**Natural Health Products Management of Applications Policy**
**Table of Contents**

# Natural Health Products Management of Applications Policy

XXXX, 2019

### Executive Summary

The Natural and Non-prescription Health Products Directorate (NNHPD) has updated the Management of Licence Application for Natural Health Products now referred to as the Natural Health Products Management of Applications Policy (NHP MAP).

NNHPD last updated the NHP MAP in 2014. The revisions to this document include changes to how applications for natural health products (NHPs) (new, or amendments and notifications for existing products) are processed, assessed and issued a decision.

The updates to this document are intended to provide predictability in the processing and timelines for the review of applications and issuance of a decision, to align with current practices as well as changes in the electronic product licence application (ePLA) system, and to achieve better outcomes for the health and safety of Canadians by ensuring that authorized NHPs meet regulatory requirements.

This document serves as a final consultation with industry prior to implementing the changes to the ePLA application system. Stakeholders have 60 days, ending on November 5, 2018 to provide comments on the document. NNHPD will take these comments into consideration prior to publishing the final NHP MAP.

## 1. Purpose

The NHP MAP outlines the process applied by NNHPD to manage product licence applications (PLAs) for natural health products (NHPs) submitted in accordance with the *Natural Health Products Regulations* (NHPR). The policy also outlines the responsibilities and expectations of NHP applicants throughout the application process.

## 2. Scope

This policy applies to all classes of NHP applications (Class I, II and III), including changes made following the licensing of a product (amendments and notifications) and all applications types (general - formally categorized as non-traditional applications, traditional and homeopathic). It is intended to aid the applicant in navigating the application process and should be used in conjunction with associated guidance documents linked throughout the document.

This policy does not apply to site licence or clinical trial applications for NHPs. It also does not apply to applications for non-prescription drugs.

# 3. Classes of Applications

An NNHPD monograph is a written description of particular elements on an identified ingredient or product. NNHPD has developed and published a Compendium of Monographs that allows applicants to support the safety and efficacy of an NHP as part of their PLA.

## 3.1 Class I

Class I applications are those that must comply with all of the parameters of an individual NNHPD monograph. Applicants can only reference one NNHPD monograph per application in Class I. Modifications to any of the parameters of a monograph are not permitted.

## 3.2 Class II

Class II applications are general and traditional applications supported entirely by a combination of NNHPD monographs as well as the following two scenarios:

- The use of a “statement to the effect of” will not be accepted in Class I. Applications supported by an individual NNHPD monograph with a “statement to the effect of” not specified on the monograph will be accepted in Class II.
- Products supported entirely by a combination of NNHPD monographs with the addition of common fruits or vegetables listed in the Canadian Nutrient File, excluding source materials listed as "refuse", with up a daily dose of up to 10 g (of crude material or quantity crude equivalent for non-standardized extracts).

Applicants are required to identify their application as Class II in the cover letter. If a Class II application is not identified as such, it will be processed as a Class III application by default. NNHPD may shift products to Class III for ingredient combination issues that may require a safety assessment (e.g. lower certainty combinations).

## 3.3 Class III

Class III applications are comprised of general, traditional and homeopathic applications requiring full assessment and include, but are not limited to, the following scenarios:

- Products with a novel preparation and/or dosage delivery system presenting unique safety and/or efficacy profiles;

Applications referencing a Master File (an NHP Master File may be submitted, when a company would like to submit confidential information on behalf of another company

(e.g. supplier submitting confidential manufacturing information on behalf of a manufacturer)) to support safety, efficacy and/or quality (see section 4.5 for information on Master Files, including a definition);

- Products with ingredient combination issues that may require a safety assessment (e.g. lower certainty combinations).
- Applications partially referencing monograph information and going beyond the parameters established in the relevant monograph(s), for example, a dosage form or route of administration not indicated on the monograph(s) that requires further assessment.

Please refer to section 4.1 for guidance documents regarding the safety, efficacy and quality requirements for Class III applications.

# 4. Pre-submission Information (before submitting an application)

NNHPD has developed a number of tools to assist industry in preparing their NHP applications, to facilitate more efficient assessment, and to reduce the number of information requests.

## 4.1 Guidance Documents

Safety and efficacy:

These documents outline the approach to assessing safety and efficacy evidence for NHPs in Canada, including standards for health claims, the use of risk information and considerations for combinations of NHPs.

- Pathway for Licencing NHPs Making Modern Health Claims (e.g. general application types),
- Pathway for Licencing NHPs Making Traditional Health Claims,
- Evidence for Homeopathic Medicines guidance documents.

The Compendium is a compilation of single ingredient and product monographs while the corresponding guidance document describes how to use a monograph to support an application.

- Compendium of Monographs
- Compendium of Monographs guidance document

Quality:

This document provides details on the requirements for ensuring high quality NHPs.

- Quality of Natural Health Products Guide

General:

This document provides details on general application requirements.

- Product Licensing Guidance Document

For a full list of NNHPD's available policies and guidance documents, consult the Guidance Documents website.

## 4.2 Submitting Large Volumes of Applications

Applicants are requested to notify NNHPD prior to submitting a large volume of applications in a short period of time (e.g., more than 20), in order to develop a submission plan with NNHPD for processing and assessing applications within service standards. If the applicant does not advise NNHPD of a large incoming volume of applications, these applications will not be held to the service standards outlined in this document.

## 4.3 Requesting a Pre-submission Meeting

The purpose of a pre-submission meeting is to discuss the evidence to be provided or required in support of a Class III PLA. Such meetings will:

- familiarize assessment staff with the proposed application prior to its arrival and provide a forum to discuss the evidence in order to facilitate its assessment;
- establish which studies the applicant is relying on to support the safety and efficacy of the NHP and discuss the adequacy and appropriateness of controls;
- provide an opportunity for the applicant to discuss details of the application with the NNHPD and obtain feedback regarding any areas of concern based on current experience and regulatory requirements; and
- provide the NNHPD an opportunity to re-align resources, if necessary, to accommodate the arrival of the application.

Pre-submission meetings do not include an assessment of the evidence by NNHPD, nor will a regulatory decision be issued.

### 4.3.1 Meeting request

A pre-submission meeting request must be submitted to NNHPD's general email address no less than one month prior to the proposed meeting date and should include the following information:

- the purpose of the meeting;
- a brief description of the product to be discussed at the meeting;
- three proposed dates for the meeting; and
- preference for a meeting by teleconference or at NNHPD's offices.

### 4.3.2 Pre-submission package

Applicants will be requested to submit a pre-submission meeting information package at least two weeks in advance of the meeting. The package should contain the following information:

- a cover letter;
- an agenda for the meeting;
- a list of participants and their titles/roles;
- a list of specific issues the applicant would like to discuss or have addressed;
- a brief summary of the NHP for which the meeting is being requested;
- proposed ingredient quantities and recommended conditions of use for the NHP;
- an overview of the market history of the product, including the foreign regulatory status of the product, if available;
- identification of the indication(s) for which authorization is sought; and
- brief summaries of the safety and efficacy data relating to the product.

### 4.3.3 Pre-submission meeting

It is the responsibility of the applicant to take minutes at a pre-submission meeting. These minutes are to be provided to the NNHPD within two weeks of the meeting for review and concurrence.

## 4.4 Product Classification Request

If you are unsure if your product is an NHP (e.g. novel ingredient or dosage form), you are encouraged to submit a product classification request to hc.ingredient_support.sc@canada.ca prior to submitting a PLA. A product classification request should include the following information for each product:

- Complete list of ingredients: medicinal (including quantity) and non-medicinal;
- Recommended use(s) or purpose(s);
- Directions for use (if applicable);
- Intended sub-population;
- Dosage form or product format (e.g. beverage, powder, bar, cream, capsule, etc.);
- The product label (if available) or proposed label text;
- Information on the product placement of sale (if available);
- Product website (if available)

NNHPD will respond to product classification requests that contain the information outlined above within 20 calendar days with a recommendation. When it is necessary to consult with other directorates or branches in Health Canada, additional time may be required.

## 4.5 Master File

A Natural Health Product Master File (MF) enables the manufacturer of a medicinal ingredient or raw material (the MF holder) to provide proprietary information directly to NNHPD without disclosing the information to the product licence applicant. The MF can be cross-referenced by one or more applicants by providing a Master File Letter of Access from the Master File holder (senior official) as described below. A MF is a confidential document; only authorized officials of Health Canada may access the file. Refer to the Master File Procedures guidance document for more information.

### 4.5.1 Submitting a Master File

The MF holder may submit any evidence required for product assessment to the NNHPD that is not published, (e.g., proprietary information not available to the public).

Due to the proprietary nature of MFs, and to ensure that information is not disclosed to unauthorised parties, the following information is required when submitting a MF:

- Ingredient/product name;
- Company name and address;
- Senior official information; and
- Contact person contact information;
- Designated Party Authorization (DPA) form for any contact person(s) submitting/signing/receiving correspondence on behalf of the MF holder, as described in section 5.1.3.

MFs do not have specific form requirements; however an ePLA form should not be submitted with a MF application. A single copy of the MF should be submitted as outlined in Section 5.2 of this document. NNHPD will not accept MFs via email or in paper form.

### 4.5.2 Processing a Master File

When a MF is received, it will be assigned a MF number and an acknowledgment letter will be sent to the MF holder. The NNHPD aims to assign a MF number within 20 calendar days from the date of receipt. A MF is not independently assessed or approved; rather assessment of the MF is triggered by the assessment of a PLA referencing the MF. Only information relevant to the PLA is assessed.

### 4.5.3 Referencing a Master File

To reference information in a MF, a Master File Letter of Access from the MF holder is required to be submitted in a PLA and must meet the following parameters:

- Be on official company letterhead of the company holding the MF, dated and signed by the MF holder company's senior official;

- Provide access directly to the applicant company (e.g., the letter cannot be addressed to the manufacturer or consulting company);
- Include the name and address of the company the MF holder is granting access to, the name of the product referencing the MF, and the assigned Health Canada MF number (e.g., MF holder Company A authorizes Company B to access and make reference to MF number: XXXXX MFXXX (MF Name)).

The MF holder can also provide authorization to a company for some or all their MFs. In this case, an individual Master File Letter of Access would not be needed for each application making reference to a MF.

In the absence of a valid Master File Letter of Access, the MF cannot be assessed in conjunction with the application referencing it. This could result in the refusal of the submission referencing the MF as there may be insufficient information to support the safety, efficacy and/or quality of the product.

## 4.6 The Natural Health Products Ingredients Database (NHPID)

The Natural Health Products Ingredients Database (NHPID) is a repository of ingredients present in Health Canada approved natural health products (NHPs), and is a key component of the Natural Health Products Online Solution. The Compendium of Monographs is also made available through the NHPID and each ingredient entry listed in the database refers to all associated monographs. The NHPID includes medicinal ingredients (MIs) and non-medicinal ingredients (NMIs) for use in NHPs as well as information related to ingredients that are not allowed or are restricted for use in NHPs. The database uses standard terminology as described in the Natural Health Products Online System Standard Terminology Guide.

### 4.6.1 NHPID modification process

The NNHPD updates the NHPID on a bi-weekly basis. If applicants wish to include ingredients in their product formulation that are not listed in the NHPID, they must submit a request to add the ingredients to the NHPID. Ingredients must be present in the NHPID to be selected on the ePLA form prior to submitting an application.

To request NHPID modifications, applicants must complete an NHPID Issue Form and send it to hc.ingredient_support.sc@canada.ca. Requests must be accompanied by at least one piece of supporting evidence (unless a typographic correction). The NHPID Issue Form includes a non-exhaustive list of references that may be considered as a helpful starting point.

Requests for NHPID modifications are processed within 4 weeks from the receipt of the request. The time required for reviewing a request may however vary depending on the quality and/or the complexity of the request, as well as on the volume of requests.

For more information and instruction on the NHPID and how to request NHPID modifications, please consult Appendix I.

# 5. Submitting an Application

## 5.1 Application Requirements

To facilitate the assessment of the product and to appropriately assign resources, NNHPD requests applicants to identify the class under which they are applying for a product licence according to the definitions of Class I, II and III applications in section 3 of this document.

The table outlines the various application requirements by class and application type.

| | Application type | | | | | |
|---|---|---|---|---|---|---|
| | Class I | | Class II or III | | | Class III |
| Requirements | Compendial | Amendment | General | Traditional | Amendment | Homeopathic |
| ePLA form | ✓ | Not applicable | ✓ | ✓ | Not applicable | ✓ |
| Amendment and Notification Form | Not applicable | ✓ | Not applicable | Not applicable | ✓ | Not applicable |
| Label text | ✓ | If applicable to the proposed changes | ✓ | ✓ | If applicable to the proposed changes | ✓ |
| Summary Report (Evidence, Safety and/or Quality)* | Not applicable | Not applicable | Recommended | Recommended | Recommended | Recommended |
| References | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Animal Tissue Form (if applicable) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Finished Product Specifications | ✓ | If applicable to the proposed changes | ✓ | ✓ | If applicable to the proposed changes | ✓ |

All information and data submitted in support of a PLA will be retained by Health Canada, in accordance with the retention requirements (keeping records on file) of the Library and Archives of Canada Act.

### 5.1.1 Application forms

There are two application forms that may be submitted depending on the type of application. Applications for new products must be provided using an ePLA form while amendments to existing products must be submitted using an Amendment and Notification Form (ANF).

The most recent version of the ePLA and ANF must always be used. Applications completed using an older version of a form will not be accepted and will result in an automatic refusal of the application. For kit applications (kit is defined as a package containing more than one NHPs OR a combination of one or more NHPs and one or more foods, cosmetics or medical devices that is intended to have a combined benefit, e.g. overarching claims or brand name.) , we encourage applicants to contact the NNHPD general email address for additional guidance.

NNHPD requests that applicants use the following format when naming their ePLA file: "Class X ePLA - brand name", where X is I, II or III.

#### 5.1.1.1 Label text

Applicants must provide, at the time of the submission of their ePLA, a generated label text or mock up that meets the requirements outlined in section 93-94 of the NHPR.

#### 5.1.1.2 Summary report

Summary Reports are recommended to assist in the assessment process and reduce the time for completion. In the event that a rationale is needed to support the safety, efficacy, or quality of the product, the rationale should be submitted in a summary report.

#### 5.1.1.3 References

Applicants must attest to NNHPD Monograph(s) from the Compendium of Monographs and/or provide evidence as stated in the Pathway for Licensing Natural Health Products Used as Traditional Medicines guidance document, the Pathway for Licensing Natural Health Products Making Modern Health Claims guidance document, the Evidence for Homeopathic Medicines guidance document, or the Quality of Natural Health Products Guide as applicable to the product.

##### 5.1.1.3.1 Attesting to NNHPD monographs

By attesting to a monograph, the applicant is confirming that the application meets all of the monograph parameters to which the applicant has attested. Applications will be verified against the monograph and deviations from monograph parameters for a Class I application will result in the automatic refusal of the application. Applicants must also identify which monograph(s) they are attesting to in their application. For more information on how to attest to a monograph or combination of monographs, consult Appendix II.

Applications attesting to meeting quality requirements must attest for the finished product, in its entirety, and must meet the quality specifications outlined in NNHPD monograph(s) and/or in the Quality of Natural Health Products Guide.

Additional safety, efficacy or quality information may be requested during screening or assessment as per section 15 of the NHPR.

The following table demonstrates the applicable attestation (safety, efficacy and/or quality) for different scenarios:

| Scenario | Applicable Attestation | | |
|---|---|---|---|
| | Safety | Efficacy | Quality |
| All monograph parameters are met | ✓ | ✓ | ✓ |
| All monograph parameters are met, with the exception of minimum daily dose and recommended use/purpose (claim) | ✓ | | ✓ |
| All monograph parameters are met, with the exception of minimum daily dose, claim and specifications | ✓ | | |
| All monograph parameters are met, with the exception of specifications | ✓ | ✓ | |
| All monograph parameters are met, with the exception of maximum daily dose and/or risk information | | ✓ | ✓ |
| Parameters of the Quality for Natural Health Products Guide are met | | | ✓ |

If applicants are not attesting to full monograph parameters in Class II or III applications, they must ensure that evidence or a rationale for not attesting to the monograph has been provided (refer to section 4.1 for a list of guidance documents on evidence and rationale requirements).

Examples include (but are not limited to):

- The required conditions of use are omitted for a product. Applicants cannot attest to safety; instead they must indicate the reason for not attesting and provide evidence or a rationale to support the omission as part of the application package.
- The claim is not supported by a monograph, but the ingredient dose is supported. Applicants can attest to safety but not efficacy and they must ensure evidence is provided to support the efficacy of the non-monographed claim.
- A statement to the effect of a monograph statement is used for the product.

For more information on attestation to NNHPD monographs please refer to Appendix II.

#### 5.1.1.4 Animal tissue form

If applicable, an Animal Tissue Form must be completed.

An animal tissue form may be required for the following types of ingredients:

1. medicinal ingredient;
2. non-medicinal ingredient; or

3. an ingredient used in processing (i.e. not present in the final product).

A separate animal tissue form should be provided for:

1. each ingredient (i.e. medicinal, non-medicinal, or an ingredient used in processing);
2. each type of process; and
3. each type of animal (i.e. mammal, bird or crustacean).

#### 5.1.1.5 Finished product specifications

By submitting a compendial (Class I) application, applicants attest to the specifications in the Quality of Natural Health Products Guide and may submit product specifications in their application package. The finished product specifications must be provided upon request by the NNHPD.

### 5.1.2 Letter of access

Applicants may reference supporting information in another company's application(s) with a Letter of Access. The Letter of Access authorizes the NNHPD to access the indicated information in the application. The Letter of Access must meet the following parameters:

- Be on official company letterhead, of the company being referenced, dated and signed by the senior official of the referenced application;
- Provide access directly to the applicant or licensee (e.g., the letter cannot be addressed to the manufacturer or consulting company); and
- Include the name of the company that is being granted access to use the referenced application, the name of the product and the submission number of the application being referenced (e.g., Company A authorizes Company B to access and make reference to Submission No. XXXXX and/or Natural Product Number (NPN)/Drug Identification Number-Homeopathic (DIN-HM) XXXXX (Product Name).

In the absence of a valid Letter of Access, the referencing application may be incomplete resulting in a request for more information/evidence or a refusal of the application.

### 5.1.3 Designated party authorization (DPA) forms

A DPA form is required when the party signing the application is a designated party acting on behalf of the senior official of the applicant or licensee according to paragraph 5(b) of the NHPR. This authorization allows the contact person(s) to act on behalf of the applicant or licensee for functions such as:

- submitting applications, signing for applications;
- receiving/responding to Information Request Notices (IRNs);

- receiving/responding to regulatory notices(e.g. safety concerns) ; or
- submitting withdrawal or discontinuation requests for a product on behalf of the applicant or licensee.

The DPA form is located on the Product Licensing Forms and Templates website.

### 5.1.4 Site information

Applicants must provide the site information for each manufacturer, packager, labeller and importer prior to the sale of the NHP according to section 22 of the NHPR. Where available, the applicant must list the company name and address, and site licence number for Canadian sites, under Part 3 – Site Information of the ePLA form for each manufacturer, packager, labeller, importer, distributor and/or storage facility for the NHP.

The NHP cannot be made available for sale in Canada until a licence is issued and the above information has been provided in full to NNHPD. If this information is not provided on the ePLA, the applicant must provide the information using the ANF.

## 5.2 Methods of Submitting an Application

Applicants must use only **one** method to submit an application and should submit only once. Duplicate applications will be refused. Please refer to section 6.2.1 for information on how to follow-up on the status of your application. Forms of electronic submission other than those listed below will not be accepted and will result an automatic refusal.

Paper applications will not be accepted, with the exception of kit applications which are not currently supported by the ePLA. We encourage applicants to contact the NNHPD general email address for additional guidance on kit applications.

### 5.2.1 Submitting applications by secure email

Applicants are requested to submit ePLAs and ANFs electronically via Canada Post's secure email service, epost Connect™. In order to use epost Connect™, applicants must be enrolled as a Trading Partner. Please refer to the Guidance document on how to interact with NNHPD electronically.

NNHPD has two separate product application-based epost Connect™ accounts:

- **nhpsn.epostel.applications**
  NNHPD uses this account to start company-specific conversation threads. New applications or amendments and notifications are to be submitted under this account.

- **nhpsn.epostel.correspond**
  NNHPD uses this account to initiate submission-specific conversation threads to

issue notices specific to a product licence application. Applicants can submit responses to Information Request Notices (IRNs) through these conversation threads. Note that once a decision has been issued for an application, these conversations are no longer be monitored and are removed from the system.

#### 5.2.2 Submitting applications on CD or DVD

Submissions on CD and DVD will not be accepted.

# 6. Processing and Assessment of Applications

The following section outlines the stages involved in processing and assessing an application as well as when and how to communicate with NNHPD throughout the application process.

## 6.1 Processing Applications

All applications (new submissions, amendments and notifications) submitted to the NNHPD will be screened for administrative requirements. If the administrative requirements are met, notifications are processed and new applications or amendments (for all classes) proceed to regulatory screening. Following regulatory screening, Class I and II applications and amendments will be issued a regulatory decision. Class III applications and amendments that have successfully completed the screening process will proceed to assessment. If additional information is required at the regulatory screening or assessment stages, an Information Request Notice (IRN) may be issued (see section 6.1.4).

#### 6.1.1 Administrative verification

NNHPD verifies all applications for administrative completeness upon receipt.

A *Notice of Refusal - Administrative Deficiency* will be issued for all applications that have administrative deficiencies. Administrative deficiencies are as follows:

- missing or incorrect (inconsistency between cover letter and application) application type;
- missing monograph attestation;
- missing contact information or Designated Party Authorization form;
- no record of change in senior official;
- incomplete application forms (including non-finalized ePLA);
- application submitted in an unacceptable format (e.g. on USB drive, password protected, paper);
- application containing damaged/corrupted file(s) that cannot be accessed;

- duplicate tracking number on the submitted ePLA (when applicants reuse the form for different applications, the same number is generated which interferes with NNHPD systems)

Class II and III applications and amendments meeting all administrative requirements will be acknowledged (within 10 calendar days) before proceeding to the screening stage (see section 6.1.2). The acknowledgement will provide applicants with the submission number and date of receipt assigned to the application.

### 6.1.2 Regulatory screening

Class I, II and III applications and amendments meeting all administrative requirements will be screened against regulatory requirements as outlined in the NHPR, this policy and NNHPD's applicable guidance documents. In addition, applications will be screened against all parameters of NNHPD monographs and for minimum application requirements as described below.

If deficiencies are identified during the screening process, a *Notice of Refusal* will be issued. Deficiencies include:

- incomplete or inaccurate information on the ePLA form;
- failure to provide minimum application requirements, such as finished product specifications, product label text, supporting evidence for safety and/or efficacy, letters of access, or attestation(s);
- product does not meet the definition of an NHP;
- failure to meet the parameter(s) of an NNHPD monograph to which was attested.

A *Notice of Refusal* will also be issued in the following circumstance:

- failure to submit the requested information in response to an IRN within the timelines specified in the notice, or submission of an incomplete or deficient response to an IRN.

### 6.1.3 Assessment

Upon successful completion of the screening process, Class III applications and amendments will be assessed for the safety and efficacy requirements outlined in the NHPR and supporting guidance documents (see section 4).

A *Notice of Refusal* will be issued at the assessment stage in the following circumstances:

- deficiencies or information omissions that preclude the ongoing assessment;

- failure to submit the requested information in response to an IRN within the timelines specified in the notice;
- submission of an incomplete or deficient response to an IRN; and/or
- failure to meet the requirements of the NHPR and the applicable provisions of the *Food and Drugs Act.*

### 6.1.4 Information request notices (IRNs)

NNHPD will provide applicants the opportunity to address non-administrative deficiencies or information omissions through an IRN, as per section 15 of the NHPR, with a maximum specified response time between 2 to 15 calendar days depending on the complexity of the information requested.

Class I applications may be issued IRNs for brand names or other deficiencies outside of monograph parameters. Class II and III applications may be issued IRNs during the regulatory screening stage, and Class III applications may be issued IRNs during the assessment stage which may include a request for a Risk Management Plan for a substance or product new to the Canadian market with limited market experience in a comparable regulatory framework and/or population. For the purpose of improving the efficiency of the assessment process, the NNHPD will aim to issue one comprehensive IRN that includes all deficiencies identified with the application at each stage of screening and assessment. In exceptional circumstances additional IRNs may be issued.

#### 6.1.4.1 Responses to an IRN

NNHPD will communicate with applicants primarily by epost Connect™. Responses to an IRN must be submitted electronically through the submission-specific epost Connect™ conversation within the specified time period.

If a response to an IRN is deemed deficient or if the applicant does not satisfy all requirements within the allotted timeframe, a Notice of Refusal will be issued.

#### 6.1.4.2 Request for an IRN response extension

Applicants may request an extension to the timeline provided for response to an IRN. Applicants should contact their Submission Coordinator listed on the IRN via the submission-specific epost Connect™ conversation thread or by phone. The request should detail the reason for the extension and a proposed alternative date of response. The NNHPD will assess the request on a case-by-case basis and provide a response to the request within 2 business days of receipt. It is the responsibility of applicants to be available (or have a designated party available) to respond to IRNs in a timely manner. NNHPD reserves the right not to grant an extension for an IRN, in which case the applicant will be notified and the reason provided.

### 6.1.5 Service standards

The following table outlines the service standards for each application type and for each stage of the application process.

| Application Type | | Administrative Verification | Type of Notice Issued | Regulatory Screening | Assessment | Regulatory Decision Issued |
|---|---|---|---|---|---|---|
| These service standards apply to PLAs submitted in electronic format using NNHPD's most recent version of the ePLA and ANF. Please refer to section 5.1. | | | | | | |
| **CLASS I (60 calendar Days)** | Compendial | 10 Calendar days | Notice of Refusal - no Acknowledgement notice applies for this class | 50 Calendar Days | Not Applicable | Product Licence or Notice of Refusal |
| | Class I Amendment | | | | | |
| **CLASS II (90 calendar Days)** | General | | Application Acknowledgement or Notice of Refusal | 80 Calendar Days | Not Applicable | Product Licence or Notice of Refusal |
| | Traditional | | | | | |
| | Class II Amendment | | | | | |
| **CLASS III (210 calendar Days)** | General | | | 20 Calendar Days | 180 Calendar Days | Product Licence or Notice of Refusal |
| | Traditional | | | | | |
| | Homeopathic | | | | | |
| | Class III Amendment | | | | | |

Novel products that require joint assessment with other directorates (e.g. Medical Devices Bureau) are not subject to the service standards outlined above.

Applicants are encouraged to withhold sending new applications while addressing compliance issues with the Regulatory Operations and Regions Branch (RORB), as unresolved compliance issues may result in an inability for the NNHPD to issue a product licence.

## 6.2 Exchange of Information

Applicants wishing to contact the NNHPD to receive advice regarding policies, guidance, procedures, tools, or initiatives, are encouraged to send their enquiry to NNHPD's general email address.

### 6.2.1 Application status updates

Applicants should wait at least 30 calendar days from the date of application before requesting confirmation of receipt or submission number. NNHPD will not respond to requests received prior to the 30 calendar days.

If it has been more than 60, 90,or 210 calendar days since the date of submission of a Class I, II or III application, respectively, and applicants have not received a regulatory decision, applicants may send a status update request to NNHPD's general email address. All status update requests must include the following information:

- submission number (if available),
- name of the applicant company,
- brand name,
- application type,
- date of submission, and
- method of submission (e.g. epost Connect™, mail, courier), of the application.

### 6.2.2 Submitting unsolicited information

Once an application is submitted, the NNHPD will not accept unsolicited information or changes to the original application, unless that information falls within the exceptions outlined in section 6.2.2.1. Otherwise, applicants wishing to make changes to a PLA that has already been submitted, are required to withdraw their application and resubmit a new application with the revisions. See section 6.4 for information on how to withdraw an application.

#### 6.2.2.1 Exceptions to submitting unsolicited information

Prior to licensing, applicants must submit information to supplement or correct information on the regulatory status of the product in other countries. If there are problem reports impacting the safety, efficacy and/or quality of the product submitted to other regulatory agencies, and/or safety information enhancing the safe use of the product, including emerging safety issues and updated safety-related labelling, the information must be submitted to NNHPD.

Applicants can also update their contact information on an application at any time during the application process.

To submit the above information, applicants must email their request to the Submission Coordinator using epost Connect™ or, if a Submission Coordinator has not been assigned, the NNHPD general email address. If the request is accepted, the request will be actioned by a Submission Coordinator who will respond with directions on how to submit the information to NNHPD.

If the request is not accepted, applicants will be notified within 20 calendar days and may be required to withdraw their application and resubmit a new application with the changes.

### 6.2.3 Request for records

Applicants should maintain records of the information they submit to NNHPD. If there is a change in licence holder or consulting company, for example, the current licence holder must have a record of the complete product licence application package. NNHPD is not responsible for maintaining records for applicants, and will not provide copies of submission information to licence holders or application contacts.

Information and data submitted to support the original application will not be returned to the applicant.

## 6.3 Decision Issuance

Once the NNHPD has completed the processing of a PLA, this will result in one of two regulatory decisions: a licence or refusal.

### 6.3.1 Issuance of a licence

A Product licence will be issued for applications satisfying regulatory requirements as outlined in the NHPR. The product licence will include the Natural Product Number (NPN) or Drug Identification Number-Homeopathic (DIN-HM) assigned to the product. Information on licensed products is available online on the Licensed Natural Health Products Database (LNHPD). The status of the licensed product on the LNHPD will appear as "Active".

### 6.3.2 Licence correction requests

As per section 14(2) of the NHPR, licensees have 60 calendar days following the issuance of a product licence to notify NNHPD of any information on the licence that the licensee knows to be incorrect. Correction requests should be submitted via NNHPD's general email address. Requests should be made only for administrative errors made on the product licence (e.g. spelling errors or other discrepancies between the submitted product licence application and the product licence). All other requests for changes must be made through an amendment or notification (see section 7.1 for more information) using the ANF or be resubmitted as a new application, as appropriate. The LNHPD will be updated within 15 calendar days to reflect the correction.

### 6.3.3 Refusal to issue a licence

A Notice of Refusal will be issued for applications that do not satisfy the requirements of the NHPR. See section 6.1 for an overview of administrative verification, regulatory screening and assessment refusal reasons.

The process available to applicants to respond to a Notice of Refusal is a reconsideration. If the applicant wishes to submit additional information on the product for which a Notice of Refusal was issued, a new application must be submitted. If an

applicant wishes to re-submit an application that was refused, please refer to section 6.5.

#### 6.3.3.1 Request for reconsideration

As per section 9 and 10 of the NHPR, an applicant may request a reconsideration of a Notice of Refusal within 30 calendar days of issuance. Refer to the Reconsideration guide for more information.

### 6.3.4 Assessment report

Following the receipt of a Product Licence or a Notice of Refusal, an applicant or licensee may request the assessment report for their application by writing to NNHPD's general email address and referencing the Submission Number. NNHPD will strive to provide a copy of the requested report via ePost within 20 calendar days from the date of receipt. This is applicable to Class II and III applications only.

## 6.4 Withdrawal

At any time during the application process, an applicant may withdraw its application by submitting a request to the NNHPD general email address or if the withdrawal is in a response to an IRN, to the Submission Coordinator as outlined in section 6.1.4.1. All withdrawal requests will be acknowledged in writing within 15 calendar days. The status of the application will be recorded internally as "withdrawn by applicant".

Withdrawal of an application is without prejudice to re-submitting. If an applicant wishes to re-submit a complete application at a future time, the application will be processed as a new application.

## 6.5 Re-submitting an Application

Applicants may re-submit previously withdrawn applications or applications for which a Notice of Refusal was issued. In all cases, a new application is required and the applicant must reference the submission number of the previous application if the application was refused. The new application will be subject to any new regulations, policies, procedures and/or guidance documents in effect at the time of submission.

# 7. Post Licensing Activities

Post licensing activities include all activities that occur once a product is licensed, such as amendment and notification applications, requests to discontinue a licence, post-licensing audit activity and NNHPD-initiated activities. Information on each of these activities is described below.

## 7.1 Post Licensing Changes

Refer to the Post Licensing guidance document for more information on post-licensing changes. Amendment and notification applications must be submitted using the Amendment and Notification Form (ANF). There are three types of post-license changes: a fundamental change, an amendment and a notification.

See Appendix III for a list of changes and what the regulatory requirements are for each change.

### 7.1.1 Fundamental changes

The NHPR do not allow for product changes considered fundamental changes following the issuance of a product licence. The following changes are considered fundamental changes as defined in section 13 of the NHPR:

- change to the quantity of a medicinal ingredient per dosage unit, addition or substitution of a medicinal ingredient;
- change to the dosage form; or
- change to the route of administration.

These changes require a new application and upon approval by the NNHPD, will receive a new NPN or DIN-HM. Licence holders must then request a discontinuation of the original licence as outlined in section 7.3.

### 7.1.2 Amendments

Amendments are changes to an NHP that may have an impact on the safety, efficacy and/or quality of the product. An amendment application must include evidence to demonstrate that the NHP remains safe and efficacious. The amendment can only be applied to a product once approval is obtained and the product licence is updated to reflect the changes. Once the amendment is approved, the applicant will be notified and sent the amended licence via ePost.

An amendment is required for all licensed products that are making any of the following changes, as per section 11 of the NHPR:

a. a change to its recommended dose;
b. a change to its recommended duration of use;
c. the deletion or modification of risk information shown on any of its labels, including the deletion or modification of a caution, warning, contra-indication or known adverse reaction associated with its use;
d. a change of its recommended use or purpose;
e. a change of the source material of any of its medicinal ingredients;
f. changing any of its medicinal ingredients to or from being synthetically manufactured;
g. a change to the potency of any of its medicinal ingredients;
h. a change affecting its safety or efficacy that does not arise as a result of
    i. a change to the quantity of a medicinal ingredient per dosage unit,
    ii. the addition or substitution of a medicinal ingredient,

iii. a change to its dosage form, or
iv. a change to its recommended route of administration; or

i. one or more of the following changes to its specifications, namely,
   i. the removal of a test method set out in the specifications,
   ii. the modification of a test method set out in the specifications in a manner that widens the purity tolerances of the natural health product or the quantity, identity or potency tolerances of any of its medicinal ingredients, or
   iii. the modification of a test method set out in the specifications in a manner that renders it less precise, accurate, specific or sensitive.

#### 7.1.2.1 Classes of amendments

Amendment applications are classified, processed and assessed in a manner similar to new applications. Please refer to section 6 for more information. A post-licence audit may also be conducted if the original application was submitted using an attestation as outlined in section 7.4.

Amendments follow the same service standards as new applications as outlined in section 6.1.5.

### 7.1.3 Notifications

Notifications are changes to an NHP that do not have a significant impact on the safety, efficacy and/or quality of the product. Licensees must notify the NNHPD of the change within 60 calendar days after the day on which the change is made, using the ANF.

A notification is required for all licenced products that are making any of the following changes, as per section 12 of the NHPR:

a) a change to any of the information submitted under paragraph 5(a) or (b);
b) a change to any of the information provided under section 22;
c) the addition or substitution of a non-medicinal ingredient, the addition or substitution of which does not affect its safety or efficacy;
d) its sale under a brand name other than one submitted under paragraph 5(e);
e) a change of the common or proper name of any of its medicinal ingredients; and
f) the addition of risk information to any of its labels, including the addition of a caution, warning, contra-indication or known adverse reaction associated with its use.

Notifications are not included in the three-class system. The NNHPD aims to process complete notification applications within 60 calendar days of receipt.

#### 7.1.3.1 Non-notifiable changes

A non-notifiable change is a change to a licenced product that is not required to be submitted to the NNHPD. These are revisions that are not outlined in sections 7, 11 or 12 of the NHPR. Non-notifiable changes include revisions to the net package quantity (e.g. 50 to 100 capsules per bottle) that do not pose a safety concern, revisions to information on the label not indicated on the PLA or requiring assessment (e.g. marketing, formatting, certain storage conditions), or revisions to manufacturing flow charts which do not impact the Finished Product Specifications.

The NNHPD will not send an Acknowledgement notice to the applicant if non-notifiable changes are submitted.

#### 7.1.3.2 Maintaining company and contact information

As per section 12 of the NHPR, licensees are responsible for notifying the NNHPD within 60 calendar days of changes to contact information, as required. This requirement applies across the full life-cycle of the product.

Changes to contact information include:

- The senior official has changed; and
- A change in contact information (email, phone, mailing address, etc.) occurs for the company not affecting a manufacturing, packaging, labelling, or importing site.

These changes must be submitted by the Senior Official of the company and must be submitted to the NNHPD as outlined in Section 5.2.

#### 7.1.3.2.1 Company transfer or merger

When a company transfers ownership of one or more licensed product(s) and its associated regulatory responsibilities, the transfer must be submitted to the NNHPD as a notification using the ANF. If the transfer is for an application that has already been submitted to the NNHPD, but has not yet been issued a regulatory decision, the information listed below should be submitted as an unsolicited information update. Please refer to section 6.2.2.1 for more information on how to submit.

In either instance, the following information is required:

- A letter from the senior official from each company on company letterhead confirming the transfer.
    - Both letters must identify which products licences are being transferred, including the NPNs/DIN-HMs and primary brand names.
- DPA form(s), if applicable.

For a post-license application transfer: an ANF with the new company information is required:

1. Select “Licence transfers” on the ANF home page
2. Identify the current licensee
3. Complete submitter information
4. Complete the new licensee information

For a pre-license application transfer via an unsolicited information update:
An updated ePLA Form with the new applicant and contact information is required.

## 7.2 Monograph Updates

It is important to note that NNHPD monographs are revised periodically. Product licence holders are expected to align products affected by monograph revisions with the most recent monographs within 12 months or the next label run (whichever is shorter), unless otherwise notified, by submitting an amendment.

## 7.3 Discontinuing a NPN or DIN-HM

Licence holders must notify the NNHPD if they no longer require an active NPN or DIN-HM for a product. The licensee must request to discontinue the NPN or DIN-HM by notifying the NNHPD. Only the senior official or contact acting on behalf of the senior official (formalized by way of a Designated Party Authorization (DPA) form) can request the discontinuation. Requests submitted by individuals other than the senior official or a recognized contact will not be processed. The request should include:

- the NPN(s) or DIN-HM(s) to be discontinued
- the associated submission number(s)
- the associated brand name(s)

A discontinuation request must be submitted to the NNHPD’s general e-mail address. The NNHPD will notify licensees when the request has been processed within 15 business days and the status on the LNHPD will be updated to “Discontinued”.

The NNHPD may also initiate an NPN or DIN-HM discontinuation. If the NNHPD attempts to contact a company post-licensing (e.g. as outlined in section 7.4) and during this process, it is determined that the company is no longer operational or bankrupt, NNHPD will take action to discontinue the licence holder’s NPN(s) or DIN-HM(s). The status will be reflected on the LNHPD as “Discontinued”. Please note that licenses cannot be reactivated once they have been discontinued.

## 7.4 Post-Licensing Audit

NNHPD may conduct post-licensing audits for any application that has provided an attestation (re: safety, efficacy and/or quality) at any time. The objective of an audit is to confirm the validity of the attestation. If there is a discrepancy noted during an audit, applicants will be notified.

## 7.5 Post-Licensing NNHPD-Initiated Activities

If a safety risk or administrative error is identified for a licensed product, the NNHPD may issue a request for additional information or clarification from the licence holder. The assessment of post-licence issues identified by Health Canada, for instance through its vigilance program or compliance and enforcement activities conducted by the Regulatory Operations and Regions Branch (RORB), and any resulting amendments required from the licence holder, are not subject to the service standards.

When a post-market issue is identified, NNHPD may issue a Post-Licence Information Request Notice requiring specific changes/modifications to the product and/or its labelling in order to mitigate a safety risk. Post-Licence Information Request Notices provide a timeline for response that is determined by Health Canada, to account for the complexity of the request and other factors. The Notice also allows the licensee to address the concerns by submitting a post-licence amendment or notification using the ANF.

Examples of post-market safety issues:

- changes made to an ingredient entry in the NHPID that must be reflected in affected licensed products;
- updates to a monograph affecting the safety of a product;
- discovery of new information or restrictions specific to an ingredient or product that impacts the safety of a licensed product;
- the identification of administrative errors during licensing;
- complaints received regarding a licensed product that identify a potential safety issue; and
- updates to products resulting from safety assessments.

A Post-Licence Information Request Notice is not the only tool used by Health Canada to address a post-market safety issue. NNHPD may also issue regulatory notices as outlined in sections 16 to 20 of the NHPR, if there is a safety concern, or other alleged contravention of the NHPR or *Food and Drugs Act* for a licensed product. In the event that a licensee receives a regulatory notice from NNHPD and is requested to update the product information by submitting an amendment, applicants must use the ANF tool and identify the application as "in response to a notice issued by the NNHPD Risk Management Division". The ANF must be submitted as outlined in section 5.2.

# Appendix I – Overview of the Natural Health Products Ingredients Database

The Natural Health Products Ingredients Database (NHPID) is a repository of ingredients and is a key component of the Natural Health Products Online Solution. The NHPID includes medicinal ingredients (MIs) and non-medicinal ingredients (NMIs) for use in NHPs. It also includes information related to ingredients that are not allowed or are restricted for use in NHPs. The database uses standard terminology as described in the Natural Health Products Online System Standard Terminology Guide.

A comprehensive listing of monographs is also available in the NHPID. Each ingredient entry also refers to applicable associated monographs.

The electronic Product License Application form (ePLA) form is linked to the ingredient entries of the NHPID. The ePLA form only allows ingredients identified with a medicinal or non-medicinal role in the NHPID to be selected in the form. The ePLA form also works in conjunction with the NHPID to provide applicants with the most current information on ingredients.

All ingredients in a product formulation must be present in the NHPID with a MI or NMI role prior to completing an ePLA form to be submitted with a PLA.

### 1. Ingredients

As ingredients may be associated with a medicinal or non-medicinal role, or both, in the NHPID, it is equally important that ingredients be listed in the ePLA form under their appropriate role. The representation of an ingredient as medicinal or non-medicinal in a product should be in accordance with applicable regulations and outlined definitions, assessment practices, policies and/or guidance, which help distinguish MIs from NMIs. Note that the representation of ingredients may be different from other jurisdictions and/or be specific to NHPs; e.g., the NHPR distinguishes MIs from NMIs, while the *Cosmetic Regulations* do not.

An entry in the NHPID does not imply that the ingredient has been fully reviewed for safety and/or efficacy. Additional evidence may be required as described in the guidance documents referenced in section 4.1. During the application review, information may be requested for the ingredient in accordance with the product's recommended conditions of use.

### 1.1 Medicinal ingredients

An MI is a substance set out in Schedule 1 to the NHPR, a homeopathic medicine or a traditional medicine. These ingredients are assigned a medicinal or homeopathic role in the NHPID and can be selected within the ePLA form as MIs. In addition, an NHP cannot include a substance set out in Schedule 2 to the NHPR or a substance that must

be sold pursuant to a prescription. These ingredients are assigned a non-NHP role in the NHPID and are generally not able to be selected within the ePLA form as MIs. Some ingredients within the NHPID may be associated with both a medicinal role and a non-NHP role (see section 1.3 below); these ingredients can be selected in the ePLA form as MIs and are only acceptable in NHPs under the restrictions outlined in the NHPID.

An MI is further interpreted as any ingredient that contributes to the pharmacological activity of the product. Ingredients should not be listed as NMIs if they are commonly recognized to possess pharmacological properties but are present in the product below known effective doses (e.g., sub-therapeutic ingredients) or contribute directly or indirectly to the product's recommended use(s) or purpose(s). These ingredients are not interpreted as meeting the definition of an NMI.

### 1.2 Non-medicinal ingredients

An NMI is defined as any ingredient that is added to a product to confer suitable consistency or form to the MIs (suitable as per dosage form and route of administration). NMIs:

- should not exhibit pharmacological effects;
- should not have any effect contradictory to the product's recommended use or purpose;
- should not exceed the minimum quantity per dosage unit or concentration required to support its intended purpose in the formulation;
- should not adversely affect the bioavailability, pharmacological activity, or safety of the MIs; and
- should be safe.

Sub-therapeutic ingredients should only be listed as NMIs in cases where there is supporting information that their primary purpose and/or intent for their addition in the product is to confer suitable consistency or form to the MIs.

NMIs are further characterized by their purpose. Consistent with the definition of an NMI, the purpose should be suitable for the dosage form and route of administration of the product. As such, hhaving a purpose associated with an NMI in the NHPID does not imply that such a purpose would be valid for all or any product. A list of NMI purposes and their description is found in the NHPID Controlled Vocabulary.

Although the NHPR only refer to a qualitative list of NMIs as information that shall be part of PLAs, applicants are encouraged to provide the quantity per dosage unit or concentration of NMIs present in the product that are associated with quantity restriction(s) in the NHPID when filing. This information may be requested during application review to fulfill other regulatory requirements of the NHPR related to safety and/or efficacy, or to determine the appropriate representation of such ingredients as per assessment practices, policies and/or guidance. The quantity of NMIs may also be

requested at any time for the purpose of characterization and mitigating of risks that the NMI may pose to consumers. However, please note that the quantities of NMIs are not listed in the LNHPID. Providing this information at the time of application is beneficial to both the applicant as well as NNHPD and may decrease the need for post-licence follow up.

### 1.3 Non-NHP ingredients

Substances not falling under Schedule 1 or falling under Schedule 2 to the NHPR, as well as substances listed in the *Prescription Drug List* (PDL) are considered non-NHP ingredients. Non-NHPs are captured in the NHPID with a non-NHP role and as such are either not permitted or are restricted to specific conditions of use in NHPs. Other regulatory requirements or safety concerns that preclude substances from being used or are restricted for use in NHPs may be outlined in the NHPID for particular substances.

### 1.4 Ingredient restrictions

Some ingredients within the NHPID are associated with restrictions and/or additional information requirements, which must be adhered to and/or provided when submitting an application. In the absence of such restrictions or additional requirements, it remains NNHPD's expectation that the use and representation of ingredients adhere to applicable regulations, outlined definitions, policies and/or guidance, as well as good manufacturing practices. Applicants are welcome to provide supporting evidence for the modifications of such restrictions or a rationale for exemptions of such restrictions/requirements for the product when submitting a PLA, however, where the totality of available information is insufficient to warrant the requested modifications or exemptions, the change will not be made.

### 1.5 Source information

MIs are characterized by their proper name and common name, their quantity per dosage unit or concentration and method of preparation, as well as by their source information. The source information is outlined in the NHPID and selectable within the ePLA form for MIs as source materials or source ingredients, or both. Source ingredients generally apply to:

- chemical substances that contain within, or provide, the MI (e.g., L-Cysteine hydrochloride, present in the product, is a source ingredient of L-Cysteine);
- source materials that apply to parts of organisms from which the MI is isolated from (e.g., Shrimp - Exoskeleton, not present in the product, is a source material of N-Acetylglucosamine); or,
- source materials that characterize the MI (e.g., *Medicago sativa* – Herb top, present in the product, is a source material characterizing a dry extract of Alfalfa).

Some MIs falling under Schedule 1 of the NHPR may only be used or are predominantly used in the form of a derivative (e.g., salt, ester, ether, isomer, resinate, polymer, complex or carrier form) in order to maintain the stability of the substance under environmental conditions such as moisture, light, temperature, acidity or alkalinity, and/or to improve the absorption of the MI into the body. These NHP substance derivatives, as is the case of L-Cysteine hydrochloride, are not assigned a medicinal role in the NHPID, but rather listed as source ingredients, and should be selected as such within the ePLA form, for their associated MIs (in this instance L-Cysteine).

To be considered acceptable NHP substance derivatives of Schedule 1 ingredients, the substances must act as sources or prodrugs (compounds that are transformed in the human body into their respective NHP substances by chemical or metabolic means), in order to achieve their respective intended effect(s). They must also have similar safety, efficacy, and other pharmacological properties (e.g., distribution, metabolism, excretion, mechanism of action) as compared to their respective parent NHP substances.

**2. Dosage form and route of administration**

Applicants should also ensure that the dosage form and route of administration of the product are recognized by the NNHPD and therefore found within the NHPID Controlled Vocabulary.

**3. How to request NHPID modifications**

If applicants wish to include ingredients in their product formulation that are not listed in the NHPID, they must submit a request to add the ingredients to the NHPID. Ingredients must be present in the NHPID to be selected on the ePLA prior to submitting an application.

To request NHPID modifications, applicants should complete an NHPID Issue Form and send it to hc.ingredient_support.sc@canada.ca. Requests should be accompanied by at least one piece of supporting evidence (unless the request is a typographic correction). The NHPID Issue Form includes a non-exhaustive list of references that may be considered as a helpful starting point to find supporting evidence.

Requests for modifications to the NHPID should be substantiated by information that is credible, verifiable, objective and suited to addressing the applicable regulations and outlined definitions, assessment practices, policies and/or guidance. The information provided should also reflect to totality of evidence available. As such, in addition to the review of the information provided as part of the request, the NNHPD also conducts literature review to ensure that the above considerations are respected. Noted discrepancies or deficiencies may result in a request for additional evidence and/or clarification during request review.

Although recognized by the NNHPD, the listing of an ingredient and associated information in one or more of the references outlined in the NHPID Issue Form, does not imply automatic acceptance of the requested NHPID modification(s).

In order to assist NNHPD in the review of NHPID modifications, applicants should provide, along with the NHPID Issue Form and supporting evidence and/or rationale, the following information, when available and/or applicable, on the product in which the ingredient is present as medicinal or non-medicinal, or to which the requested NHPID modifications would apply:

- name of the product, its dosage form, route of administration, and subpopulation(s);
- lists of medicinal and non-medicinal ingredients, with their quantity per dosage unit or concentration;
- the recommended use(s) or purpose(s) associated with the product; and
- any other relevant conditions of use, such as duration of use, directions of use, and risk information.

The above may be requested during review of NHPID modifications, if not provided.

**4. NHPID modification process**

Requests for NHPID modifications are processed within 4 weeks from the receipt of the request. The time required for reviewing a request may however vary depending on the quality and/or the complexity of the request, as well as on the volume of requests.

Accepted modifications to the NHPID will be made available to applicants in the next load of the NHPID and published in the What's New in the NHPID website. Applicants will only be informed via email in cases of refused modifications to the NHPID and/or for modifications to the NHPID that are exactly as requested. If it has been more than 2 load cycles and a decision has not been published or issued, applicants are encouraged to send a status update request by email to hc.ingredient_support.sc@canada.ca.

Licence holders are expected to align products affected by NHPID modifications with current information, as applicable. This can be accomplished by submitting a post-licensing change. Refer to section 7.1 for information on post-licensing changes.

It is important to acknowledge that the as NHPID contains thousands of ingredient entries, there are inconsistencies within it. The NNHPD is committed to addressing any inconsistencies in the NHPID to improve the completeness and accuracy of the database.

# Appendix II - Attestation to NNHPD monographs

## 1. Monograph Parameters

When attesting to a monograph the PLA must match the monograph content exactly or fall within its parameters. The following parameters of a monograph must be met upon attestation:

1. Proper name
   The proper name must be chosen from one of the options provided in the monograph.

2. Common name
   The common name must be chosen from one of the options provided in the monograph.

3. Source material
   The source material must be chosen from the options provided in the monograph. More than one source material is acceptable, provided that all source materials listed on the PLA form reflect the same dose and/or use or purpose on the referenced monograph.

4. Route of administration
   The route of administration must be chosen from the options provided in the monograph. Please see the NHPID Controlled Vocabulary for a description of the routes of administration.

5. Dosage form
   The dosage form must reflect the route of administration for the product and be chosen from the options provided on the monograph, where applicable, or as outlined in the Compendium of Monographs guidance document. Food-like dosage forms are not acceptable (e.g., bars, chewing gums, or beverages).

   - Please note that an NHP in a modified formulation (e.g., liposomal, phytosomal etc.) intended to improve the bioavailability and/or absorption of its medicinal ingredients is not considered equivalent to an NHP in a non-liposomal/phytosomal formulation or conventional dosage form. Therefore applicants cannot attest to a monograph for the safety and efficacy of an ingredient unless the monograph specifically states that liposomal/phytosomal formulations are acceptable. Products with liposomal/phytosomal formulations or any other formulation with enhanced bioavailability must be submitted through the appropriate application type (e.g. “General” application type) with specific evidence to support the corresponding formulation/dosage form.

6. Recommended use or purpose

Claims have been identified for each monographed ingredient based on NNHPD's evaluation of the safety and efficacy data. Applicants may choose one or more claims provided in the monograph. Applicants must ensure that any conditions surrounding the claim (dose, source material, etc.) are met.

7. Dose
   The total daily dose must be equal to that noted in the monograph, or, when a range is specified, fall within the range indicated in the monograph. The dose indicated on the monograph may be specific to:
   - Subpopulation
     - All monographs are intended for adults, unless otherwise specified.
   - Method of preparation
     - Must be chosen from the list of acceptable methods, if indicated. Furthermore, to make a traditional use claim, the method of preparation must be one that was traditionally used. Please see the Pathway for Licensing NHPs Used as Traditional Medicines guidance document for a list of traditional methods of preparation.
   - Potency
     - When a monograph includes potency, it must be included in the PLA, unless otherwise specified.
     - The inclusion of a potency when not permitted by the monograph is not acceptable for attestation.
   - Frequency
     - The frequency must be the same as or fall within the range of the frequency on the monograph, when specified. When the monograph specifies a divided dose, the frequency must be more than once daily. If no frequency is specified, the applicant may select an appropriate frequency.
   - Directions for use
     - Where specified, all directions for use must be included in the PLA.

8. Duration of use
   When the monograph includes a duration of use, it must be included on the PLA.

9. Risk information
   All risk information contained in the monograph must be included in the PLA, as applicable.

10. Non-medicinal ingredients
    Only non-medicinal ingredients listed in the NHPID may be used with an appropriate excipient purpose. Any applicable restrictions indicated in the database must be met.

    The presence of non-medicinal ingredients without conditions on the Cosmetic Ingredient Hotlist: Prohibited and Restricted Ingredients (the hotlist) indicates that

there are potentially significant safety issues with these ingredients. If the hotlist indicates that additional evidence is required for an ingredient or if an ingredient is listed with no specified conditions, it is not permitted in a Class I topical product. If the hotlist specifies certain conditions for an ingredient, or label requirements, it is the responsibility of the licence holder to ensure that the ingredient meets the conditions outlined.

Requirements for non-medicinal ingredients are outlined in the following documents: Quality of Natural Health Products Guide, "Pathway for Licensing Natural Health Products Making Modern Health Claims", "Pathway for Licensing Natural Health Products Used as Traditional Medicines" and the "Evidence for Homeopathic Medicines Guidance Document".

11. Storage conditions
When the monograph includes storage conditions, they must appear on the product label as per section 87 of the NHPR.

12. Specifications
Note that certain monographs include additional specifications relevant to that ingredient or product. This information must be considered when establishing product specifications.

## 2. Attesting to Multiple Monographs

When attesting to more than one NNHPD monograph in support of safety and/or efficacy of a Class II or III product, monograph conditions of use (duration of use, risk information, etc.) may be omitted in the following situations:

- Sub-population-specific risk information is not required if the product is not indicated for that sub-population
    - E.g. the risk statement "consult a health care practitioner prior to use if pregnant or breastfeeding" is not required for a product indicated for an "adult male" sub-population
- The risk information being omitted is considered less stringent and covered by the risk information required by another monograph attested to within the application.
    - E.g. "consult a health care practitioner if you are pregnant or breastfeeding" is considered less stringent and covered by "do not use if you are pregnant or breastfeeding"
- The duration of use being omitted relates to the efficacy of the claim and is shorter than the duration of use relating to efficacy required by another monograph attested to within the application.
    - E.g. "Use for a minimum of 3 months to see beneficial effects" relates to the efficacy of the claim and is shorter than "use for a minimum of 6 months to see beneficial effects."

- The duration of use being omitted relates to the safety of the ingredient and is longer than the duration of use relating to safety required by another monograph attested to within the application.
    - E.g. "Consult a health care practitioner for use beyond 1 month" relates to the safety of the ingredient and is longer than "consult a health care practitioner for use beyond 1 week."

Applicants omitting conditions of use in a Class II or III application within the situations described above must still attest to the monograph for all other monograph parameters that are met.

### 3. Monograph Revisions

Suggestions for revisions to currently published monographs and suggestions for ingredients that should be the subject of a monograph can be submitted to the NNHPD via the Natural Health Product Ingredients Database Issue Form. This form should include the name of the monograph to which amendments are being proposed along with the rationale and supporting scientific data for consideration.

### 4. Position on "Statements to the effect of"

The use of "statements to the effect of" will no longer be permitted in Class I applications. The use of "statements to the effect of" will continue to be permitted in Class II and III applications. When this policy becomes effective, at the time of final publication of this policy, applications that make use of statements that deviate from the exact wording provided in monographs will be processed as a Class II or III application.

# Appendix III

# Post-license Changes and Associated Regulatory Requirements

√ - Required
▲ - May be required depending on the proposed change

| Type of Change | Regulatory Requirement | Safety & Efficacy Evidence | Finished Product Specifications |
|---|---|---|---|
| **Recommended dose** | | | |
| Change to amount of dosage unit | Amendment | √ | |
| Change to frequency | Amendment | √ | |
| Change to sub-population group | Amendment | √ | |
| Change to directions of use appearing on the label | Amendment | ▲ | |
| **Recommended duration of use** | | | |
| Lengthening the recommended duration of use | Amendment | √ | |
| Shortening the recommended duration of use | Amendment | ▲ | |
| **Risk information shown on any label** | | | |
| Deletion of risk information | Amendment | √ | |
| Addition of risk information | Notification | ▲ | |
| Modification of risk information | Amendment | ▲ | |

| | | | |
|---|---|---|---|
| **Recommended use or purpose** | | | |
| Modification to the recommended use or purpose | Amendment | ▲ | |
| Deletion of part of the recommended use or purpose | Amendment | | |
| Addition to the recommended use or purpose | Amendment | √ | |
| **Source material of any medicinal ingredients** | | | |
| Change to the part or tissue used | Amendment | ▲ | |
| Change to the source material from a monograph source to a source not listed on a monograph | Amendment | √ | |
| Change of source within a monograph | Amendment | | |
| Change from a source not listed on a monograph to a source listed on a monograph | Amendment | | |
| Change of source material to an animal-derived source | Amendment | | |
| Change to information submitted on the Animal Tissue Form | Amendment | | |
| Change to the salt or derivative used | Amendment | ▲ | |
| Change to the strain used | Amendment | √ | |
| **Changing any of medicinal ingredients to or from being synthetically manufactured** | | | |
| Change from being synthetically manufactured to a natural ingredient | Amendment | | |
| Change from a natural source to a synthetically source | Amendment | | |

| | | | |
|---|---|---|---|
| **Potency of any medicinal ingredients** | | | |
| Addition of a potency | Amendment | ▲ | √ |
| Deletion of a potency | Amendment | ▲ | √ |
| Change in the potency | Amendment | ▲ | √ |
| **Change affecting safety and efficacy (other than those listed in paragraph 11(h))** | | | |
| Change in manufacturing information | Amendment | | ▲ |
| **Change to the quantity of a medicinal ingredient per dosage form** | | | |
| Decrease in quantity | Fundamental Change | ▲ | √ |
| Increase in quantity | Fundamental Change | ▲ | √ |
| **Addition or substitution of a medicinal ingredient** | | | |
| Adding a medicinal ingredient | Fundamental Change | √ | √ |
| Removing a medicinal ingredient | Fundamental Change | ▲ | √ |
| Substituting a medicinal ingredient for one not already found in the product | Fundamental Change | √ | √ |
| **Dosage form** | | | |
| Change in the dosage form | Fundamental Change | √ | √ |
| **Recommended route of administration** | | | |
| Any change in route of administration | Fundamental Change | √ | |
| **Removal of a test method set out in the specifications** | | | |
| Any removal of test methods in the specification | Amendment | | √ |
| **Modification of a test method set out in the specifications** | | | |

| | | | |
|---|---|---|---|
| Any modification to test methods in the specification | Amendment | | √ |
| **Change to information submitted under paragraphs 5(a) and (b)** | | | |
| Change in the name of the product licence holder or applicant | Notification | | |
| Change in ownership of the product licence | Notification | | |
| Mergers between companies | Notification | | |
| Change of senior official | Notification | | |
| Change of title, phone number, fax number, e-mail address or mailing address of senior official | Notification | | |
| Change of contact person for the application | Notification | | |
| Change of title, phone number, fax number, e-mail address or mailing address of the contact person for application | Notification | | |
| Change of company name for Regulatory Affairs Information in Canada | Notification | | |
| Change to contact information for Regulatory Affairs Information in Canada | Notification | | |
| **Information provided under section 22** | | | |
| Addition of a manufacturer, packager, labeller, importer or distributor | Notification | | |
| Removal of a manufacturer, packager, labeller, importer or distributor | No need to communicate with the NHPD | | |

| | | | |
|---|---|---|---|
| **Addition or substitution of a non-medicinal ingredient** | | | |
| Changing to a different ingredient in the NHPID | Notification | | |
| **Sale under a brand name other than one submitted under paragraph 5(e)** | | | |
| The addition or modification of a brand name | Notification | | |

# Glossary

***Adverse reaction (or known adverse reactions)***
A noxious and unintended response to a natural health product that occurs at any dose used to test for the diagnosis, treatment or prevention of a disease or for modifying an organic function. Examples include flushing, nausea, diarrhea and constipation.

***Applicant or Licensee***
The company in whose name the NHP application is submitted and the product licence will be registered (the applicant will be referred to as the licensee once a licence has been granted or amended). For product licence applications, the licensee/applicant is not necessarily the company that fabricates the product (e.g. may be the distributor of the product or the importer, etc.). The licensee/applicant is responsible for: submitting the complete product licence application package to the NNHPD for assessment; designating a representative in Canada if the senior official is outside Canada; ensuring the NHP is properly labeled; providing information or samples to the NNHPD, if requested; submitting any notifications and amendments; stop sale, if requested by the NNHPD; providing site information before commencing sale of an NHP; maintaining records, as required; reaction reporting; and recall reporting.

***Brand name***
A name in English or French, whether or not it includes the name of a manufacturer, corporation, partnership or individual (a) that is used to distinguish the natural health product; and (b) under which a natural health product is sold or advertised. The brand name may or may not include a trade name.

***Cautions and warnings***
Information which identifies special care that must be exercised by the consumer prior to using the product to ensure safe and effective use of the NHP. Cautions and warning 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. For example, “If you have known kidney problems or are taking diuretics consult your health care practitioner”.

***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. Acceptable common names are listed in the NHPID. NHPID does not include an exhaustive list of common names.

***Compendial***
An application type used on the ePLA form for Class I products which meet all parameters of an individual NNHPD monograph.

***Directions of use***
How the product should be taken. This may include time of administration, or administration with respect to food or drink.

***Discontinuation***
An action taken by a licence holder or by NNHPD to remove the active status of a NPN or DIN-HM.

***Dosage form***
The final physical form of the natural health product which may be used by the consumer without requiring any further manufacturing. Acceptable dosage forms are outlined in the NHPID Controlled Vocabulary.

***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.

***Duration of use***
The time frame in which an NHP can be consumed safely for its intended purpose.

***Efficacy***
The extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions.

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

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

***Finished product specifications***
Quality standards for an NHP that contains the information described in section 44(2) of the NHP Regulations which include tests, references to analytical procedures and appropriate tolerance limits which are numerical limits, ranges or other criteria for the tests described. Specifications establish the criteria to which a finished product should conform in order to be considered acceptable for its intended use.

***Frequency***
How often the product is to be taken in a given time or time interval (e.g. 3 times daily).

***General Application***
An application type used on the ePLA form for products formally categorized as non-traditional applications and for all products which cannot be classified into the Compendial (Class I), Traditional, and Homeopathic application types.

***Good manufacturing practices***
Measures to ensure an overall effective approach to product quality control and risk management. They apply to places, people, processes and products with respect to which activities are being conducted. Please refer to Part 3 of the Natural Health Products Regulations and the Good Manufacturing Practices for Natural Health Products Guidance Document.

***Health claim***
See "Recommended use or purpose".

***Homeopathic Application***
An application type use on the ePLA form for products categorized as a homeopathic medicine (See Homeopathic Medicine).

***Homeopathic medicine***
To be considered a homeopathic medicine, a product must meet two criteria. It must be:
(1) Manufactured from, or contain as medicinal ingredients, only substances referenced in a homeopathic monograph in one of the following homeopathic pharmacopoeias, as they are amended from time to time:

- Homeopathic Pharmacopeia of the United States (HPUS)
- Homöopathische Arzneibuch (HAB) or German Homeopathic Pharmacopoeia
- Pharmacopée française or French Pharmacopoeia (PhF)
- European Pharmacopoeia (Ph.Eur.)
- Encyclopedia of Homeopathic Pharmacopoeia (EHP)

(2) Prepared in accordance with the methods outlined in one of the homeopathic pharmacopoeias listed above, as they are amended from time to time.

***Ingredient***
A single substance that is a component part of any product formulation.

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

***Kit***
A kit is defined as a package containing more than one NHPs OR a combination of one or more NHPs and one or more foods, cosmetics or medical devices that is intended to have a combined benefit, e.g. overarching claims or brand name.

***Label***
Includes any legend, word or mark attached to, included in, belonging to or accompanying an NHP. Product to be labelled in both official languages.
Please refer to Part 5 of the Natural Health Products Regulations and the Labelling Guidance Document.

***Licensee***
See "applicant".

***Master File***
An NHP Master File may be submitted, when a company would like to submit confidential information on behalf of another company (e.g. supplier submitting confidential manufacturing information on behalf of a manufacturer).

***Medicinal ingredient***
Any substance set out in Schedule 1 of the Natural Health Products Regulations that is intended to provide pharmacological activity or other direct effect in: (a) the diagnosis, treatment, mitigation, or prevention of a disease, disorder or abnormal physical state or its symptoms in humans; or (b) restoring or correcting organic functions in humans; or (c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health. In other words, the ingredient is considered to be medicinal in nature if it contributes to the therapeutic activity associated with the recommended use or purpose. All medicinal ingredients found in the product must be listed as such within the NHPID. Please note that some ingredients within the NHPID have associated limits or restrictions and these must also be considered when filing. An entry in the database does not imply that the ingredient has been reviewed for safety or efficacy.

***Natural Health Product***
Under the Natural Health Products Regulations, which came into effect on January 1, 2004, natural health products (NHPs) are defined as:

•Vitamins and minerals
•Herbal remedies
•Homeopathic medicines
•Traditional medicines such as traditional Chinese medicines
•Probiotics
•Other products like amino acids and essential fatty acids

***NNHPD monograph***
A written description of particular elements on an identified ingredient or product. The *Compendium of Monographs* is comprised of single and product monographs to be used to support the safety and efficacy of the medicinal ingredient(s). Single ingredient monographs indicate only one medicinal ingredient, while product monographs indicate multiple ingredients or describe the conditions of use for a product category.

***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.

***Non-NHP***
A substance set out in Schedule 2, any combination of substances that includes a substance set out in Schedule 2 or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2.

***Schedule 2****:* A list of Natural Health Product substance that exclude:

- A substance set out in Schedule C to the Act
- A substance set out in Schedule D to the Act, except for the following:
    - a drug that is prepared from any of the following micro-organisms, namely, an alga, a bacterium or a fungus; and
    - any substance set out on Schedule D when it is prepared in accordance with the practices of homeopathic pharmacy
- A substance regulated under the Tobacco Act
- A substance set out in any of Schedules I to V of the *Controlled Drugs and Substances Act*
- A substance that is administered by puncturing the dermis
- An antibiotic prepared from an alga, a bacterium or a fungus or a synthetic duplicate of that antibiotic

***NPN/DIN-HM***
Natural Product Number (NPN) is an eight (8) digit numerical code assigned to each natural health product approved to be marketed under the NHPR. The Drug Identification Number for Homeopathic Medicines (DIN-HM) is an eight (8) digit numerical code assigned to each homeopathic medicine approved to be marketed under the NHPR.

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

- if the ingredient is a vitamin, the name for that vitamin set out in item 3 of Schedule 1;
- if the ingredient is a plant or a plant material, an alga, a bacterium, a fungus, a non-human animal material or a probiotic, the Latin nomenclature of its genus and, if any, its specific epithet; and
- if the ingredient is other than one described in paragraphs (a) or (b), the chemical name of the ingredient.

Acceptable proper names are listed in the NHPID.

***Quantity***
The amount of medicinal ingredient(s) per dosage unit. This should be expressed as a concentration (e.g. %) for non-discrete dosage forms.

***Quantity crude equivalent***
The amount of crude ingredient used in an extract, expressed per dosage unit.

***Potency***
The amount per dosage unit of the standardized component that further characterizes the quantity of the ingredient. Potency may reflect the active constituent, a marker compound or the "activity" of the medicinal ingredient.

***Recommended conditions of use***
As defined in section 1(1) of the Natural Health Products Regulations, 'conditions of use' or 'recommended conditions of use' for a natural health product include:

- its recommended use or purpose;
- its dosage form;
- its recommended route of administration;
- its recommended dose;
- its recommended duration of use, if any; and
- its risk information, including any cautions, warnings, contraindications or known adverse reactions associated with its use.

***Recommended use or purpose (or 'health claim' or 'claim')***
A statement that indicates the intended beneficial effect of an NHP when used according to the recommended dose, duration of use and route of administration listed on the label.

***Regulatory decision***
The assessment of a product licence application, including post-licensing applications resulting in the issuance of a product licence or notice of refusal.

***Risk information***
Any cautions and warnings, adverse reactions and contraindications associated with the use of the NHP.

***Route of administration***
The method by which the NHP is to be delivered to the body. Routes of administration include, but are not limited to oral, buccal, dental, nasal and topical.

***Safety***
The ability for a natural health product to produce a beneficial health outcome, outweighing the risk associated with using it, in humans, according to the recommended conditions of use.

***Senior official***
The principal contact person for the licensee/applicant, to whom regulatory mail is sent. This is not the contact person for product application-specific questions, but the person who will represent the company. This should be a senior person in the company such as a Chief Executive Officer or director. In some cases, especially small businesses, one person may be indicated as both the senior official and contact for this application. A single senior official must always be designated for the applicant company. If the senior official of the applicant company changes, the NNHPD must be notified of this change.

***Site***
A place of or for an activity specified under the NHPR.

***Source material***
The substance from which the medicinal ingredient as defined in Schedule 1 of the NHPR was prepared or derived. There may be multiple sources for a medicinal ingredient.

***Specifications***
A description of an NHP that contains the information described in section 44(2) of the NHPR.

***Submission coordinator***
The Regulatory Project Officer assigned to coordinate a product licence application through the assessment process. In order to contact the Submission Coordinator, applicants should send an email to hc.nnhpd_dpsnso.sc@hc-sc.gc.ca.

***Submission number***
The six-digit processing number assigned to an individual application, including post-licensing applications. The submission number should be referenced in all correspondence and enquiries referring to the product application.

***Sub-population group***
The group to which the NHP is targeted (may be more than one) that may require different dosing from the standard. For example, most NHPs are for adults, but seniors or children may take them at different doses.

***Traditional Application***
An application type use on the ePLA form for products categorized as a traditional medicine (See Traditional Medicine).

***Traditional medicine***
The sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or

treatment of physical and mental illness. Traditional medicine has a long history (at least 50 consecutive years) of use.

***Withdrawal***
An action taken by the applicant to remove an application from the application review process.

# Acronyms

ANF - Amendments and Notification Form

DIN-HM - Drug Identification Number-Homeopathic Medicine

DPA - Designated Party Authorization

ePLA - electronic Product Licence Application

IRNs - Information Request Notices

LNHPD - Licensed Natural Health Products Database

MAP – Management of Application Policy

MF - Master File

MIs - Medical Ingredients

NAF - Notice of Audit Failure

NHPID - Natural Health Products Ingredients Database

NHPR - Natural Health Products Regulations

NHPs - Natural Health Products

NMIs - Non Medical Ingredients

NNHPD - Natural and Non-prescription Health Products Directorate

NPN - Natural Product Number

PDL - Prescription Drug List

PL - Product Licence

PLA - Product Licence Application

RSS - Really Simple Syndication

TCMI - Traditional Chinese Medicine Ingredient

TCM -Traditional Chinese Medicine