the REB.

1.4.2 Phase IV clinical trials

These types of studies do not require authorization from Health Canada but require REB approval (see section 1.1 of this document).

2.0 Pre-CTA Consultation Meeting

The NHPD invites sponsors to request a pre-CTA consultation meeting, if

the sponsor feels it is necessary. Such consultations may be particularly useful for new active substances or applications that will include complex issues that may be new to Health Canada. If the only issue is whether the investigational product is an NHP, the sponsor (or delegated person) may simply contact the NHPD CT Unit - Submission Management Division by email. The email should include 1) a detailed description of the investigational product and 2) a summary of the protocol.

The pre-CTA consultation meeting provides an opportunity for the sponsor to present relevant data, discuss concerns and resolve issues regarding the product and protocol. It also gives the NHPD an opportunity to provide guidance on the acceptability of the proposed trial(s). The NHPD will not provide guidance on the commercial development of the NHP.

Sponsors may invite the qualified investigator(s) and other persons who will be involved in the proposed trial(s) to attend the meeting. The sponsor and other persons have the option of attending the meeting in person or via teleconference.

Requests for a pre-CTA consultation should be submitted by the sponsor in writing to the NHPD at the address in section 13 of this document. Requests should include a cover letter proposing three dates and times suitable for a pre-CTA consultation meeting. A request for a pre-CTA consultation should be provided to the NHPD at least 30 days prior to the meeting date. The NHPD will acknowledge the request for consultation, indicate the numbers of copies of the information to be provided, and confirm a pre-CTA consultation meeting date. Two weeks prior to the meeting, the sponsor must provide an agenda and the Pre-CTA Consultation Package (see outline below) clearly labelled with "Pre-Clinical Trial Application Consultation" on the outside of the envelope.

The Pre-CTA Consultation Package should be sent to the address given in section 13 of this document.

The Pre-CTA Consultation Package should contain:

1. The purpose of the meeting, including the questions or issues to be discussed
2. A brief description and summary of the product in question, such as:
    - a quantitative list of all the medicinal ingredients and a quantitative list of non-medicinal ingredients
    - dosage form, proposed **dose**, and purpose
    - general chemistry and manufacturing information, such as a summary of the manufacturing process, impurity profile, stability data and finished product specifications
    - an overview of the market history of the product, including the regulatory status of the product worldwide
    - a brief summary of pre-clinical and clinical data relating to the product
3. Information on the placebo and comparator, if applicable
4. The purpose of the CT
5. A copy of the most recent version of the CT protocol
6. Informed Consent Form (if available)

The sponsor must record pre-CTA consultation meeting minutes and provide a draft of the minutes to the NHPD within two weeks post-meeting. The minutes will be circulated for approval. The NHPD may issue a Record of Decision (ROD) based on the meeting minutes. Both the minutes and the ROD will subsequently be part of the CTA to be submitted to the NHPD (see section 3 of this document).

3.0 Clinical Trial Application

3.1 Submission Format

CTAs should be submitted in the Common Technical Document (CTD) format and consists of all components outlined below and in Appendix 2. The CTD format is a standard format prescribed by ICH for the submission of information to regulatory authorities in the ICH regions. The entire CTA must be submitted in hard copy and items marked with an asterisk (*) must also be submitted in an electronic format approved by Health Canada (e.g. on CD or diskette in PC compatible Word, WordPerfect or editable PDF format).

Two hard and two electronic copies of the CTA should be provided.

3.2 Module 1: Administrative/Clinical Information

A cover letter that provides a brief introduction to the proposed CT, the NPN, DIN-HM, or DIN of the NHP if applicable, as well as any waivers or justification for the submitted data package should be submitted as part of Module 1. The following information must also be included in Module 1:

1.1 Table of Contents (Modules 1-3)
1.2 Application information
    1.2.1 Completed and signed Clinical Trial Application and Attestation Form (Appendix 3a). Instructions on how to complete this form can be found in Appendix 4.
    1.2.2 Information on prior-related applications.
    *1.2.3 A copy of the current **Investigator's Brochure** (see section 3.2.1 of this document).

*1.2.4 A summary of the protocol in the format of the Protocol Synopsis and Evaluation Review Template (PCERT) (Appendix 5) (see section 3.2.2 of this document). For information on how to prepare the PCERT, please visit our website.

*1.2.5 A copy of the final proposed protocol (see section 3.2.2 of this document). **This must be provided in addition to the PCERT. The REB application or PCERT cannot be submitted in lieu of a protocol**.

1.2.6 A copy of the **informed consent** documents to be used in conjunction with the CT. The document should outline the risks and anticipated benefits to the CT subjects as a result of participation in the CT(s) (see section 3.2.3 of this document). The Informed Consent Form Guidelines can be found in Appendix 6.

1.2.7 A completed Clinical Trial Site Information Form for each proposed CT site known at the time of application (Appendix 3b). All fields must be completed before the form is submitted.

1.2.8 The name, address and telephone number and, if applicable, the fax number and e-mail address of any REB(s) in Canada that has previously refused to approve the CT protocol, its reasons for doing so and the date on which the refusal was given, if known at the time of application.

1.2.9 Applicable information regarding refusals by other regulatory authorities or REB(s), outside Canada.

1.2.10 Letters of Access allowing the NHPD to access proprietary information in support of the CTA, if applicable (e.g., an NHP Master File or a previously approved CTA).

1.2.11 Other application-related information, which may include:

- A completed Qualified Investigator Undertaking form (Appendix 3c) or similar document containing the same information for

each proposed CT site known at the time of application

- A completed REB Attestation form (Appendix 3b) or a similar document containing the same information if available at the time of application
- Authorization form for a Third Party to Import the NHP (Appendix 3e), if applicable
- Designated Party Authorization Form (Appendix 3g), if applicable
- A list of related ongoing (authorized) CTs in Canada, if applicable
- A copy of the record of the discussions and decisions of the pre-CTA consultation meeting, if applicable (see section 2.0 of this document)

Although the NHP Regulations state that REB approval must be submitted at the time of application, it is understood that REB approval may be withheld until NHPD authorization is granted. When this occurs, the REB Attestation form (or similar document) must be submitted (by fax or mail) to the NHPD prior to commencement of the CT. Given that the sequence of approval may vary, the applicant must ensure that both the NHPD and the REB have approved the identical protocol.

Similarly, if the information required to complete the Clinical Trial Site Information Form and the Qualified Investigator Undertaking form is not available at the time of application, these forms must also be submitted (by fax or mail) to the NHPD prior to commencement of the CT at that site.

Forms/templates in Appendices 3, 5, 7, and 8 can be found online. Please note that faxed or electronic signatures are acceptable.

1.3 Electronic Review Documents

See section 3.1 of this document.

3.2.1 Investigator's Brochure

The Investigator's Brochure is widely acknowledged as a document required to support a clinical trial. In the case where some of this information normally included in an Investigator's Brochure is not available, the sponsor is expected to provide a strong scientific rationale for not including the missing data. This may include a long history of use by humans, in which case, the normal pre-clinical information (e.g. pharmacological properties) may be waived. The Investigator's Brochure is a stand-alone document and is assessed accordingly. It should provide strong support for the use of the product in the proposed CT and should be presented in this context. It is understood that NHPs are not conventional pharmaceuticals and that much of the information required in a conventional pharmaceutical Investigator's Brochure may not apply to an NHP. The NHPD may request additional information when necessary.

Information regarding the format of the Investigator's Brochure can be found in the ICH Guidance Document *Good Clinical Practice: Consolidated Guideline ICH Topic E6*, section 7. Sponsors should always provide the most recent copy of the Investigator's Brochure with their CTA.

As identified in *Guidance for Industry: Good Clinical Practice: Consolidated Guideline ICH Topic E6*, components of an Investigator's Brochure are:

1. Title page and table of contents
2. Confidentiality statement
   This statement instructs the investigator to treat the Investigator's Brochure as a confidential document for the sole information of and

use by the investigator's team, the REB and Health Canada.

3. Summary of the product to be evaluated
   This section should include a brief summary highlighting the available significant physical, chemical, pharmacological, toxicological, and clinical information relevant to the stage of clinical development of the **investigational product**.

4. Introduction
   This section should include a brief introductory statement that outlines the chemical name of the investigational product, all medicinal ingredients, the placebo and the comparator, and the rationale for performing research with the investigational product.

5. Physical, chemical and, if any, pharmaceutical properties and formulation information
   This section is a summary of the information provided in the Quality Overall Summary (QOS)-NHP (CTA-Phases I/II/III) Template and should include a description of the investigational product including the chemical and/or structural formula, if known, the relevant physical, chemical and pharmaceutical properties; chemistry and manufacturing information; dosing information; and instructions for the storage and handling of the **dosage form**.

6. Comprehensive summary of pre-clinical data
   This section should include the results of all available relevant pre-clinical pharmacological and toxicological studies. This summary should address the methodology used and the results and should discuss the relevance of the findings as well as any possible unfavourable and unintended effects in humans. The following sections should discuss the most important findings from the

studies, including the dose response of observed effects, the relevance to humans and any aspects to be studied in humans.

- pre-clinical pharmacology (e.g., pharmacokinetics in animals), if any
- toxicology, which may include information from single-dose, repeated-dose, carcinogenicity, reproductive toxicity and genotoxicity (mutagenicity) studies

7. Comprehensive summary of clinical data
   This section should include the following information, if any, on the effects of the investigational product in humans:
   - extrapolations from pre-clinical studies
   - clinical pharmacodynamics (e.g., dose-response relationship and mechanism of action)
   - clinical pharmacokinetics (e.g., absorption, distribution, metabolism and excretion)
   - history of use in humans, including the results of previously authorized completed trials (*include in all subsequent CTAs*)
   - discussion and evaluation of clinical results (i.e., effectiveness/efficacy and safety)
   - conclusions from clinical studies including:
     - benefit assessment and risk acceptability
     - effective and recommended clinical dose
     - interactions with other NHPs, foods or pharmaceuticals
     - cautions, warnings, contraindications and adverse reactions

- **rescue medication**
- any additional information (e.g., **scientific monographs,** expert opinion reports). The criteria for expert opinion reports are described in section 3.5 of the *Evidence for Safety and Efficacy of Finished NHPs Guidance Document*

8. Marketing experience
   This section should identify countries where the NHP under investigation has been marketed or has obtained regulatory approval. The Investigator's Brochure should also identify all the countries where the investigational product was the subject of a licence application but did not receive approval/ registration for marketing or was withdrawn from marketing/registration. **Product monographs**, product information sheets or marketed/approved labels should be included in this section, if available.
9. Summary of data and guidance for the investigator
   This section should provide an overall discussion of the clinical and non-clinical data and when possible, should summarize the information from various sources on different aspects of the investigational product.

The most recent version of the Investigator's Brochure must be submitted to the NHPD at the time of application. Please include, in the title page of the Investigator's Brochure, the date the document was finalized.

For ongoing clinical trials, a revised Investigator's Brochure, with additional information and any changes highlighted should be submitted to the NHPD annually. Please include, in the title page of the Investigator's Brochure, the date the document was revised. If an

Investigator's Brochure is updated more frequently, it should be submitted as required.

For products being used outside the conditions of use approved by Health Canada, a copy of the currently approved product monograph, with the supplemental information supporting the conditions of use for the proposed trial, may be submitted in lieu of the Investigator's Brochure. For products not approved by Health Canada, the Investigator's Brochure must be submitted.

3.2.2 PCERT

The Protocol Synopsis and Evaluation Review Template (PCERT) originates from the Preclinical and Clinical Evaluation Review Template, which is no longer in use. The PCERT used by the NHPD is similar to the PCERT used by the TPD. The PCERT serves to summarize the pertinent information described in the protocol (see section 3.2.3) and is used by the NHPD as a review template to expedite the review process. Both a PCERT and a protocol are to be submitted in the CTA, but the NHPD approves the information in the protocol, as it is the protocol that is distributed to the investigators conducting the CT. Furthermore, as per ICH guidelines *Good Clinical Practice: Consolidated Guideline ICH Topic E6*, section 6, ALL the information contained in the PCERT must be included in the protocol. Please ensure the information in the PCERT is consistent with the information in the protocol. All sections of the PCERT must be completed. For sections that are not relevant, please state "not applicable." Please do not erase any of the section headings when completing the PCERT.

3.2.3 Protocol

This document is distributed to all investigators involved in the clinical

trial once the CT has been authorized by Health Canada and the REB. Guidelines for generating a CT protocol are located in the ICH Guidance Document *Good Clinical Practice: Consolidated Guideline ICH Topic E6* section 6. While the protocol and PCERT will contain some of the same information, the protocol will describe the CT procedures in greater detail, and will also include a section on: direct access to source data/documents, ethics, and data handling and record keeping.

Some required items frequently omitted from the CT protocol exclusion criteria that should be included are:

- possible allergies to the study products (i.e. NHP, comparator or placebo)
- use of foods, NHPs or pharmaceuticals that may interact with the study products, if applicable
- the use of NHPs containing the same medicinal ingredient(s) as the investigational product
- the use of NHPs that alter the outcome measure(s) of the trial

3.2.4 Informed Consent Form

Guidelines for generating an Informed Consent Form are located in Appendix 6 and in the ICH Guidance Document *Good Clinical Practice: Consolidated Guideline ICH Topic E6*, section 4. Some required items frequently omitted from Informed Consent Forms that should be included are:

- Should the trial be randomized, blinded or cross-over in design, these terms must be clearly defined. For example:
    - Randomized: Selections are made in a manner similar to

drawing numbers from a hat.

- Double-Blind: Neither the subjects nor the investigators know who has been given which medication until the end of the study. Should it become necessary, that information can be obtained.
- Cross-over: Each subject will be given each study product in turn. There may be a washout period between study products to ensure that the first product has cleared the body before giving the next product.
- Parallel: Subjects are divided into different arms of the trial that occur concurrently. For example, one half of the subjects take the investigational product while the other half of the subjects take a placebo.

- If there is a placebo and/or comparator, please identify their composition and appropriate cautions, such as possible allergies or contraindicated medications.
- Outline the subject's responsibilities and include a statement that they should not take any other medications without first consulting the trial investigators. However, it is recognized that emergency medication may be required in which case the trial investigator must be informed immediately. This may result in the subject's exclusion or withdrawal from the clinical trial.
- Any lifestyle or dietary changes required by, or unrelated to, the trial should be discussed between the subject and the investigators.
- If blood is to be drawn, the site, manner (e.g., venipuncture or finger prick), amount, frequency, impacts and pre-requisites should be clearly described. This may include indicating that there will be a

slight chance of bruising from the site where blood is to be drawn, that alcohol will be used to minimize the chance of infection and that the subject must fast beforehand.

- Health Canada may require access to trial records.
- There should be a place for each subject to initial every page of the Informed Consent Form.
- If the study involves a population that may not have the capacity to provide informed consent (e.g., pediatric, geriatric, etc.), the subject's signature for consent (if possible) and the parent's or guardian's signature for consent are required. Two different Informed Consent Forms, one for the subject to read (at their level) and one for the parent or guardian should be provided.
- If pregnancy is a condition for exclusion from the trial then the subject should be informed that adequate birth control measures must be taken throughout the trial and that female subjects of child bearing potential will undergo pregnancy tests at the screening visit. Subjects must also be informed of the risks or lack of knowledge of risks to a fetus or mother and that should she become pregnant, she must stop taking study medications immediately and will be withdrawn from the study.
- Detailed directions for use of the study products should be provided.
- The Informed Consent Form should be dated and given a version number to ensure consistency with any revisions to the protocol.

The language of the Informed Consent Form must be clear to the patients (e.g., "damage to the heart" instead of "cardiotoxicity").

3.3 Module 2: Common Technical Document Summaries

This module should include:

2.1 Common Technical Document Table of Contents

2.2 (Not applicable to clinical trials).

2.3 Quality Overall Summary

This section is intended to provide the applicant with guidelines to aid in completing the Quality Overall Summary-Natural Health Product Template (QOS-NHP Template) found in Appendix 7. This template is prepared in order to fulfill the quality (i.e. Chemistry and Manufacturing) requirements of the investigational product used in the clinical trial. This template should be used by the sponsor to summarize the information about the quality of medicinal substances and finished products that meet the definition of an NHP (see section 1.1 of this document) to be used in the CT. This quality overall summary is not required if the NHP to be used in the CT has been previously approved by Health Canada for a CT or for marketing, but appropriate cross-reference must be provided. With regard to previously approved CTA information, please provide confirmation that the information has not changed.

The purpose of these guidelines is to help the CTA submission sponsor understand the quality requirements referred in the QOS-NHP template. These guidelines should be followed when completing the QOS-NHP Template. Alternate approaches are acceptable provided they are supported by adequate scientific justification. Sponsors are advised to discuss in advance with NHPD about alternate approaches in the completion of the quality requirements in their CTA submission to avoid rejection or withdrawal of the submission. Sponsors are encouraged to devote the sufficient time necessary to prepare a clear, precise QOS-NHP Template. The submission of an inaccurate or an incomplete template

will result in greater expenditure of an Assessment Officer's time in reviewing and summarizing data which may delay the process.

In this template, section **S** refers to Substance (e.g., medicinal ingredients or raw material), while section **P** refers to Finished Product.

It is the sponsor's responsibility to complete those sections and fields that apply. It is understood that certain sections and fields may not be applicable and should be indicated as such by reporting "not applicable" in the appropriate area with an *accompanying explanatory note* describing the reasons for the inapplicability. The use of tabular format is encouraged to summarize information (e.g. in the specification for a medicinal substance when more than one substance is being used). The tabular format included in this template may need to be expanded, as necessary. These tables are included as illustrative examples of how to summarize information. Other approaches to summarize the information can be used if they fulfil the *same purpose*. If scanned images are incorporated into the document (e.g., extraction and isolation schemes, synthetic schemes, molecular structures), sponsors should ensure that resolution is sufficient for legibility.

Based on the natural health product substances set out in *Schedule 1* of the NHP Regulations, medicinal ingredients have been divided into three categories under Part A. Select a category (from Part A) that applies to your product. If more than one category applies (e.g., in a combination product), complete the necessary combination of categories. To prepare the chemistry and manufacturing information for the finished product, complete Part B. The template in Part C for the Finished Natural Health Product Specifications is also required.

Sponsors are also encouraged to consult the *Evidence for Quality of*

Finished Natural Health Products guidance document also available on our website when completing the QOS-NHP Template for further guidance on areas such as acceptable test methods and tolerance limits.

Introduction

The introduction section is intended to provide a brief summary of the investigational product, a brief summary of the clinical trial protocol, information about the comparator product if applicable, and a summary on previously submitted/approved information, e.g. DIN/NPN, if applicable.

The introduction should include proprietary name, non-proprietary name or common name of the investigational product, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

Sponsors may provide a contact person's name, phone number, fax number, and e-mail address for ease of communication.

Part A: Chemistry & Manufacturing Information of Medicinal Ingredient(s)

The following are the categories of substances from Schedule 1 of the NHP Regulations for which specific quality requirements are described in detail below.

Category I: Plant, Plant material, Alga, Fungus, Bacterium, Non-Human Animal Material

Category II: Isolate, Synthetic Duplicate, Non-Standardized and Standardized Extract, Amino Acid, Essential Fatty Acid, Vitamin, Minerals

Category III: Probiotics

2.3.S Medicinal Ingredient(s)

This section is intended to provide the quality requirements of the medicinal ingredients to be used in the finished product. Considering the variety of natural health products used as medicinal substances (as indicated in Schedule 1 of the *NHP Regulations*), this section highlights the chemistry and manufacturing requirements of the medicinal ingredients to review their quality, stability and safety. If some of the information included under this section is not available to the sponsor from the supplier or is proprietary in nature, the NHPD has a mechanism called the Natural Health Product Master File (NHPMF), where the supplier can supply any proprietary information concerning their products directly to the NHPD in the form of a NHPMF. The supplier would then be considered the NHPMF Holder. This NHPMF will be held in strict confidence and will be used in support of the CT submission only upon receipt of written authorization from the supplier/NHPMF Holder of the medicinal ingredient (i.e., via a letter of access issued to the NHPD).

The sponsor should be able to provide most of the information on the medicinal ingredient, except possibly the proprietary information found in section 2.3.S 2.2 of QOS-NHP template. It is the responsibility of the sponsor to obtain all other information from the supplier of the medicinal ingredient and include this in the clinical trial submission package.

Regardless of the information provided by the supplier of the medicinal ingredient, the manufacturer of the final dosage form is responsible for ensuring that acceptable specifications and analytical procedures are in place for the finished product.

2.3.S.1 General Information

In the general information section, the sponsor needs to provide the

information for the medicinal ingredient. For the identity of organisms (plants, algae, fungi, bacteria, and non-human animals), the applicant should provide the common name of the organism, its proper name consisting of the Latin binomial of genus and specific epithet, and strain number in the case of probiotics, and a description of the part used where applicable (e.g. leaf). For chemicals (isolates, amino acids, fatty acids, their synthetic duplicates and derivatives), the information required in this section includes an unambiguous name, structural information such as the structural and molecular formula; a physical description, for example organoleptic properties; and the source material (derivative, source organism, or synthesis), and any other relevant information that can help in identifying a specific characteristic of the medicinal ingredient.

In addition to physical methods of identification of plant materials, chemical fingerprint testing, e.g., TLC, HPLC or HP-TLC analysis, must be performed to properly characterize the identity of the plant since there are often similar-looking varieties of the same species with different chemical and pharmacological properties.

2.3.S.2 Manufacturing Information

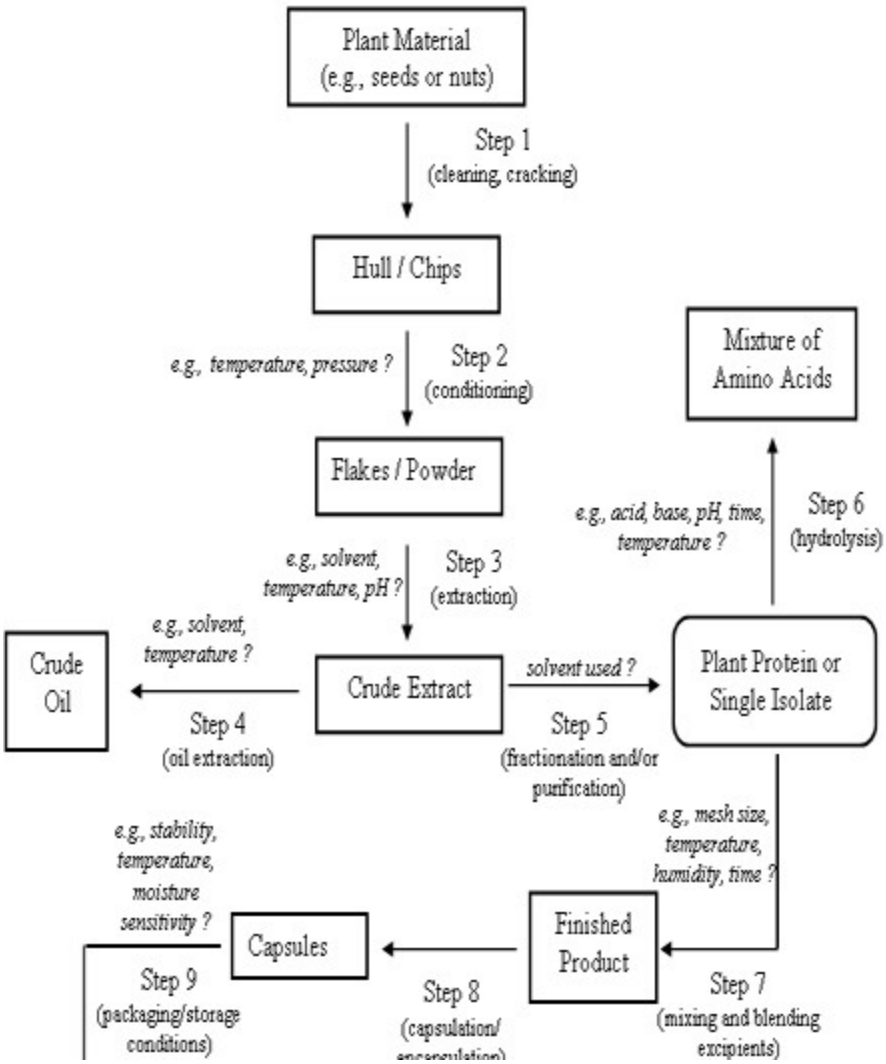
2.3.S.2.1 Manufacturer(s)

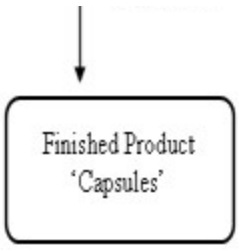
The manufacture section is intended to provide the contact information and responsibilities of each manufacturer and contractor including each proposed production site and facility involved in manufacturing the batches. This includes the facilities involved in the fabrication, packaging, testing, importing, storage and distribution of the medicinal ingredient used in the clinical studies.

2.3.S.2.2 Description of Manufacturing process and Process Controls

A flow chart and brief description of the manufacturing process and process control should be provided that describe the extraction, synthesis or isolation of the medicinal ingredient, and process conditions such as temperature, pH, drying, aeration, or specific fermentation conditions. As an example, a flow diagram of the synthetic process(es) should include chemical structures of starting materials, intermediates, reagents and drug substance while a flow diagram of an isolation procedure should includes source material, solvents used for extraction, conditions of extraction and purification procedure. See the example of a flow diagram given below.

Flow Diagram Showing Manufacturing Process and Process Conditions





This flow chart is an example to highlight the manufacturing process.

Provide product specific steps and process conditions where it is marked as ?

Medicinal ingredients that are of animal origin or have been processed using animal material should be free of the causative agents of Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE). A completed Animal Tissue Form (found in Appendix 3 of the *Clinical Trials for Natural Health Products* guidance document) should be provided.

If a NHPMF or a Drug Master File (DMF) is filed with Health Canada and cross-referenced for certain proprietary information (e.g., section 2.3.S 2.2 of QOS-NHP template), provide the NHPMF number or the DMF number assigned by Health Canada and a copy of the letter of access from the manufacturer allowing the NHPMF to be used in support of the clinical trial submission. It should be ensured that the information included in the NHPMF or DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. If a Canadian agent is used by the NHPMF or DMF holder, a letter from the NHPMF or DMF holder should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

2.3.S.3 Characterization

2.3.S.3.1 Identification of Medicinal Ingredient

This section should include a list of studies performed and conclusions from the studies to confirm the structure of the medicinal ingredient. The studies carried out to elucidate and/or confirm the identity of organisms such as plants as medicinal ingredients includes physical descriptions and chromatographic/DNA fingerprinting studies. For the identification of the chemical structure of the new medicinal ingredient the following types of evidence are normally included: elemental analysis, GC, HPLC, LC-MS, IR, UV, MS, and/or NMR. This list is by no means exhaustive, but provides an indication as to the types of information that could be included.

For well known medicinal substances, it is sufficient to provide copies of the studies performed on the NHP from the proposed suppliers run with a suitable reference standard.

A discussion should be included of the possible isomers that can result from the manufacturing process, the steps where they were introduced, and a summary of the results of the studies carried out to investigate the physical, chemical, and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, the medicinal substance specification should include a test to ensure isomeric identity and purity. If the medicinal substance is a single isomer or a fixed ratio of isomers, provide the rationale for this decision.

Foreign matter tests are important to ensure that the plant, fungal, algal, or non-human animal material is entirely free from visible signs of contamination such as sand, dirt, insect parts, glass and metal. Testing should be done according to WHO or Pharmacopoeial methods.

Determination of acid-insoluble ash is important to measure the amount of inorganic impurities in the form of extraneous (non-physiological)

materials in a plant, fungal, algal, or non-human animal material. Testing should be done according to USP, Eur.Pharm, or WHO methods.

Loss on drying is required where a substance is known to be hygroscopic. The loss on drying procedure (such as drying in an oven) may be adequate, but in some cases (e.g. volatile (essential) oil containing plants), a detection procedure that is specific for water content is required (e.g. Karl Fischer method).

2.3.S.3.2 Impurities

The tables in the QOS-NHP template can be used to summarize the names, structures, test methods, and limits of detection of the impurities. The sponsor is responsible to provide the identity of any product and process related impurities and their limits. It should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". If more than one batch is used, complete a table for each batch.

For plant materials the nature of the chemical fertilizers and pesticides used should be recorded, if these have been employed during cultivation.

2.3.S.4 Control of the Medicinal Ingredient

This section is intended to summarize the specifications for the medicinal ingredients to be used in finished product. The specifications are a list of tests, references to analytical procedures, and appropriate tolerance limits, which are numerical limits, ranges, or other criteria for the tests described. This would include tests for description, identification, purity, quantity and potency as well as other tests specific to the medicinal ingredients. The specifications can be summarized according to the table in the QOS-NHP template including the Tests, Test Methods, and Tolerance Limits. The Test Method should indicate the kind of analytical

procedure used (e.g., visual, IR, UV, HPLC, Atomic Absorption, Mass Spectrometry etc.) and a brief description of any in-house method. It should be ensured that actual numerical results are provided for the Tolerance Limits, rather than vague statements such as "within limits" or "conforms".

Please refer to the *Evidence for Quality of Finished Natural Health Products* guidance document for further information

If different batches of the ingredients are being used, a description of the batches and results of batch analyses should be provided. Analytical results should be either summarized in the QOS-NHP template or provided as a copy of the Certificate of Analysis for each batch used in the clinical trial. Batch number, batch sizes and dates and sites of production should also be provided.

2.3.S.6 Container Closure System

Information about any specific storage conditions required for maintaining the quality of the medicinal ingredients or for its shipment should be provided along with a description of the container closure system(s).

2.3.S.7 Stability

In this section actual stability results (i.e., raw data) used to support the clinical trial should be provided. Full long term stability data may not be required at the time of filing, provided some preliminary stability data is available (e.g. accelerated stability data) on representative batches together with a commitment that the stability of the clinical trial samples will be monitored throughout the duration of the trial. It should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms".

Part B: Chemistry & Manufacturing Information of the Finished Product

2.3.P FINISHED NATURAL HEALTH PRODUCT

2.3.P.1 Description and Composition of the Finished Product

A description of the finished product and its composition should be provided. The description of the finished product dosage form should include the physical description, proposed strength(s), release mechanism (dissolution and/or disintegration) and any other distinguishable characteristics (e.g., "The proposed finished product is available as oval, brown capsule with disintegration time of 45 min. in two strengths: 100 mg and 250 mg").

Composition should express the quantity of each medicinal and non-medicinal ingredient on a per dosage basis (e.g., mg per capsule) and percentage basis including a statement of total weight of the dosage unit.

Each ingredient should be listed by its proper or common name, quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., USP NF). The quantitative composition should be provided for all proprietary mixtures or blends of medicinal ingredients. The identity and quantity of all dyes and marking inks must be provided (e.g. Cochineal Red, FD&C Blue No. 1).

If applicable, a quantitative list of all components of the placebo sample used in the clinical trial should be provided.

2.3.P.2 Formulation Development

The sponsor needs to provide any available discussion on the development of the dosage form, the formulation, manufacturing

process for a new combination, standardized extract, or complex dosage form such as a transdermal patch.

2.3.P.3 Manufacturing Information of the Finished Natural Health Product

2.3.P.3.1 Manufacturer(s)

Similar to section 2.3.S.2.1, this section should include the contact information of the facility involved in fabrication, packaging, testing and storage.

If a NHPMF or a DMF is filed with Health Canada and cross-referenced for certain proprietary information (e.g., section 2.3.P. 3.1 of QOS-NHP template), provide the NHPMF number or the DMF number assigned by Health Canada and a copy of the letter of access from the manufacturer allowing the NHPMF to be used in support of the clinical trial submission. It should be ensured that the information included in the NHPMF or DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. If a Canadian agent is used by the NHPMF or DMF Holder, a letter from the NHPMF or DMF holder should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

2.3.P.3.2 Batch Formula

A batch formula should be provided that includes strength, batch size, date and a list of all components on a per batch basis including a statement of the total weight or measure of the batch. This should include all components used in the manufacturing process, regardless if they appear in the finished product. All overages for individual ingredients should be clearly indicated that could have been used to compensate any possible manufacturing losses. If more than one batch

is produced (e.g., additional lots of finished product or different strengths), complete the batch formula analysis for each batch.

2.3.P.3.3 Description of Manufacturing process and Process Controls

A flow diagram should be provided giving the steps of the manufacturing process and process control. This information should include the process parameters (e.g., temperature, mixing time, mesh size, etc.) that are specific to finished product manufacturing. For sterile products, details and conditions of sterilization and/or lyophilization should be provided. See the example of a flow diagram given in section 2.3.S.2.2.

2.3.P.4 Control of Non-medicinal Ingredients

Confirmation should be provided if a non-medicinal ingredient (NMI) used is included in the NHPD's List of Acceptable Non-medicinal Ingredients. For NMIs obtained from non-human animal origin, an Animal Tissue Form should be submitted that includes the name of the material, its source and country of origin of that source material. Specified Risk Materials for the transmission of BSE/TSE must not be used.

Confirmation should be provided that none of the NMIs which appear in the finished product are prohibited for use in drugs by the Canadian *Food and Drug Regulations*.

For NMI(s) used for the first time in a finished NHP or by a new route of administration (novel NMIs), full details of the manufacturing, characterization, and controls, with cross references to supporting safety data (non-clinical and/or clinical) should be provided.

2.3.P.5 Control of Finished Natural Health Product

2.3.P.5.1 Specification(s)

The Control of the Finished Product section is intended to summarize the specifications for the finished product. The specifications are a list of tests, references to analytical procedures, and appropriate tolerance limits which are numerical limits, ranges, or other criteria for the tests described. This would include tests for identity, purity, quantity and potency as well as other tests specific to the finished NHP. The specifications can be summarized according to the table in the QOS-NHP template including Tests, Test Methods, and Tolerance Limits. The Test Method should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, Atomic Absorption, Mass Spectrometry, etc.). It should be ensured that actual numerical results are provided for the Tolerance limits, rather than vague statements such as "within limits" or "conforms".

Particle size may have a significant effect on disintegration rates, product use characteristics (e.g. if too fine powder will escape tea bag), bioavailability, and/or stability, particularly for plant or fungal materials intended for use in herbal teas or solid medicinal products. Particle size determination may also be required for preparations of isolates, vitamins, etc., depending on the finished product, e.g. time-released capsule. Testing may be done according to Pharmacopoeial methods depending on the finished product characteristics.

Please refer to the *Evidence for Quality of Finished Natural Health Products* guidance document for further information on the specifications of the finished product.

2.3.P.5.4 Batch Analyses

If there is more than one batch of the finished product used in the clinical trial, a description of the additional batches accompanied with a batch

analysis should be provided. The batch number, batch sizes and dates and sites of production should be stated in the table. If available, a Certificate of Analysis should be provided for each batch.

2.3.P.5.5 Characterization of Impurities

Information on the characterization of any product and process related impurities and their limits impurities should be provided. This information should include degradation products, possible microbial and chemical contaminants, and solvents used in the manufacturing process of the finished product. A copy of the tables in the QOS-NHP template in section 2.3.S.3.2 can be used to summarize this information.

2.3.P.7 Container Closure System

Information about any specific storage conditions required for maintaining the quality of the finished product should be provided along with a description of the container closure system(s).

2.3.P.8 Stability

The types of studies conducted to support the stability of the finished product, protocol used, and the results of the studies should be summarized in the stability section. The tables in the QOS-NHP template can be used to summarize the stability information required of the batches used in the clinical trial. Full long term stability data may not be required at the time of submission, provided accelerated stability testing is performed with a commitment that the stability of the clinical trial samples will be monitored throughout the duration of the trial. The actual stability results (i.e., raw data) used to support the clinical trial should be provided. It should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms.

Part C: Finished Natural Health Product Specifications Template

This template should be completed and signed, and for any revisions in the finished product specifications, a revised copy of this template should be submitted.

3.4 Module 3: Quality Data

This module should include any supporting data that is not being captured in the QOS- NHP Template, such as signed and dated **specifications**, certificates of analyses, Animal Tissue Form (Appendix 3f), expert reports, published papers and signed attestation. The following sections are included in Module 3:

- 3.1 Table of Contents for Module 3
- 3.2 Body of data
- 3.2.R.1 (Not applicable to the NHPD)
- 3.3 Quality literature references

Clearly label the envelope containing the CTA with "Attention: Clinical Trial Unit" and send to the address in section 13 of this document.

4.0 Review Process

Note: A phase I-III clinical trial cannot begin until authorization from Health Canada and the REB has been received by the sponsor.

4.1 Level 1: Verification

The NHPD screens CTAs and gives the CTA a company file number and submission number. The NHPD then sends out an acknowledgement

notice confirming the receipt of the CTA. The letter lists the file and submission number and notes the date of receipt. Applicants should use the file number assigned on all subsequent correspondence about the CTA.

4.2 Level 2: Processing

The NHPD verifies that all information is correctly identified in all application forms (Appendix 3) submitted and that all appropriate supporting information is submitted and in acceptable format (see section 3 of this document). Faxed or electronic signatures are accepted in lieu of original signatures.

When minor deficiencies are identified, clarification will be obtained through e-mail or a telephone call. For major deficiencies, the NHPD will issue a Processing Deficiency Notice (PDN) requesting the missing information or clarification related to the completeness of the CTA forms and supporting information. The PDN is faxed directly to the Contact for this Application (identified in the Clinical Trial Application and Attestation Form), who may be the sponsor, the sponsor's representative in Canada or a consultant. The recipient is allowed up to 30 days to provide an adequate response. An adequate response is considered to be the provision of the requested data, or a strong scientific justification why this data is not required. Once all of the concerns have been addressed, the CTA will proceed to level 3.

4.3 Level 3: Assessment

When the application reaches this level, the clinical and quality data packages will be reviewed to determine if the CT is suitable for authorization. If more information is required to make a judgment,

concerns will be outlined in an Information Request Notice (IRN). The sponsor will be given up to 30 days to respond. If the response to the IRN is incomplete or the NHPD identifies new concerns based on the responses provided by the applicant, the NHPD will issue another IRN. When all concerns are adequately addressed by the applicant, the CTA will proceed to level 4.

In responding to an IRN, the sponsor should follow these procedures:

- To facilitate a review of the IRN response, the revisions to CTA documents must be formatted to make all changes easily identifiable (e.g., new text in bold or highlighted and old text struck out). This formatting, especially highlighting, should not rely on colour differences. The sponsor should confirm that all other information is identical to the information previously submitted.
- If a revision needs to be reflected in different parts of the QOS-NHP template for chemistry and manufacturing requirements, a revised QOS-NHP template must be submitted by the sponsor.
- A revised copy of the finished product specifications sheets must be provided in response to a Quality IRN to reflect any modifications in the chemistry and manufacturing specification.
- A separate document should itemize the responses to each of the issues in the IRN by first repeating the question, then providing the response below. If a revision that has been requested in the IRN is not made, a strong rationale must be provided to justify why the revision is not needed. The IRN response may be sent to the NHPD by e-mail and/or by courier. If the response is provided by e-mail, a hard copy should also be provided by courier to avoid delays in processing.

4.4 Level 4: Decision

If the decision is to approve the CT, a Notice of Authorization, addressed to the sponsor, will be faxed to the Contact for this Application (identified in the Clinical Trial Application and Attestation Form).

Health Canada will not grant authorization if there are reasonable grounds to believe, based on assessment of the application, that:

- the use of the NHP for the purposes of the CT will endanger the health of a CT subject or other person
- the CT is contrary to the best interests of the CT subjects
- the objectives of the CT will not likely be achieved

Once a Notice of Authorization is issued by the NHPD, the sponsor may start the trial at any time, but must notify the NHPD 15 days prior to the commencement of the trial (see section 13 of this document). The sponsor should also inform the NHPD when the trial has been completed. At this time, the Notice of Authorization does not have an expiry date.

5.0 Notifications

Changes can be made to an approved CTA or CTA-Amendment (CTA-A) but must be submitted to the NHPD in the form of either a notification (see below) or an amendment (see section 6 of this document). The type of change determines whether a notification or an amendment is required. In either case, if NHPD approval is obtained before REB approval, all changes to the CTA requested by the REB must be communicated to the NHPD through a notification or an amendment.

If a change to the protocol of an approved CTA increases the safety or

quality of the trial, and if no aspects of the risks to people are increased, then a notification to the NHPD is appropriate. The changes may be implemented immediately, but the NHPD must be informed in writing within 15 calendar days [Section 70 of the NHP Regulations].

Types of changes requiring notification:

Changes to the protocol that increase or do not affect the safety of the trial and would not be considered an amendment, under section 6 of this document. For example:

- addition of clinic visits, criteria for exclusion, a questionnaire to study the efficacy of the NHP or laboratory test(s) that do not require additional samples from the subject as well as improvements to the randomization, stratification or blinding processes. Please note that if the CT has been completed, but a sponsor is interested in conducting further laboratory tests on the samples collected during the CT, the sponsor must first obtain REB approval. Health Canada approval is not required.
- information on site closure or completion of the CT
- a change in qualified investigator(s) at a CT site after the trial has started at that site (include the Qualified Investigator Undertaking form; Appendix 3c). Please see section 3.2 for the forms that must be submitted to the NHPD prior to commencement of a CT.

Changes to the quality (chemistry and manufacturing) information that do not adversely affect the quality or safety of the NHP, for example:

- changes in **common name** or **brand name** of the investigational product or common name of medicinal substance
- changes in contact information for the manufacturer or sponsor

- optimization of the manufacturing process which does not change the quality of the product
- production scale-ups with no changes in the process
- tightening of existing test specifications
- changes to contract testing laboratories
- changes in packaging material
- extension of shelf life
- change in shape of dosage form
- any other changes not requiring an amendment

A notification submitted to the NHPD should include a cover letter outlining the changes made to the CTA and any supporting documentation (e.g., any of the forms in Appendix 3). The information will be reviewed and added to the file. Notifications may be sent by FAX (613) 954-2877 or mail (see section 13 of this document).

The NHPD will notify the applicant if the changes made to the CTA need to be re-submitted to the NHPD as an amendment.

6.0 CTA Amendment (CTA-A) or New CTA

6.1 When Changes to an Approved Clinical Trial Require an Amendment

Some changes to an approved CTA require that a CTA-A be submitted to the NHPD. Changes to an approved CT can only be implemented once authorized by both the NHPD and the REB unless the subject's health is at risk (see section 6.1.1 of this document). In other cases, changes to a CT are so substantive that a new CTA will be needed (see section 6.2 of

this document).

Sponsors must file a CTA-A [Section 71 of the *NHP Regulations*] when changes to the protocol:

- affect selection, monitoring or dismissal of CT subject
- affect the evaluation of clinical efficacy of the NHP
- alter the risk to health of a CT subject
- affect the safety evaluation of the NHP
- extend the duration of the CT

Changes to the protocol that require a CTA-A include:

- addition of an approved (phase IV) pharmaceutical or NHP (the pharmaceutical may affect both the efficacy and safety evaluation of the NHP)
- removal of specific clinic visit(s), criteria for exclusion or laboratory test(s) used to monitor safety
- addition of laboratory test(s) that require additional samples from the subject
- changes in allowed concomitant medication
- changes in dose taken at one time, frequency or total daily dose within established safety range
- substitution of the questionnaire that is used to measure the primary outcome

Changes to quality (chemistry and manufacturing) that require a CTA-A include:

- certain changes to the formulation of the finished product (e.g.,

change in dosage form from capsule to tablet)

- changes in quantity of medicinal ingredient per dosage unit within established safety range
- substitution of placebo
- changes to the manufacturing process and process controls
- changes to the chemistry and manufacturing information regarding **synthetic duplicates** of NHP medicinal ingredients that may affect safety or quality
- identification of a new impurity or degradation product
- elimination or modification of a test method
- changes to the sterilization process and conditions
- changes to the specifications of the medicinal substance and/or finished product that may increase risk (e.g., tolerance limits are relaxed, changes in test method)
- changes to the stability protocol for the finished product
- addition or substitution of a non-medicinal ingredient not on the NHPD List of Acceptable Non-medicinal Ingredients

Changes to the chemistry and manufacturing may require revisions to Module 1 as well as Modules 2 and 3.

6.1.1 Implementing changes described in amendments

Amendments can be implemented immediately if the safety of the subjects or other persons is at stake [Section 71(2) of the *NHP Regulations*]. Amendments which increase the risk to subjects or other persons must not be implemented until authorized. The NHPD will issue

a Notice of Amendment to the sponsor once it has been approved by the NHPD. If changes were not implemented earlier due to safety reasons, the newly amended protocol can be implemented upon receipt of the Notice of Amendment and REB approval.

6.1.2 CTA-A contents

The contents of a CTA-A are described in section 71(3) of the *NHP Regulations*. They include:

- A cover letter indicating the original CTA title, with the file and submission number. The cover letter should include a summary of and reason for the change to the CTA.
- The Clinical Trial Application and Attestation Form (Appendix 3a), indicating in Part 3a and 4 that the application is a CTA-A. A Designated Party Authorization Form must also be submitted, if applicable. These forms must be signed and dated by the appropriate people specified in the form.
- Components of the CTA to be changed need to be included in the CTA-A. This includes two hard copies and two electronic copies of the revised protocol and, if applicable, the Informed Consent Form and Investigator's Brochure. The revisions to the original CTA should be formatted in such a way that all changes are easily identified (e.g., new text in bold or highlighted and old text struck out). This formatting, especially highlighting, should not rely on colour differences. The sponsor should confirm that all other information is identical to the information previously submitted and approved.
- Sections of the QOS-NHP (CTA - Phase I/II/III) Template can be used to summarize the quality information contained in the CTA-A. Two

hard copies and two electronic copies should be provided.

- For each CT site, confirmation of REB approval.
- For each CT site, the name, address, and telephone number, and if applicable, the fax number and e-mail address of the REB that approved the amendment.
- For each CT site, the name, address, and telephone number, and if applicable, the fax number and e-mail address of the REB that refused to approve the amendment, its reasons for doing so and the date on which the refusal was given.

Send the contents of the CTA-A to the NHPD at the address in section 13 of this document. Clearly label the outside of the envelope with "Attention Clinical Trial Unit"

6.2 When Changes to an Approved Clinical Trial Require a New CTA

Note that certain fundamental changes to an NHP of an approved CTA should be submitted as a **new CTA**, with reference to the previously approved CTA. These changes include:

Changes to safety and efficacy that require a new CTA include:

- addition or substitution of a non-phase IV treatment arm
- changes in dose taken at one time, frequency, or total daily dose outside the established safety range

Changes to the quality information that require a new CTA include:

- changes to the extraction or purification process
- some changes in formulation (e.g., from immediate to modified

release)

- addition or substitution of a medicinal ingredient
- change in quantity of medicinal ingredient per dosage unit outside the established safety range
- change in **route of administration** (e.g., topical to oral)

7.0 Continuous Assessment

7.1 Refusals by Research Ethics Board or Other Regulatory Authority

Following Health Canada approval of a CTA or CTA-A, information regarding refusals by a REB or other regulatory authority should be submitted as a notification.

7.2 Adverse Reactions

Definitions of an **adverse event, adverse reaction, serious adverse reaction** and **serious unexpected adverse reaction** can be found in the Glossary of this document.

Sponsors of CTs must maintain records of all adverse events associated with the NHP that have occurred inside or outside Canada [Section 76(3)(c) of the *NHP Regulations*]. These records shall include information on dosage form, and the use and purpose of the NHP at the time of the adverse event. **These records must be maintained for 25 years.** If there are reasonable grounds for concern, including if the trial involves a risk to health of a CT subject or other person, records must be made available to the NHPD no later than two days after the day the request is received. In any other case, records must be provided within seven days of a

request [Section 77 of the *NHP Regulations*].

7.2.1 Expedited reporting

During the CT, the sponsor is required to inform the NHPD Clinical Trial Unit of any serious unexpected adverse reaction to the NHP that has occurred inside or outside Canada [Section 78 of the *NHP Regulations*, ICH Guidance Document *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*].

- If the serious unexpected adverse reaction is fatal or life threatening, the NHPD should be notified immediately if possible, and no later than seven days after the sponsor becomes aware of the information
- If the serious unexpected adverse reaction is neither fatal nor life threatening, the NHPD should be notified immediately if possible, and no later 15 days after the sponsor becomes aware of the information
- Within eight days after having informed the NHPD of a serious unexpected adverse reaction to the NHP, the sponsor must submit a report as complete as possible that includes an assessment of the importance and implication of any findings. **The final report should include relevant previous experience with the same or similar health products.**

Serious adverse events unrelated to the NHP being studied do not require expedited reporting to the NHPD. In situations in which the cause of the adverse event is uncertain, the report should be submitted in the expedited manner and the problem in ascribing a cause should be addressed in a cover letter. For further information, please refer to ICH Guidance Document *E2A: Clinical Safety Data Management: Definitions and*

Standards for Expedited Reporting.

Each serious unexpected adverse reaction to an NHP should be reported individually in accordance with the data elements specified in the ICH Guidance Document *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.* Expedited adverse reaction reports for CTs should be submitted by fax to the Clinical Trial Unit, NHPD (FAX (613) 954-2877).

7.3 Other reports requiring accelerated reporting

Other situations than those described above may require rapid communication to the NHPD. Appropriate scientific and medical judgment should be applied to each situation.

For example, the discovery of information that might influence the risk-benefit assessment of an NHP, or that would be sufficient to consider changes in dose administered or in overall conduct of a CT, should be communicated rapidly. Specific examples include:

- a clinically significant increase in the rate of occurrence of an expected serious adverse reaction to an NHP within a population
- a significant hazard to the patient population, such as a lack of efficacy with an NHP used in treating a life-threatening disease
- a major safety finding from a newly completed animal study

For further information refer to the ICH Guidance Documents: *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and E6: Guideline for Good Clinical Practice.*

All adverse reaction reports should be submitted by fax to the Clinical Trial Unit using the form found in Appendix 8 or a similar form

containing the same information. Please fax this form to (613) 954-2877.

8.0 Discontinuation of a Clinical Trial

If the sponsor prematurely discontinues an NHPD authorized trial, in its entirety or at a CT site inside or outside of Canada, the NHPD must be notified within 15 calendar days after the date of discontinuance [Section 79 of the *NHP Regulations*]. The notification should include:

- a detailed rationale for the action
- description of the impact on proposed or ongoing trials, in respect of the NHP conducted in Canada by the sponsor
- confirmation that all qualified investigators have been notified of the discontinuance and the reason for the discontinuance, and have been advised in writing of any potential risks to the health of CT subjects or others persons
- confirmation that the importation, sale, or distribution of the NHP to all sites involved has been stopped
- confirmation that reasonable measures will be taken to ensure the return of all unused quantities of the NHP

The sponsor may resume the trial in its entirety (through a CTA-A) or at a site that was previously discontinued (notification) if the sponsor submits the following information [Section 79(2) of the *NHP Regulations*]:

- name, address and telephone number, and if applicable the fax number and e-mail address of the qualified investigator for each site and of the REB that approved the re-initiation of the trial at each site
- name, address and telephone number and if applicable, the fax

number and e-mail address of any REB that has previously refused to approve the re-initiation of the trial, if applicable

- an attestation signed and dated by the REB for each CT site (Appendix 3d)
- the proposed date of commencement of the CT at each CT site

9.0 Suspension and Cancellation

Health Canada can suspend authorization of the use of an NHP in a CT or at a particular CT site if it appears that:

- the sponsor has violated the legal requirements relating to the NHP
- any information provided in respect of the NHP or CT is false or misleading
- the CT is not being conducted in compliance with GCPs
- the sponsor has failed to provide required information, samples, notifications, or appropriate adverse reaction reports to the NHPD

Normally before suspending a CT, the NHPD will send the sponsor a notice stating that the authorization may be suspended in its entirety or at a specific CT site and the reason for the suspension. Suspension will begin 30 days after the day on which the notice is received, unless the sponsor provides, within the 30 days, information demonstrating that the authorization should not be suspended because the situation giving rise to the suspension did not exist or has been corrected [Section 80(2) of the *NHP Regulations*].

If there are reasonable grounds to believe suspension is needed to prevent harm to the participants of the CT or another person, the NHPD

will suspend the CT in its entirety or at a particular CT site *before* giving the sponsor an opportunity to respond [Section 81 of the *NHP Regulations*]. In this case, the NHPD will send the sponsor a notice giving the reason for the suspension, the day the suspension begins and indicating if the authorization is suspended in its entirety or at a particular CT site.

The authorization for the CT will be restored if, within 30 days *after* the day on which the suspension is effective, the sponsor provides the NHPD with information demonstrating that the situation causing the suspension either did not exist or has been corrected. If the required information has not been received by the NHPD within 30 days *after* the day on which the suspension is effective, the authorization for the CT will be cancelled in its entirety or at a particular CT site [Section 82 of the *NHP Regulations*].

10.0 Labelling and Instructions For Use of an NHP

The label of the NHP to be used in a CT must conform to the requirements in section 75 of the *NHP Regulations*.

The sponsor must ensure that the label of the NHP provided to the investigators has the following information in both official languages:

- a statement indicating that it is an investigational product to be used only by a qualified investigator
- the brand name or code of the study product(s)
- the expiry date, if applicable
- the storage conditions, if applicable

- the lot number
- the name and address of the manufacturer and the sponsor
- the protocol code or identification

Written instructions on how to use the study product(s) should be provided to the subject as part of the Informed Consent Form.

11.0 Records

The sponsor must keep records of the CT [Section 76 of the *NHP Regulations*]. The records must be created and stored in a way that allows complete and accurate reporting of the trial. Records should be adequate to indicate that the CT has been conducted in accordance with GCPs and the *NHP Regulations*, and must include a copy of the Notice of Authorization from Health Canada.

Records should include:

- a copy of all versions of the Investigator's Brochure for the NHP
- records of each change made to the Investigator's Brochure, including the rationale for each change and the documentation that supports each change
- records of all adverse events in respect of the NHP that have occurred inside or outside Canada, including information that specifies the indication for use and the dosage form of the NHP at the time of the adverse event
- records of the enrollment of CT subjects, including information sufficient to enable all subjects or other persons involved in the CT to be identified and contacted in the event that the use of the NHP may

endanger their health

- records of the shipment, receipt, disposition, return and destruction of the NHP
- for each CT site, a signed and dated undertaking from the qualified investigator prior to the commencement of his or her responsibilities in respect of the CT
- for each CT site, a copy of the protocol, Informed Consent Form and any amendments to the protocol or Informed Consent Form that have been approved by the REB for that CT site
- for each CT site, an attestation, signed and dated by the REB, stating that it has reviewed and approved the protocol and Informed Consent Form and that the board will carry out its functions in a manner consistent with GCPs

The sponsor must maintain printed copies of all of these records for a period of 25 years.

Records must be made available to the NHPD within two days if there is a concern that the use of the NHP for the purposes of the CT may endanger the health of the subjects involved in that trial, that the CT is contrary to the best interests of the subjects, that GCPs are not being followed, or that information about the trial submitted to Health Canada was false or misleading. In any other case, records must be provided within seven days of a request [Section 77 of the *NHP Regulations*].

12.0 Roles and Responsibilities of Those Involved in Clinical Trials

Note that one person may have one or more roles in the clinical trial.

Some of the terms defined in this section appear in the application form(s) in Appendix 3.

Sponsor - A sponsor is defined by section 63 of the *NHP Regulations* as the individual, corporate body, institution or organization that conducts or provides funding for a CT. A sponsor is responsible for:

- submitting the complete CTA package to the NHPD for assessment
- having a representative in Canada if the sponsor is outside Canada
- informing the NHPD if a REB has refused to approve the CT protocol
- ensuring the NHP is properly labelled
- providing information or samples to the NHPD, if requested
- ensuring authorization from the NHPD and REB has been received prior to commencement of the trial
- providing a commencement notice to the NHPD at least 15 days before the CT begins
- ensuring that the CT is conducted according to GCPs
- submitting any notifications (including discontinuations) and amendments
- if the safety of subjects is at risk, implementing necessary changes to the CT immediately and submitting a CTA-A to the NHPD within 15 days
- conveying ongoing NHP safety information to investigators and the REB
- maintaining accurate records on the CT

It is mandatory that the sponsor submit REB approval, Qualified

Investigator Undertaking and Clinical Trial Site Information forms to the NHPD prior to commencement of the trial.

Contact for this Application - This is the person who will be faxed the Notice of Authorization and who will be contacted by the NHPD for specific questions throughout the course of the clinical trial. This person may be an employee of the applicant company or may be contracted from another company on behalf of the applicant, such as a contract research organization.

Senior Official - In the case where the sponsor is a company, institution or organization, this is the person who will represent the sponsor and to whom the Notice of Authorization will be addressed. This should be a senior person, such as a Chief Executive Officer (CEO for a company), Department Head or Centre Director (for institution-investigator initiated CTs). The senior official must sign "Part 7: Attestation" of the Clinical Trial Application and Attestation Form (Appendix 3a).

Senior Medical or Scientific Officer - A scientific or medical officer residing in Canada, representing the sponsor, who is responsible for providing an attestation with respect to the Clinical Trial Application/Amendment at the time of filing, as outlined in Part 7 of the Clinical Trial Application and Attestation Form (Appendix 3a).

Representative in Canada - In the case of a sponsor who is located outside of Canada, this is a person with a Canadian address and to whom the Notice of Authorization is addressed. This person is often the qualified or principal investigator.

Qualified Investigator - This is a medical doctor or a dentist who is entitled to provide health care under the laws of the province where the CT site is located. A dentist may serve as the qualified investigator of

dental CTs, but not other types of CTs. A complementary or alternative health care (CAHC) (or a complementary and alternative medicine (CAM)) practitioner can be a principal or co-investigator, but cannot function as a qualified investigator unless he or she is also a licensed physician or dentist. There must be a qualified investigator identified for each CT site, but one qualified investigator may be responsible for more than one site if feasible (i.e., if the locations are relatively close). There must be no more than one qualified investigator for each site. The qualified investigator(s) must sign the Qualified Investigator Undertaking form (Appendix 3c) or a similar document.

The qualified investigator is responsible for:

- the safety of the CT subjects at a particular site
- supervising medical care and medical decisions respecting the CT
- ensuring that the CT is conducted in accordance with GCPs
- immediately notifying both subjects and REB of discontinuation of the trial by the sponsor and of any potential risks

Principal Investigator - This person is the team leader for the entire CT. They are responsible for coordination of the clinical research, including data collection and analysis. The sponsor or qualified investigator frequently takes on this role.

Co-investigator - This is a member of the CT team designated and supervised by the principal investigator. Co-investigators contribute expertise relevant to the CT.

For clinical research in CAHC it is strongly recommended that a naturopathic doctor, herbalist, homeopathic practitioner, traditional medicine practitioner, or other expert in CAHC be a member of the

clinical trial team.

Importer - The individual responsible for bringing an NHP into Canada for use in a CT. Health Canada can issue a Notice of Authorization to a Canadian sponsor. However, if the sponsor is not located in Canada, then an importer located in Canada must be designated by the sponsor using the "Authorization for Third Party to Import the NHP" form (Appendix 3e).

Research Ethics Board - The body of individuals not affiliated with the sponsor, and whose principal mandate is to approve the initiation of, and conduct periodic reviews of biomedical research involving human subjects in order to ensure the protection of the rights, safety and well-being of these subjects and other persons. For each clinical trial site, an REB must review and approve the clinical trial protocol, Informed Consent Form, and clinical trial amendments. Different sites may be subject to different REBs.

The board must have at least five (5) members including the following (note that one member may satisfy more than one of the requirements in the following list):

- two (2) who are in a scientific discipline with broad expertise in the research to be approved
- one (1) from a medical or dental discipline (as appropriate)
- one (1) knowledgeable in ethics
- one (1) knowledgeable in relevant Canadian laws
- one (1) whose primary experience and expertise is in a non-scientific discipline
- one (1) representative from the community or an interested

organization

- one (1) knowledgeable in CAHC. This member may be permanent or ad hoc and should be knowledgeable about the particular paradigm or the NHP to be studied

The REB board member with knowledge of CAHC can serve on the board for just the review of the CT involving the NHP. This individual must be named and their expertise described in the cover letter and should be indicated by checking the appropriate box in the Clinical Trial Application and Attestation Form, Part 2 (Appendix 3a).

The REB representative must sign either the NHPD REB Attestation form (Appendix 3d) or, the approving REB's similar documentation that meets the same requirement.

Both NHPD and REB approvals must be obtained by the sponsor prior to commencement of the CT.

Sources of information useful in finding an REB member knowledgeable in CAHC include:

- National Council on Ethics in Human Research
- Canadian Interdisciplinary Network for CAM Research
- Canadian Interdisciplinary Network for Complementary and Alternative Medicine

13.0 Contact Information

The envelope containing the Pre-CTA Consultation Package, CTA, CTA-A and CT notifications must be sent to the address below. Please ensure that "Attention: Clinical Trial Unit" appears on the envelope.

Visit our "Contact Us" page.

Glossary

All guidance documents referenced in the glossary are available on the NHPD's website.

adverse event - any adverse occurrence in the health of a clinical trial subject who is administered an NHP that may or may not be caused by the administration of the NHP, and includes an adverse reaction, a serious adverse reaction and a serious unexpected adverse reaction [Section 63 of the *NHP Regulations*].

adverse reaction - a noxious and unintended response to an NHP that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function [Section 1(1) of the *NHP Regulations*].

biologic - a category of conventional pharmaceuticals as set out on Schedule D to the Food and Drugs Act, prepared from a biological starting or source material, either conventional manufacturing methods, recombinant DNA technology, and/or other novel approaches. Some examples of biologics include vaccines, blood products, living tissues and organs, certain hormones, and certain enzymes.

brand name - a name in English or French, whether or not it includes the name of a manufacturer, corporation, partnership or individual, that is used to distinguish the NHP and under which an NHP is sold or advertised. The brand name may or may not include a trade name.

clinical trial - an investigation in respect of an NHP that involves human subjects and that is intended to discover or verify its clinical,

pharmacological or pharmacodynamic effects, to identify any adverse events that are related to its use, to study its absorption, distribution, metabolism and excretion, or to ascertain its safety or efficacy [Section 63 of the *NHP Regulations*].

clinical trial site - The location(s) where trial-related activities are actually conducted.

common name - for any medicinal or non-medicinal ingredient contained in an NHP, the name by which it is commonly known and is designated in a scientific or technical reference. For example:

common name: Ginger
proper name: *Zingiber officinale*

The NHPD recognizes that there may be cases where the common name and proper name will be identical, for example: vitamin C.

comparative bioavailability studies - for the purpose of this document, studies comparing the pharmacokinetics of two NHP formulations in healthy adult volunteers.

comparator - a product which is already licensed in Canada or in those countries in ICH regions (European Union, Switzerland, Japan, and United States) and Australia that is being used within its approved recommended conditions of use as a comparison to the NHP under investigation. Products that are not licensed in the above mentioned countries are considered to be other investigational products which require the evidence for safety, efficacy and quality as described in section 3 of this guidance document.

conditions of use,

- its use or purpose

- its dosage form
- its route of administration
- its dose (including frequency, directions of use and sub-population)
- its duration of use, if any and
- its risk information, including any cautions, warnings, contra-indications or known adverse reactions associated with its use.

conventional pharmaceutical - a drug for human use that falls under the regulation of the TPD (*Food and Drug Regulations*) and not the NHPD (*NHP Regulations*).

date of commencement of a clinical trial - this is defined as the date when the clinical trial site will be ready to enroll subjects in the clinical trial. If known at the time of application, this date should be included in the Clinical Trial Application and Attestation Form.

DIN - the Drug Identification Number is an eight digit numerical code assigned to each drug product marketed under or in accordance with the *Food and Drugs Act* and the *Food and Drug Regulations*.

dosage form - the final physical form of the NHP which may be used by the consumer without requiring any further manufacturing. The NHPD has developed an administrative list for classification of recognized dosage forms, related routes of administrations, synonyms and the applicable definitions. Applicants are not limited to using dosage forms on this list (see Appendix 3 of the *Product Licensing Guidance Document*).

dose - the amount of finished product in dosage form used for the recommended purpose, including any directions of use. The dose is represented as the amount of dosage units, the frequency of use, and directions for use, if any, by a sub-population group. When the dosage

unit is a discrete (separate) dosage form, the dose should be stated as the number of dosage units, such as the number of tablets. For non-discrete dosage forms, such as powder, liquid, ointment and cream, the dosage unit should be stated as a standard equivalent of 5 mL or 15 mL per dose, or as "apply sparingly" or "apply as needed".

- frequency - how often the product is to be taken in a given time or time interval (e.g., 3 tablets per day, 3 times per day, every 4 hours up to a maximum of ...)
- directions for use - how the product should be taken. This may include time of administration, or administration with respect to food or drink (e.g., 2 tablets, 3 times a day, take on a full stomach, take at bedtime).

duration of use - the time frame during which an NHP will be consumed.

Good Clinical Practices - generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons, and the good clinical practices referred to in section 74 of the *NHP Regulations*.

import - for the purpose of this document, to bring an NHP into Canada for the purpose of use in a clinical trial.

importer - for the purpose of this document, a person who imports an NHP into Canada for use in a clinical trial.

informed consent - written informed consent, given in accordance with the applicable laws governing consent, must obtained from every person before that person participates in a clinical trial but only after that person has been informed of:

- the risks and anticipated benefits to his or her health arising from

participation in the clinical trial

- all other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial.

Investigator's Brochure - in respect of an NHP, a document containing the pre-clinical and clinical data on the NHP that are described in section 66(e) of the *NHP Regulations*.

investigational product - for the purpose of this document, it is the NHP that is to be tested in the clinical trial.

medical device - covers a wide range of health or medical instruments used in the treatment, mitigation, diagnosis or prevention of a disease or abnormal physical condition. Some examples include pacemakers, artificial heart valves and contraceptive devices.

medicinal ingredient - any substance set out in Schedule 1 of the NHP Regulations, or a substance in a homeopathic medicine or traditional medicine that is intended to furnish pharmacological activity or other direct effect in:

- the diagnosis, treatment, mitigation, or prevention of a disease, disorder or abnormal physical state or its symptoms in humans; or restoring or correcting organic functions in humans; or modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

natural health product (NHP) - please see Sections 1(1) and 2(2), and Schedules 1 and 2 of the *NHP Regulations* or section 1.1 of this document for detailed information.

non-medicinal ingredient - any substance added to an NHP to confer suitable consistency or form to the medicinal ingredients. Non-medicinal

ingredients may include, but are not limited to, diluents, binders, lubricants, disintegrators, colouring agents and flavours. Some examples of the purposes of non-medicinal ingredients have been included in the "List of Purposes for Non-medicinal Ingredients" (see Appendix 6 of the *Product Licensing Guidance Document*). The NHPD has developed a list of non-medicinal ingredients that are generally regarded to be of minimal toxicological concern (refer to the "List of Acceptable Non-medicinal Ingredients" which appears as an appendix to the *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document*). When used under the limitations outlined in the "List of Acceptable Non-medicinal Ingredients", these ingredients are considered to be safe, and will not require further assessment by the NHPD.

Other types of non-medicinal ingredients may require safety assessment by the NHPD. Thus, care must be taken to identify the proper submission requirements for non-medicinal ingredients. Applicants are encouraged to submit additional information with their initial CTA, so as to not delay the assessment process.

NPN/DIN-HM - the Natural Product Number or the Drug Identification Number for Homeopathic Medicines is an eight digit numerical code assigned to each NHP approved to be marketed under the *NHP Regulations*.

observational study - a study where the investigator's do not manipulate the use of, or deliver, an intervention (e.g., do not assign patients to treatment and control groups) nor collect samples from the patients outside of the scope of normal medical practice but only observe patients who are (and sometimes as a basis of comparison, patients who are not) exposed to the intervention, and interpret the outcomes.

phase I - initial safety studies on an NHP, including the first administration of the NHP into humans, usually conducted in healthy volunteers. These trials may be conducted in subjects when administration of the NHP to healthy volunteers is not ethical. Phase I clinical trials are primarily designed to determine the pharmacological actions of the NHP and the side effects associated with increasing doses. Pharmacokinetic studies as well as studies of interactions between health products, are usually considered as phase I trials regardless of when they are conducted during drug development, as these are generally conducted in healthy volunteers. Phase I trials also include trials in which new drugs are used as research tools to explore biological phenomena or disease processes.

phase II - clinical trials to evaluate the efficacy of an NHP in subjects with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with the NHP. If a new indication for a marketed NHP is to be investigated, then those clinical trials may generally be considered phase II trials.

phase III - controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the NHP has been demonstrated. These are intended to gather the additional information about efficacy and safety that is needed for further risk/benefit assessment of the NHP. In this phase, clinical trials are also conducted in special patient populations (e.g., renal failure patients), or under special conditions dictated by the nature of the NHP and disease.

phase IV - all studies performed after the NHP has been approved by the regulator for the market and related to the approved conditions of use. These studies are often important for optimizing the NHP's use. They may be of any type but must have valid scientific objectives. Commonly

conducted studies include safety studies and studies designed to support use under the approved conditions of use, such as mortality and morbidity studies or epidemiological studies.

placebo - an inactive substance (or therapeutic procedure with no intrinsic therapeutic value) that is used in clinical trials for comparison with the active treatment to determine the safety and efficacy of investigational treatments.

potency - the amount per dosage unit of the standardized component that further characterizes the quantity of the ingredient. For information on standardized products, please see the Evidence for Quality of Natural Health Products Guidance Document. For example,

quantity: 500 mg *Echinacea purpurea* extract
potency: 0.4% echinacoside

product code - the identification code assigned to the product by manufacturer or sponsor.

product monograph - a scientific monograph that is a product-specific document approved by a regulatory authority.

proper name - in reference to medicinal and non-medicinal ingredients, one of the following names:

- when the ingredient is a vitamin, a name set out for that vitamin in item 3 of Schedule 1: biotin, folate, niacin, pantothenic acid, vitamin A, thiamine, riboflavin, vitamin B6, vitamin B12, and vitamins C, D and E. To maintain consistency, the proper name is the name included in the Dietary Reference Intakes publications, since this will be the international standard.
- when the ingredient is a plant or a plant material, an alga, a fungus,

a bacterium, a non-human animal material or a probiotic, the Latin name of its genus and, if any, its specific epithet.

- the *genus* is the first part of the standard two-part (binomial) scientific name for an organism, often derived from the classical Greek or Latin name for the organism. Members of a genus are various species that are all descended from a common ancestor and that are more closely related to each other than to species of other genera in the same family
- the *specific epithet* is the second, generally descriptive, part of the standard two-part (binomial) scientific name for an organism. Together the genus and specific epithet comprise the name of a species. For example:
  genus: *Angelica*
  specific epithet: *archangelica*
- when the ingredient is other than one described above, the chemical name of the ingredient. The acceptable chemical name of an ingredient may be the one determined using the International Union of Pure and Applied Chemistry (IUPAC) nomenclature or any unambiguous chemical name. For example:
  common name: Alcohol
  proper name: Ethyl alcohol or Ethanol

The following websites may be used in identifying the proper names of ingredients:

- For plants
- For animals
- For chemicals

protocol - a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial.

quantity per dosage unit - the amount of medicinal ingredient per dosage unit (for example, per tablet). Each medicinal ingredient in the product must have a quantity associated with it. The quantity of medicinal ingredient should be based on the proper name of the medicinal ingredient. For example, the quantity of vitamin C in a product should be the quantity of ascorbic acid, not of sodium ascorbate.

The term "potency" in homeopathic medicines is equivalent to quantity when making the declaration to the NHPD(e.g., 6X, 12CH).

When the ingredient is an extract, the applicant must provide the quantity of the liquid or solid extract per dosage unit, the extraction ratio and the crude dried material equivalent.

The extraction ratio is always expressed as crude dry material to extract, regardless of whether it is a liquid or a solid. For example, a tincture ratio of 1:5 means that 1 g of crude dried material was used to prepare 5 ml of alcoholic extract. In a solid extract, a ratio of 5:1 means that 5 g of crude dried material was used to prepare 1 g of solid extract.

Crude dried material is the material from which the ingredient was extracted. When the extracted ingredient has a potency associated with it (see definition of potency), the crude material equivalent and ratio may not be necessary.

rescue medication - recommended treatments in the event of an overdose, lack of efficacy or adverse event.

risk information - cautions, warnings, adverse reactions and contra-indications associated with the use of the NHP.

- cautions and warnings - information concerning special care to be exercised by the user to ensure safe and effective use of the NHP. Cautions and warnings may also include information on the occurrence of serious potential hazards, and on particular conditions or situations in which a specific hazard may be anticipated.
- contraindications - situations in which the NHP should not be used because of risk that outweighs any potential benefit. For example, flaxseed should not be used by subjects with acute abdominal pain or intestinal obstruction.
- adverse reactions - any noxious and unintended response to an NHP that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function. Examples include flushing, nausea, diarrhea and constipation.

route of administration - the method by which the NHP is to be delivered to the body. These routes include, but are not limited to oral, buccal, nasal and topical. As per Schedule 2 of the *NHP Regulations*, products to be administered by puncturing the dermis are not covered by the *NHP Regulations*. These products are regulated as drugs, administered by the TPD. The NHPD has developed a list of recognized routes of administration, with the associated dosage forms (see Appendix 3 of the *Product Licensing Guidance Document*), to be used to describe the route of administration when completing the CTA form.

scientific monograph - a factual, scientific document on a study substance that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the study substance, and that contains any other information that may be required for optimal, safe, and effective use of the study substance.

serious adverse reaction - a noxious and unintended response to an NHP that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death [Section 1(1) of the *NHP Regulations*].

serious unexpected adverse reaction - a serious adverse reaction to an NHP that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the NHP.

source material - substance from which the medicinal ingredient is derived.

specifications - a description of an NHP that contains the information described in section 44(2) of the *NHP Regulations*.

study products - investigational product(s), placebo(s), and/or comparator(s) used in the clinical trial.

sub-population group - the group to which the subject NHP is targeted. Most often this will be adults, if there are additional doses, list these as well. For example: children, type 2 diabetics.

synthetic duplicate - a substance that shares an identical chemical structure and pharmacological properties with its natural counterpart. A synthetic duplicate may be manufactured entirely by chemical processes, or by a semi-synthetic process that chemically changes a related starting material that has been extracted or isolated from a plant or a plant material, an alga, a fungus or a non-human animal material. Two examples are the synthetic duplicate of vitamin C and the semi-synthetic ginsenoside Rh2 prepared from betulafolienetriol. Refer to the Evidence

for *Quality of Finished Natural Health Products Guidance Document* for further information on synthetic duplicates and their requirements.

traditional product - is (1) based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, or in the prevention, diagnosis, improvement or treatment of a physical or mental illness and (2) a product for which the traditional use extends back at least fifty years.

use or purpose - the intended beneficial effect of an NHP when used according to the dose, duration of use and route of administration proposed in the CTA.

Appendices

Appendix 1: List of Abbreviations

BGTD

Biologics and Genetic Therapies Directorate

BSE/TSE

bovine spongiform encephalopathy/transmissable spongiform encephalopathy

CAHC

complementary and alternative health care

CAM

complementary and alternative medicine

CT

clinical trial

CTA

clinical trial application

CTA-A

clinical trial application-amendment

DIN

drug identification number

DIN-HM

drug identification number for homeopathic medicine

GCP

good clinical practice

ICH

international conference on harmonization

IRN

information request notice

NHP

natural health product

NHPD

Natural Health Products Directorate

NPN

natural product number

OTC

over the counter

PDN

processing deficiency notice

QOS

quality overall summary

REB

research ethics board

ROD

record of decisions

TPD

Therapeutic Products Directorate

Appendix 2: Outline of a CTA / CTA-A

Please use the following outline that conforms to the Common Technical Document format. Please note that for a CTA-A only new data should be submitted and other fields in the form can be labelled "No new information". The items marked with an asterisk (*) should be submitted in hard copy and electronic format.

Table - Outline of a CTA / CTA-A

Module	Content
1	Administrative / Clinical Information
1.1	Table of Contents (Modules 1-3)
1.2	Application Information
1.2.1	NHPD Clinical Trial Application Forms
1.2.2	Information on Prior-related Applications
1.2.3*	Investigator's Brochure
1.2.4*	Protocol Synopsis and Evaluation Review Template (PCERT)
1.2.5*	Study Protocol(s)

Module	Content
1.2.6	Informed Consent Document(s)
1.2.7	Clinical Trial Site Information
1.2.8	Canadian Research Ethics Board(s) Refusals
1.2.9	Foreign Refusals
1.2.10	Letters of Access
1.2.11	Other Application-related Information
1.3	Electronic Review Documents
2	Common Technical Document Summaries
2.1	Common Technical Document Table of Contents
2.2	(Not Applicable to Clinical Trials)
2.3*	Quality Overall Summary
3	Quality Data (supporting data)
3.1	Table of Contents of Module 3
3.2	Body of Data
3.2.R.1	(Not Applicable to the NHPD)
3.3	Quality Literature References

Appendix 3: Application Forms

All forms can be found online under Forms.

3a) Clinical Trial Application and Attestation Form

3b) Clinical Trial Site Information Form

3c) Qualified Investigator Undertaking form

3d) Research Ethics Board Attestation form

3e) Authorization form for Third Party to Import the NHP

3f) Animal Tissue Form

3g) Designated Party Authorization Form

Appendix 4: Clinical Trial Application and Attestation Form Instructions

Instruction sheet can be found online under Forms.

The Clinical Trial Application and Attestation Form has 7 parts:

- Part 1: Applicant and Contact Information
- Part 2: Research Ethics Board(s)
- Part 3: Clinical Trial Application Information
- Part 4: Clinical Trial Application - Amendment
- Part 5: Clinical Trial Site Information
- Part 6: Study Product Information
- Part 7: Clinical Trial Attestation

For detailed definitions of terms and guidance on completing Clinical Trial Applications (CTAs) and CTA-Amendments (CTA-As), please consult the *Clinical Trials for Natural Health Products Guidance Document*. The following sections may be particularly useful: Section 3, "Clinical Trial Applications"; Section 6.1, "When Changes to an Approved Clinical Trial Require a CTA-A"; Section 12, "Responsibilities of Those Involved in CTs";

and the Glossary.

All guidance documents and forms referenced in these instructions are available on the Natural Health Products Directorate (NHPD) website.

Part 1: Applicant and Contact Information

Telephone and fax numbers must include the area code and extension, where applicable.

If a P.O. Box is part of the address, the land location must also be provided.

Indicate the language of preference for correspondence by checking the boxes as appropriate. If no preference is indicated, correspondence will default to English. Following approval of the CTA, a Notice of Authorization, addressed to the sponsor, will be faxed to the contact for this application, who may be the sponsor, the sponsor's representative in Canada, or a consultant. Refer to section 12 of the *Clinical Trials for Natural Health Products Guidance Document* for definitions of sponsor, contact for this application, representative in Canada, and senior official.

Part 2: Research Ethics Board(s)

A Research Ethics Board Attestation must be submitted to the NHPD prior to commencing the trial if approval is not obtained at the time of application. Research Ethics Boards (REBs) must include a member knowledgeable in complementary or alternative health care (CAHC). This person does not need to be a permanent member of the REB and may be brought in ad hoc.

The NHPD must be made aware of any REB which has refused the study protocol. Please provide their contact information and reasons for refusal

in Module 1 of the CTA, if applicable.

Part 3: Clinical Trial Application Information

Refer to section 3 of the *Clinical Trials for Natural Health Products Guidance Document* for additional information on submission requirements for CTAs.

Identify the type of application being submitted by checking the appropriate box(es) in section 3A. Definitions of biologic and medical device can be found in the Glossary of the *Clinical Trials for Natural Health Products Guidance Document*. Please note that if a pharmaceutical, biologic, or medical device is being used in the clinical trial, it must be used according to its approved conditions of use. Please refer to section 1 of the *Clinical Trials for Natural Health Products Guidance Document* for guidance on whether a CTA should be submitted to the NHPD.

If the CTA is an amendment, please check the CTA-Amendment box in section 3A and fill out part 4.

The forms listed in section 3C are available online under Forms.

Part 4: Clinical Trial Application - Amendment

Refer to section 4 of the *Clinical Trials for Natural Health Products Guidance Document* for additional information on submission requirements for CTA-As.

To ensure that the CTA-A is processed as quickly as possible, please provide the submission number of the approved CTA to which changes will be made.

Since amendments must also be approved by the REB, please ensure that Part 2 of the application is completed.

The forms listed in section 4B are available online under Forms.

Part 5: Clinical Trial Site Information

A completed Clinical Trial Site Information Form and a Qualified Investigator Undertaking form must be included for each proposed site known at the time of application. A qualified investigator may oversee more than one site, however, each site may have only one qualified investigator. If the information required to complete these forms is not available at the time of application, these forms must be submitted to the NHPD prior to the commencement of the trial. If additional CT sites are added after approval has been obtained from the NHPD, the information must be submitted as a notification to the NHPD.

Part 6: Study Product Information

Section 1A: Medicinal ingredient(s) of the NHP

[Product Monograph] Indicate whether a product monograph has been submitted (refer to section 3.1.1 of the *Clinical Trials for Natural Health Products Guidance Document)*. The product monograph should be submitted as part of the Investigator's Brochure.

[Common Name] If the common name and proper name are the same, it is acceptable to leave the common name blank.

[Synthetic] See Glossary of the *Clinical Trials for Natural Health Products Guidance Document.*

[Quantity per Dosage Unit] See Glossary of the *Clinical Trials for Natural Health Products Guidance Document*.

[Source] Substance from which the medicinal ingredient is derived. See

Glossary of the *Clinical Trials for Natural Health Products Guidance Document*.

Additional copies of this section may be required if there are more than 10 medicinal ingredients in the investigational product or if multiple investigational products are used, where each product has a different medicinal ingredient(s) or the same medicinal ingredient(s), but in different quantities per dosage unit.

Section 1B: Non-medicinal ingredient(s) of the NHP

[Purpose] Some examples of purposes for non-medicinal ingredients can be found in Appendix 6, "Non-medicinal Ingredient List of Purposes", of NHPD's *Product Licencing Guidance Document*.

Please note that if a non-medicinal ingredient is found on NHPD's List of Acceptable Non-medicinal Ingredients (refer to the *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document*), its proper name and source do not need to be provided in the Clinical Trial Application and Attestation Form.

Additional copies may be required if more than 10 non-medicinal ingredients are contained in the investigational product. If multiple investigational products are used, but non-medicinal ingredients are the same, only one copy of this section is needed.

Section 1C: Proposed conditions of use of the NHP according to protocol

[Amount to be taken at one time] Dosage forms of NHPs can be discrete forms, such as tablets and capsules, or non-discrete forms, such as powders and liquids.

As an example of a discrete dosage form, 3 tablets would be written as

follows:

No. of dosage units: 3
Dosage unit: tablets

Dosage units of non-discrete dosage forms may be given in grams (g), teaspoons, tablespoons, millilitres (mL), or drops among others. As an example of a non-discrete dosage form, 2 tablespoons would be written as follows:

No. of dosage units: 2
Dosage unit: Tablespoon (15 mL)

Please refer to Appendix 3 of the *Product Licencing Guidance Document* for further information on dosage forms, dosage units, and routes of administration.

[Risk Information] The risk information from the marketed label, product monograph or Investigator's Brochure is to be provided in the Clinical Trial Application and Attestation Form and the Informed Consent Form. Information from marketed label is required when the investigational product is an approved product (i.e. has an NPN, DIN, or DIN-HM) and is being used in the clinical trial outside its approved conditions of use.

Additional copies of this section may be required if multiple investigational products are used, where each product contains different medicinal ingredients or the same medicinal ingredient(s), but in different quantities per dosage unit.

Section 2: Placebo ingredients

The placebo ingredients will be identified in the same table format as required for the medicinal ingredients. Please refer to the instruction for section 1A of part 6: Medicinal ingredient(s) of the NHP.

The Designated Party Authorization Form can be found online under Forms.

Part 7: Clinical Trial Attestation

Telephone and fax numbers must include the area code and extension, where applicable.

[Senior Medical Officer or Scientific Officer in Canada] See section 12 of the *Clinical Trials for Natural Health Products Guidance Document.*

[Senior Executive Officer or Department Head] See definition of senior official in section 12 of the *Clinical Trials for Natural Health Products Guidance Document.*

Appendix 5: Protocol Synopsis and Evaluation Review Template

This form can be found online under Forms.

Protocol Synopsis & Evaluation

Date Submitted *HPB Use Only*

Submission Number *HPB Use Only*

Trial Title and Number

Background / Rationale

Trial Objectives

Study Design

Study Duration

Number of Sites (inside and outside of Canada)

List of Investigators

Sample Size

Patient Population

Inclusion Criteria

Exclusion Criteria

NHP Formulation

Dosage Regimen

Prestudy Screening and Baseline Evaluation

Treatment Visit

Premature Withdrawal/Discontinuation Criteria

Rescue Medication

Washout Period

Concomitant Medication

Variables to be Assessed

Efficacy Analysis

Safety Analysis

Statistical Analysis

Current Problems/Concerns

Patient Consent Form Evaluation

Requirement	Evaluation Status

Requirement	Evaluation Status
Full Disclosure of Risk	☐ Acceptable ☐ Requires Revision
Clarity of Language	☐ Acceptable ☐ Requires Revision
Description of Procedure	☐ Acceptable ☐ Requires Revision
Confidentiality for Patient	☐ Acceptable ☐ Requires Revision
Lack of Bias	☐ Acceptable ☐ Requires Revision
Placebo and/or Comparator Disclosure	☐ Acceptable ☐ Requires Revision

Investigatory Brochure Evaluation

Requirement / Version Dated:	Evaluation Status
Accuracy of Information	☐ Acceptable ☐ Requires Revision
Rationale for Investigation	☐ Acceptable ☐ Requires Revision
Completeness	☐ Acceptable ☐ Requires Revision

Requirement / Version Dated:	Evaluation Status
Numerical Data	☐ Acceptable ☐ Requires Revision
Tabulation of Actual Results	☐ Acceptable ☐ Requires Revision
Side Effects	☐ Acceptable ☐ Requires Revision
Summary of ADR: Deaths, Serious, Other	☐ Acceptable ☐ Requires Revision
Information on Patient Exposure, Duration of Study, Location of Study, NHP Dosage	☐ Acceptable ☐ Requires Revision
Dosage Formulation	☐ Acceptable ☐ Requires Revision

Appendix 6: Informed Consent Form Guidelines

Please include the following information (if applicable):

1. Title
2. Purpose of the clinical trial

3. Design of the clinical trial (including definitions of randomized, double blinded, and parallel or cross-over design, as well as the probability of random assignment to each treatment group)
4. Reason why the subject has been chosen to participate
5. Description of the composition and direction of use of the study product(s) (investigational product, placebo, comparator)
6. Duration of the clinical trial
7. Duration of subject's involvement
8. What will occur during the clinical trial, specifically:
    - Study procedures
    - Treatment visits
    - Subject's responsibilities (before, during and after trial)
9. Risks/disadvantages of participating in the clinical trial
10. Side effects to the investigational product, placebo and comparator
11. Contraindicated medications (prescription and non-prescription) to the investigational product, placebo and comparator
12. A statement indicating there may be unknown risks with taking the investigational product
13. Benefits/advantages of participating in the clinical trial
14. Alternative treatment options
15. Subjects will be informed should new information become available on the investigational product
16. A statement informing subjects that investigators must be informed when a new medication (including natural health products) is taken

during the clinical trial

17. Participation is voluntary and that subjects may drop out at any time without consequence
18. Subjects will not be giving up any legal rights by participating in the clinical trial
19. What the subject should do if they experience an adverse event and how the subject should report them and to whom
20. Circumstances under which the subject could be removed from the clinical trial
21. How confidential information will be treated
22. What will happen to the subject's information when the clinical trial has ended
23. Who is organizing and funding the clinical trial
24. Who has approved the clinical trial
25. Contact information
26. Please provide a place for the subject to initial on every page

Note: Subjects are to receive their own copy of the signed consent form to keep.

Appendix 7: Quality Overall Summary-NHP (CTA - Phases I/II/III) Template

This form can be found online under Forms.

Module 2.3: Quality Overall Summary -

Natural Health Products Introduction

(a) Summary of investigational finished product(s) information (copy table as needed):

Proprietary (Brand) Name of Finished

Natural Health Product

Non-proprietary or Common Name of Finished Natural Health

Product

Non-proprietary or Common Name of Medicinal Ingredient(s)

Manufacturer Name

Dosage Form

Strength(s) (Quantity per dosage unit)

Route of Administration

Proposed Indication(s)

(b) Excerpt from Protocol Synopsis:

Trial Title, Number, and Phase

Trial Objectives

Study Design

Study Duration

Number of Sites (inside and outside of Canada)

Sample Size

Patient Population

NHP Formulation

Dosage Regimen

(c) Information on the comparator product:

Proprietary (Brand) Name of Finished Natural Health Product

Non-proprietary or Common Name of Medicinal Ingredient(s)

Manufacturer Name

Dosage Form

Strength(s) (Quantity per dosage unit)

Country from which the Comparator Product Was Obtained

Registration Number

Lot Number(s)

(d) If the information in any section (or subsection) has previously been submitted (in its entirety, without changes), and approved by Health Canada, do not resubmit that section. Provide the following information on the cross- referenced submission(s):

Provide the following information on the cross- referenced submission(s):

Section (and subsections)	Cross-Referenced Submission Name	File Number and Control Number	Date Approved
Medicinal Ingredient			
Finished Natural Health Product			

Note: Based on the natural health product substances set out in *Schedule 1* of the NHP Regulations, the medicinal ingredients have been divided into three categories as indicated below. To prepare the chemistry and manufacturing information for the medicinal ingredient(s) used in your study product, please select a category (from Part A) that applies to your

product. If more than one category applies (e.g., in a combination product), please complete the necessary combination of categories. To prepare the chemistry and manufacturing information for the finished product, please complete Part B. The template in Part C for the Finished Natural Health Product Specifications is also required. If any specific section does not apply to your product, please indicate as "Not Applicable". Sections that are "Not applicable" should not be deleted and should be accompanied by an explanatory note describing the reasons for the inapplicability. For more detailed information on the category of ingredients and their requirements, please see the *Evidence for Quality of Finished Natural Health Products Guidance Document*.

Part A: Chemistry & Manufacturing Information of Medicinal Ingredient(s)

The following are the categories of substances from Schedule 1 of the NHP Regulations for which specific quality requirements are described in detail below.

Category I: Plant, Plant material, Alga, Fungus, Bacterium, Non-Human Animal Material

Category II: Isolate, Synthetic Duplicate, Non-Standardized and Standardized Extract, Amino Acid, Essential Fatty Acid, Vitamin, Minerals

Category III: Probiotics

Category I - Plant, Plant material, Alga, Bacterium, Fungi, Non-Human Animal Material

2.3.S Medicinal Ingredient(s)

2.3.S.1 General Information

2.3.S.1.1 Nomenclature

a. Latin Binomial Name (genus and, if any, its specific epithet):
b. Common name:
c. Other (e.g., strain number for microbial cultures):

2.3.S.1.2 Structure

a. Structural formula, including relative and absolute stereochemistry:
b. Molecular formula:
c. Molecular mass:

2.3.S.1.3 General Properties

a. Physical description (e.g., organoleptic, colour, shape):
b. Part of the Plant used (e.g., leaf, stem):
c. Part of the non-human animal used (e.g., cartilage):
d. Other relevant information:

2.3.S.2 Manufacturing Information

2.3.S.2.1 Manufacturer(s)

a. Name, address, and responsibility of each manufacturer, including contractors (if any) and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:

b. List of referenced NHP or Drug Master Files (NHP-MFs or DMFs) and NHP-MF or DMF Numbers (copies of NHP-MF or DMF letters of access should be located in Module 1):

2.3.S.2.2 Description of Manufacturing Process and Process Controls

a. Manufacturing information is not required for plant, algal, fungal,

bacterial and non-human animal material and their non-standardized extracts. However, for all non-standardized extracts a list of solvents used in the extraction is required:

2.3.S.3 Characterisation

2.3.S.3.1 Identification of Medicinal Ingredient

a. List of spectroscopic methods and/or chromatographic fingerprinting studies performed (e.g., UV HPLC, TLC, and GC) (for plant, plant material, alga, bacterium and fungus):

b. If applicable, DNA fingerprinting studies and summary of the interpretation (e.g. non-human animal material)

c. Summary of studies performed to identify Foreign Matter (e.g., sand, dirt, insect parts, glass and metal) and Acid-insoluble Ash, if applicable:

d. Summary of studies performed to identify water content (for plant, plant material, and their non-standardized extracts):

e. Other identification evidence such as phenotypic and genotypic identification methods (e.g. comparison of plant sample with herbarium specimen, microscopic characterization of bacterium, DNA fingerprint):

2.3.S.3.2 Impurities

a. Identification of potential and actual chemical impurities:

List of possible chemical and microbial contaminants. If more than one batch used, complete a table for each batch:

Type of Contaminant	Test	Test Method Used	Medicinal Substance Tolerance Limits	Acceptable NHPD's Tolerance Limits
Chemical Contaminants	Arsenic			< 0.14 (µg /kg b.w./day)
	Cadmium			< 0.09 (µg /kg b.w./day)
	Lead			< 0.29 (µg /kg b.w./day)
	Total mercury			< 0.29 (µg /kg b.w./day)
	PCD&PCDF			Dioxins < 2 pg/kg/b.w./day;
	PCBs			PCBs < 0.13 µg/kg/b.w./day
	Mycotoxins			Aflatoxins:< 0.02 µg/g of substance
	Loss on Drying			Pharmacopoeial Limits
	Foreign Matter			Pharmacopoeial Limits

Type of Contaminant	Test	Test Method Used	Medicinal Substance Tolerance Limits	Acceptable NHPD's Tolerance Limits
	Ash Content			Pharmacopoeial Limits
	Pesticides			Pharmacopoeial Limits
	Solvent residues			ICH or pharmacopoeial limits
Microbial Contaminants	Contaminating fungus			For acceptable NHPD microbial contaminant tolerance limits for each category of products, refer to Appendix 2, Table 1 in the *Evidence for Quality of Finished Natural Health Products* guidance document
	Total Aerobic Count			
	Escherichia coli			
	Salmonella spp.			
	Staphylococcus aureus			
	Enterobacter spp.			
	Pseudomonas aeruginosa (if product is in <50% aqueous ethanol)			

Note: Please duplicate this table for each medicinal ingredient used in your study product

2.3.S.4 Control of the Medicinal Ingredient

2.3.S.4.1 *Quantity*

a. Quantity requirements for plant, plant material, alga, fungus, bacterium, non-human animal material:

Medicinal Ingredient	Name of Medicinal Ingredient (s)	Test Method Used	Medicinal Ingredient Tolerance Limits	Acceptable NHPD's Tolerance Limits
Plant or Plant Material				80-120%
Alga				80-120%
Fungus				80-120%
Bacterium				80-120%
Non-Human Animal Material				80-120%

2.3.S.4.4 Batch Analyses

a. Description of the batches to be used in this clinical trial:

Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical)

Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical)

2.3.S.6 Container Closure System

a. Description of the container closure system(s) for the storage and shipment of the medicinal substance:

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

a. Summary of stability studies to support this clinical trial (e.g., studies conducted, protocols used, duration of test, results obtained):

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment

a. If full long-term stability data are not available at the time of submission, provide the stability protocol, accelerated stability data and a commitment for the continued monitoring of the medicinal substance stability according to the protocol for the duration of the clinical trial (i.e., so that if the product degrades below the tolerance limit during the trial, more product can be taken out of cold storage. If a new batch needs to be used, sponsor should notify NHPD as a notification in order to maintain the same quality and specifications):

2.3.S.7.3 Stability Data

a. The actual stability results (i.e., raw data) used to support the clinical trial:

Category II: Isolate, Synthetic Duplicate, Non-Standardized and Standardized Extract, Amino Acid, Essential Fatty Acid, Vitamin, Minerals

2.3.S. MEDICINAL INGREDIENT(S)

2.3.S.1 General Information

2.3.S.1.1 *Nomenclature*

a. Proper Name:
b. Common Name:
c. If an isolate or a standardized extract, proper name of source organism:
d. If an isolate or a standardized extract, common name of source organism:
e. Company or laboratory code:
f. Other non-proprietary name(s) (e.g., national name, USAN, BAN
g. Chemical Abstracts Service (CAS) registry number, if available:

2.3.S.1.2 Structure

a. Structural formula, including relative and absolute stereochemistry:
b. Molecular formula and/or molecular mass:

2.3.S.1.3 General Properties

a. Physical description (e.g., appearance, colour, taste, smell, physical state):
b. pH and pKa values:
c. Other relevant information:

2.3.S.2 Manufacturing Information

2.3.S.2.1 *Manufacturer(s)*

a. Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:
b. List of referenced NHP or Drug Master Files (NHP-MFs or DMFs) and NHP-MF or DMF Numbers (copies of NHP-MF or DMF letters of access should be located in Module 1):

2.3.S.2.2 Description of Manufacturing Process and Process Controls

a. Flow diagram of the extraction, isolation and/or synthetic process(es):
b. Brief narrative description of the manufacturing process(es), e.g. temperature, solvents used, and reagents:

2.3.S.2.3 Control of Materials

a. For medicinal ingredient(s) either obtained from non-human animal sources or processed using materials that present a risk of transmitting BSE/ TSE agents (e.g., ruminant origin), a completed Animal Tissue Form (ATF) must be submitted ; see Appendix 3 of the Clinical Trials for Natural Health Products Guidance Document.

2.3.S.3 Characterization

2.3.S.3.1 Characterization of Chemical Identity

a. List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis or HPLC, GC, with MS or UV-diode array detector) and summary of the interpretation of evidence of structure:
b. Discussion on the potential for isomerism and identification of stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations):
c. Other characteristics (product specific):

2.3.S.3.2 Impurities

Identification of potential and actual impurities arising from the extraction, isolation, synthesis, manufacture, fermentation and/or degradation. If more than one batch used, complete a table for each batch :

Process Related Impurities	Chemical Name or Structure	Test Method (e.g. HPLC)	Limit of Detection (e.g. %)
Starting material impurities			
By-products			
Intermediates			
Chiral Impurities			
Residual Solvents			
Residual Reagents			

Process Related Impurities	Chemical Name or Structure	Test Method (e.g. HPLC)	Limit of Detection (e.g. %)
Other			

Note: Please add to the above table other types of impurities if applicable.

2.3.S.4 Control of the Medicinal Ingredient

2.3.S.4.1 Specification

Specification for the medicinal substance:

Assessment Criteria	Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
Identity	Physical Description (Organoleptic)			
	Chemical Identity (HPLC)			
	Assay (Purity/impurity profile)			
	Loss on Drying			

Assessment Criteria		Test		Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
Purity	**Chemical Contaminants**	Arsenic				< 0. b.w
		Cadmium				< 0. b.w
		Lead				< 0. b.w
		Total Mercury				< 0. b.w
		Specific Toxins (when applicable)	PCD, PCDD, PCDF			Dio pg/
			PCBs			PCE µg/
		Pesticides (when applicable)				Pha limi
		Solvent Residues (when applicable)				ICH pha limi
		Mycotoxins				Afla 0.02 sub

Assessment Criteria	Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
Microbial Contaminants	Contaminating fungus			**For NH mic con tole lim cat pro to A Tab Evi Qua Fini Nat Pro gui doc**
	Total Aerobic Count			
	Escherichia coli			
	Salmonella spp			
	Staphylococcus aureus			
	Enterobacter spp.			
	Pseudomonas aeruginosa (if product is in < 50% aqueous ethanol)			

Assessment Criteria	Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
Quantity/Potency	Quantity of the Medicinal Ingredient per dosage unit			For NHI tole for cate pro to s in t for Fini Nat Pro gui doc

2.3.S.4.4 Batch Analyses

a. Description of the batches to be used in this clinical trial:

Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical)

Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical)

2.3.S.6 Container Closure System

a. Description of the container closure system(s) for the storage and shipment of the medicinal substance:

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

a. Summary of stability studies to support this clinical trial (e.g., studies conducted, protocols used, duration of test, results obtained). If not available at time of submission, provide accelerated stability data:

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment

a. If full long-term stability data are not available at the time of submission, provide the stability protocol, accelerated stability data and a commitment for the continued monitoring of the medicinal substance stability according to the protocol for the duration of the clinical trial (i.e., so that if the product degrades below the tolerance limit during the trial, more product can be taken out of cold storage. If a new batch needs to be used, sponsor should notify NHPD as a notification in order to maintain the same quality and specifications):

2.3.S.7.3 Stability Data

a. The actual stability results (i.e., raw data) used to support the clinical trial:

Category III - Probiotics

2.3.S Medicinal Ingredient(s)

2.3.S.1 General Information

2.3.S.1.1 Nomenclature

a. Genus, specific epithet, strain:
b. Common name(s):

2.3.S.1.3 General Properties

a. Physical description (e.g., appearance, pellet, powder, colour):
b. Other relevant information:

2.3.S.2 Manufacturing Information

2.3.S.2.1 Manufacturer(s)

a. Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:
b. List of referenced NHP or Drug Master Files (NHP-MFs or DMFs) and NHP-MF or DMF Numbers (copies of NHP-MF or DMF letters of access should be located in Module 1):

2.3.S.2.2 Description of Manufacturing Process and Process Controls

a. Flow diagram of the mother culture preparation and fermentation conditions used:
b. Brief narrative description of the manufacturing process(es). In addition to this information, data provided for a medicinal ingredient produced by fermentation should include source and type of micro-organism used, composition of media, precursors, reaction

conditions (e.g., time, temperature, rate of aeration etc.), name and composition of preservatives, if any:

2.3.S.2.3 Control of Materials

a. For medicinal ingredient(s) processed using materials that present a risk of transmitting BSE/ TSE agents (e.g., ruminant origin), a completed Animal Tissue Form (ATF) must be submitted see Appendix 3 of the Clinical Trials Guidance Document.

2.3.S.3 Characterization

2.3.S.3.1 Characteristics of the culture

a. Phenotypic and/or genotypic identification:
b. Other characteristics:

2.3.S.3.2 Impurities

a. Identification of microbial impurities:

i. List of related microbial impurities, if applicable. If more than one batch used, complete a table for each batch:

List of related microbial impurities

Microbial Contaminant(s)	Test Method Used	Medicinal Ingredient Tolerance Limits	NHPD's Acceptable Tolerance Limits

Microbial Contaminant(s)	Test Method Used	Medicinal Ingredient Tolerance Limits	NHPD's Acceptable Tolerance Limits

2.3.S.4 Control of the Medicinal Ingredient

2.3.S.4.1 Total Viable Count

a. Total viable count requirements for the probiotic culture(s):

Probiotic Culture(s)	Test Method Used	Test Limits (CFU/g or CFU/ml)	NHPD's Acceptable Tolerance Limits
			80-300%

2.3.S.4.4 Batch Analyses (name, manufacturer, if applicable):

a. Description of each batch to be used in this clinical trial:

Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical)

Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical)

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

a. Summary of stability studies to support this clinical trial (e.g., studies conducted, protocols used, duration of test, results obtained). If not available at time of submission, provide accelerated stability data:

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment

a. If full long-term stability data are not available at the time of submission, provide the stability protocol, accelerated stability data and a commitment for the continued monitoring of the medicinal substance stability according to the protocol for the duration of the clinical trial (i.e., so that if the product degrades below the tolerance limit during the trial, more product can be taken out of cold storage. If a new batch needs to be used, sponsor should notify NHPD as a notification in order to maintain the same quality and specifications):

2.3.S.7.3 Stability Data

a. The actual stability results (i.e., raw data) used to support the clinical trial:

Part B: Chemistry & Manufacturing Information of the Finished Natural Health Product

2.3.P Finished Natural Health Product

2.3.P.1 Description and Composition of the Finished Product

a. Description of the dosage form:

b. Composition of the dosage form:

i. Composition - list of all medicinal and non-medicinal ingredients of the dosage form, and their amounts on a per unit basis (including overages, if any):

Medicinal and non-medicinal ingredients of the dosage form

Medicinal and Non-Medicinal Ingredients and Quality Standard (and grade, if applicable)	**Intended Functions For NMIs**	**Quantity/Dosage Unit**	
Quantity per Unit	**%**		
Medicinal Ingredients:			
Non-Medicinal Ingredients:			
Total			

c. Description of accompanying reconstitution diluent(s), if applicable:

d. Quantitative list of the components of the placebo samples to be used in this clinical trial:

Name of Each Component of the Placebo	Quantity of Each Component in the Placebo
Total Amount	

2.3.P.2 Formulation Development

a. or a new formulation (new combination, standardized extract, or new dosage form such as transdermal patch) provide a rationale on the development:

b. For sterile, reconstituted products, provide a summary of compatibility studies with diluents/containers:

2.3.P.3 Manufacturing Information

2.3.P.3.1 Manufacturer(s)

a. Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:
b. List of referenced NHP or Drug Master Files (NHP-MFs or DMFs) and NHP-MF or DMF Numbers (copies of NHP-MF or DMF letters of access should be located in Module 1:

2.3.P.3.2 Batch Formula

a. List of all components of the dosage form to be used in the manufacturing process, and their amounts on a per batch basis (including overages, if any):

Quantity per Dosage Unit (strength)	
Batch Size(s) (number of dosage units)	
Date of Manufacture	
Component and Quality Standard (and grade, if applicable)	**Quantity Per Batch**
Medicinal Ingredient:	
Non-Medicinal Ingredient:	
Total	

Note: If more than one batch produced (e.g., additional lots of finished product or different strengths), duplicate table as needed.

2.3.P.3.3 Description of Manufacturing Process and Process Controls

a. Flow diagram of the manufacturing process:
b. Narrative description of the manufacturing process and process parameters:
c. For sterile/pasteurized products, details and conditions of sterilization and/or lyophilization :

2.3.P.4 Control of Non-medicinal Ingredients

a. Confirmation if the non-medicinal ingredients (NMI) used are included in the List of Acceptable Non-medicinal Ingredients:

   If not, please provide the following information:

b. List and summary of the information of NMIs that are of non-human animal origin (including country of origin):

c. For NMIs obtained from sources that are at risk of transmitting BSE/TSE agents, a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area.

d. Confirmation that none of the non-medicinal ingredients which appear in the finished product are prohibited for use in drugs by the Canadian Food and Drug Regulations:

2.3.P.4.1 Novel Non-medicinal Ingredients

a. Summary of the details on the manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) on novel NMIs (e.g., those used for the first time in the finished product or by a new route of administration):

2.3.P.5 Control of Finished Natural Health Product

2.3.P.5.1 Specification(s)

Specification(s) for the finished product:

Assessment Criteria		Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
Identity		Physical Description (Organoleptic)			
		Chemical Identity (HPLC)			
		Assay (Purity/impurity profile)			
		Disintergration and/or Dissolution			45 r (un 60 r coa
		Particle Size Distribution, (if applicable, e.g. for tea)			
Purity	**Chemical Contaminants**	Arsenic			< 0. b.w
		Cadmium			< 0. b.w

Assessment Criteria	Test		Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
	Lead				< 0. b.w
	Total Mercury				< 0. b.w
	Specific Toxins (when applicable)	PCD, PCDD, PCDF			Dio pg/
		PCBs			PCE µg/
	Pesticides (when applicable)				Pha limi
	Solvent Residues (when applicable)				ICH pha limi
	Mycotoxins				Afla 0.02 sub
Microbial Contaminants	Contaminating fungus				For NHI con tole for cate
	Total Aerobic Count				
	Escherichia coli				

Assessment Criteria	Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
	Salmonella spp			pro to A
	Staphylococcus aureus			Tab *Evic* *Quc* *Fini* *Hea* gui doc
	Enterobacter spp.			
	Pseudomonas aeruginosa (if product is in < 50% aqueous ethanol)			
Quantity/Potency	Quantity of the Medicinal Ingredient per dosage unit			For NHI tole for cate pro to s in t *for* *Fini* *Hea* gui doc

Note: In this table all information that is required to support finished product specifications should be included.

2.3.P.5.4 Batch Analyses

a. Description of the batches to be used in this clinical trial:

Strength (Quantity / Dosage Unit)	Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical)

2.3.P.5.5 Characterisation of Impurities

Information on the characterization of impurities derived from the processing of the finished product, interaction between medicinal and non-medicinal ingredients, and/or other medicinal ingredient related impurities.

2.3.P.7 Container Closure System

a. Description of the container closure systems, container size or volume:
b. Materials of construction of each primary packaging component:
c. For sterile products, details of washing, sterilization, pasteurization, depyrogenation procedures or other process for container closures, e.g. for ophthalmic use.

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

a. Summary of stability studies to support this clinical trial (e.g., studies conducted, protocols used, duration of test, results obtained):

i. Description of stability study:

Stability Summary and Conclusions

Batch Number	Time Interval	Storage Conditions (°C, % RH, light)	Description of Product	Strength (Quantity per Dosage Unit)/Potency of Product

ii. Summary and discussion of stability study results:

b. Proposed storage conditions and shelf life:

2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment

a. If full long-term stability data are not available at the time of submission, provide the stability protocol, accelerated stability data and a commitment for the continued monitoring of the medicinal substance stability according to the protocol for the duration of the clinical trial (i.e., so that if the product degrades below the tolerance limit during the trial, more product can be taken out of cold storage. If a new batch needs to be used, sponsor should notify NHPD as a notification in order to maintain the same quality and specifications):

2.3.P.8.3 Stability Data

a. The actual stability results (i.e., raw data) used in support of this clinical trial:

Part C: Finished Natural Health Product Specification Template

Name of the Finished Product:

Name of Manufacturer of Finished Product:

Batch Number:

Specification(s) for the finished product:

Assessment Criteria	Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
Identity	Physical Description (Organoleptic)			
	Chemical Identity (HPLC)			
	Assay (Purity/impurity profile)			

Assessment Criteria		Test		Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
		Disintergration and/or Dissolution				45 r (un 60 r coa
		Particle Size Distribution, (if applicable, e.g. for tea)				
Purity	**Chemical Contaminants**	Arsenic				< 0. b.w
		Cadmium				< 0. b.w
		Lead				< 0. b.w
		Total Mercury				< 0. b.w
		Specific Toxins (when applicable)	PCD, PCDD, PCDF			Dio pg/
			PCBs			PCE µg/

Assessment Criteria	Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
	Pesticides (when applicable)			Pha limi
	Solvent Residues (when applicable)			ICH pha limi
	Mycotoxins			Afla 0.02 sub
Microbial Contaminants	Contaminating fungus			For NHI con tole for cate pro to A Tab *Evic* *Quc* *Fini* *Hea* gui doc
	Total Aerobic Count			
	Escherichia coli			
	Salmonella spp			
	Staphylococcus aureus			
	Enterobacter spp.			
	Pseudomonas aeruginosa (if product is in < 50% aqueous ethanol)			

Assessment Criteria	Test	Test Method	Medicinal Ingredient Results / Tolerance Limits	NH Acc Tol Lim
Quantity/Potency	Quantity of the Medicinal Ingredient per dosage unit			For NHI tole for cate pro to s in t *for Fini Hea* gui doc

Signature:

Date:

Note: For any revisions in the product specifications, resubmit a revised copy of this template.

Appendix 8: Adverse Reaction Report Form for Clinical Trials

This form can be found online under Forms.

Adverse Reaction Report Form For Clinical Trials

Date modified:

2016-06-27