NHPD Monthly Communiqué

Natural Health Products Directorate | Vol. 2, Issue 4 - December 2006

The *NHPD Monthly Communiqué* is a publication of Health Canada's Natural Health Products Directorate (NHPD), the federal department responsible for the regulation of natural health products sold in Canada. The communiqué is released to the Canadian public the first week of each month via the NHPD's electronic bulletin. Subscription to this *e*-bulletin is available at **www.hc-sc.gc.ca/dhp-mps/prodnatur/activit/education/list/index_e.html**.

Questions or comments regarding the content of the NHPD Monthly Communiqué may be addressed to **NHPD_DPSN@hc-sc.gc.ca**.

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PRODUCT LICENSING INFORMATION:

New and Revised Natural Health Product Monographs

Recognizing the important role monographs can play both in facilitating the review and processing of product licence applications and as reliable sources of product information for consumers, the NHPD is committed to developing new monographs as well as revising and updating existing monographs to reflect new research and evidence.

Revised Single Ingredient Monographs

Revisions have recently been made to the monographs for **Feverfew**, **Melatonin** and **Vitamin A**. The revised versions are currently available on-line in the *Compendium of Monographs* along with their previous versions, which have been archived for comparison purposes.

- **Revised Feverfew Monograph :** http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_feverfew-camomille_e.html
- **Revised Melatonin Monograph :** http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_melatonin_e.html
- **Revised Vitamin A Monograph :** http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_vitamin_a_e.html

Note that the modifications made to the revised monographs for **Feverfew** and **Vitamin A** do not significantly impact the safety or efficacy of products previously authorized for sale under the old monographs. As such, no immediate action is required on the part of licensees. Adopting these changes by way of an amendment or notification is left to the discretion of the licensee.

With respect to the revised **Melatonin** monograph, the revisions made to this monograph have an impact on the safety of products previously authorized for sale under the old monograph. Licensees of melatonin natural health products have been identified and notices are being sent to them detailing what actions are required to mitigate the safety concerns and when they must be completed.

New Single Ingredient Monographs

- **Beta- Carotene Monograph :** http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_beta-carotene_e.html

New Product Monographs

The NHPD has recently completed two product category monographs for **Carbon Dioxide-Releasing Laxatives** and **Hyperosmotic Laxatives**. Product monographs, as opposed to single ingredient NHP monographs, provide detailed information and guidelines for a wide range of products falling within a specific product category. Individuals and companies seeking approval to market these types of products may now attest to one of these monographs in their product licence applications. Those applications satisfying the criteria listed in the monograph will be processed within sixty (60) days.

- **Carbon Dioxide-Releasing Laxatives Product Monograph :** http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_laxa_carbon_dioxide_e.html

- **Hyperosmotic Laxatives Product Monograph :** http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_laxa_hyperosmo_e.html

Additional Guidance on Evidence for Quality of Finished Natural Health Products

Tests and requirements other than those listed in the current *Evidence for Quality of Finished Natural Health Products guidance document* may be needed in specific situations or as warranted by additional product quality requirements. These tests may be applicable on a case-by-case basis and should be conducted when necessary to ensure the quality of products. The procedures used to conduct such tests should be pharmacopoeial, if possible, or otherwise conform to other recognized testing methods such as AOAC guidelines. Based on the valuable experience gained by assessing several thousand product licence applications for a wide variety of products, the following specific tests and criteria for finished natural health products are considered necessary under the circumstances described below.

Specific Tests and Criteria for Finished Products

1. **Antimicrobial Preservative Effectiveness Testing:**

   Antimicrobial preservatives are ingredients added to dosage forms to reduce the initial microbial load or to prevent the proliferation of microorganisms already present in the product and also to protect the products from microbiological contamination that may be introduced either:

   - Inadvertently during or subsequent to the manufacturing of the finished dosage form, or
   - From repeatedly withdrawing individual doses.

   Where antimicrobial preservatives are added to a product, applicants are required to conduct tests demonstrating that the effectiveness of antimicrobial protection is performed on the product. Test methods used and acceptance criteria should be as specified in an acceptable Pharmacopoeia (e.g. current USP <51>; Ph.Eur. 5.1.3), and should be performed on the final dosage form with suitable limits included. This test should be performed at the end of the shelf life.

   The concentration of the preservatives shown to be effective in the final dosage form should be below a level that may be toxic to human beings, and should be at the lowest concentration necessary to preserve the product.

2. **Oxidative stability of oils (fish and seal oils):**

   Testing should be done according to AOAC and/or Pharmacopoeial analytical methods for peroxide, anisidine, and totox values of fish/seal oils or omega-3 fatty acids derived from the fish oils to ensure their oxidative stability. The following limits should be applied:

Item	NHPD tolerance limits
Peroxide value (PV)	5meq/kg
Anisidine value (AV)	<20
Totox Value	≤ 26 (calculated as (2 x PV) + AV)

   This requirement is applicable to all oils that have a high degree of unsaturation to ensure stability.

3. **Contaminants in oils (fish):**

   Specifications should include test methods and tolerance limits for polychlorinated dibenzo-para-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), and pesticides. Testing should be performed using appropriate analytical methods. Applicants are advised to consult the Council for Responsible Nutrition's (CRN) monograph on fish oils, referred to as the *CNR Omega-3 Voluntary Monograph* (http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf).

Minor Corrections to the current Evidence for Quality of Finished Natural Health Products guidance document:

1. **Aflatoxin tolerance limits:**

   The NHPD has noticed that the tolerance limit was erroneously reported as 0.20 µg/kg of substance [20 ppt] in Table 2, Appendix 2 of the current *Evidence for Quality of Finished Product* guidance document. The correct tolerance limit should be **20** µg/kg of substance [20**ppb**].

2. **Testing for Mycotoxins**

   Testing for mycotoxins is required where fungal contamination is known to occur. As an example, aflatoxin testing is required for nuts and ginseng. Other products where mycotoxin testing may be required are Evening Primrose Oil, Sugar cane and sugar beets, cottonseed and Corn derived products. The need for mycotoxin testing will be evaluated on a case-by-case basis during the quality assessment. Justification will be requested if a product has documented cases of fungal contamination.

3. **Antibiotic residues in Honey and Royal jelly**

   Since chloroaminophenicol and 5-nitrofuran are banned substances in honey products according to section C.01.610.1 of the *Food and Drugs Act and Regulations*, natural health products cannot contain any of these two antibiotics. Applicants of products containing Honey and Royal jelly must provide a test for the detection of 5-nitrofuran and chloroaminophenicol. Alternatively a justification for why the testing is not required may be submitted.

4. **Toxic metal Chromium testing:**

   Specific testing and tolerance limits for the toxic metal Chromium (VI) are no longer required by the NHPD.

5. **Homeopathic Finished Products**

   Certain test requirements are not applicable to homeopathic medicines (HMs) which have a higher dilution than 1C, e.g., chemical purity tests, such as heavy metals and pesticides. These tests need not be included in the finished product specifications for HMs. Applicants of homeopathic medicines should refer to Chapter 9.0 of the *Evidence for Homeopathic Medicines guidance document (Version 2.0 – November 2006)* for details on the quality specifications and requirements for homeopathic medicines.

6. **Inaccurate summarization of data**

   Information provided on the specifications, label and product licence application must be uniform and relevant. Applicants must ensure that the information provided is accurate. Contradictory information

results in confusion and may delay the assessment process. If any discrepancies are noted, the manufacturer's finished product specifications will be regarded as the reference document for assessment purposes.

Update on Beta-Carotene

Beta-carotene as a medicinal ingredient

The NHPD has received a number of requests that beta-carotene be permitted as a medicinal ingredient (MI) on product labels. As a result of the NHPD's assessment of the scientific evidence, the decision has been made to allow applicants to list beta-carotene as a MI. When listed on the label as a MI, beta-carotene must be cited in terms of quantity of beta-carotene and retinol activity equivalents (RAE) in the "Quantity per dosage unit" column (column 77) of Part 4 – Medicinal Ingredients of the PLA Form and the product label. The rationale for this quantity requirement is that beta-carotene is a source of vitamin A, and listing RAE gives consumers opportunity to compare vitamin A quantity between products.

Beta-carotene to vitamin A conversion factor

In the October 2005 and February 2006 issues of the *NHPD Monthly Communiqué*, vitamin A conversion factors were explained. Since the publication of these communiqués, the conversion factor for the ratio of beta-carotene to vitamin A activity has been modified from 1:1 to 2:1 based on the most recent *Dietary Reference Intakes* (2006). This 2:1 ratio translates to an upper limit of 20,000 IU of beta-carotene being equivalent to 10,000 IU of vitamin A.

Applicants should note that natural health products providing daily doses of vitamin A greater than 10,000 IU require a prescription in Canada (as per Schedule F of the *Food and Drug Regulations*). Given that natural health products must be suitable for self-care, the NHPD will not grant product licences to natural health products providing more than 20,000 IU of beta-carotene per day (the equivalent of 10,000 IU of vitamin A).

Clarification with regards Evidence for Non-Traditional Product Licence Applications (NHPD Monthly Communiqué Volume 2. Issue 2 - October, 2006)

In the October 2006 issue of the *NHPD Monthly Communiqué*, the article titled "*Inappropriate and Insufficient Evidence for Non-Traditional Product Licence Applications*" provided detailed instructions on the evidential requirements for non-traditional product licence applications. In this article, the NHPD provided misleading information regarding the literature search strategy and the non-acceptance of in vitro and animal studies as evidence to support safety and efficacy. The NHPD would like to apologize for the confusion this has caused and will take this opportunity to provide clarification and outline the intent of the text in the Communiqué.

Literature Search Strategy No Longer Required

Chapter 4 of the current *Evidence for Safety and Efficacy of Finished Natural Health Products guidance document* instructs product licence applicants to include a literature search strategy in the summary report accompanying their product licence submissions. The NHPD has since revisited this requirement and applicants should note that they are no longer required to submit a literature search strategy. Applications without a literature search strategy will not be considered deficient. The intent of the search strategy was to provide a guideline to applicants on how to search for safety and efficacy information.

With regards to the statement "The NHPD will not accept in vitro or animal studies to support efficacy"

The intent of this October 2006 NHPD Monthly Communiqué was to inform applicants to submit appropriate evidence to support a claim. This is a deficiency that has been found in many applications received thus far. While animal and in vitro studies can provide plausible explanations of how a medicinal ingredient will work, they are not sufficient evidence on their own to support effectiveness in humans.

If human studies are available, only the human safety and efficacy information needs to be provided in the Evidence Summary Report and Safety Summary Report. Chapter 1.2 - Totality of Evidence of the current *Evidence for Safety and Efficacy of Finished Natural Health Products guidance document* notes that "When experience with human use provides sufficient evidence to support safety and efficacy, other studies involving animals or in vitro studies may not be necessary". Evidence must come from human use; animal or in vitro experimental evidence may be considered as additional, supporting information but cannot be the basis for approval of an application.

Common Deficiencies at the Product Licensing Assessment Level (Level 3)

The following table lists a number common deficiencies encountered by the NHPD at the assessment level of the product licence application review process and how applicants can address/avoid these deficiencies. These errors, though they may seem minor in some cases, can lead to major time delays and can be easily avoided if applicants take the time to properly prepare and review their applications before submitting them to the NHPD.

Deficiency	How to address the deficiency
Applicants consistently do not submit adequate evidence (copies of full-text scientific articles) to support the safety and efficacy of the medicinal ingredient(s) at the recommended conditions of use.	*Provide evidence to support the safety and/or efficacy of the medicinal ingredient in humans/adults/children according to the recommended conditions of use (i.e. daily dose). The evidence must be in the form of full-text scientific articles.* Information resources for applicants: *NHPD Monthly Communiqué – October 2006: Evidence for Non-Traditional PLAs.* **NOTE** clarification on this article provided in this issue of the NHPD Monthly Communiqué under the article "Clarification with regards Evidence for Non-Traditional Product Licence Applications (NHPD Monthly Communiqué Volume 2. Issue 2 - October, 2006)." *NHPD Monthly Communiqué – November 2006: Evidence for Traditional PLAs.* *Evidence for Safety and Efficacy of Finished Natural Health Products guidance document.*

Duration of use is often not indicated on the Product Licence Application but it is evident that one is required from the evidence provided.	*If there are safety concerns with using the product for an extended period of time, duration of use must be indicated.* *Duration of use is the time frame within which a natural health product can be consumed safely for its intended use or purpose. For example, if there are safety concerns with the use of the ingredient for longer than 4 months, applicants must add the statement "Consult a health care practitioner for use beyond 4 months" to the Product Licence Application form and label.*
The term "health care provider/professional" is often indicated on the Product Licence Application form and label.	*Replace the term "health care provider/professional" with "**health care practitioner**" in all instances where it appears on the Product Licence Application form and label.*
Applicants often submit insufficient evidence to warrant not including the statement "Do not use if pregnant or breastfeeding" on the Product Licence Application form and label.	*Applicants may chose one of the following two options:* 1. *Add the risk statement to the application form and label and do not provide additional evidence **OR*** 2. *Submit adequate evidence that establishes the product's safe use during pregnancy and breastfeeding.*
The proposed label text often does not meet NHPD labelling requirements or is not consistent with the information provided on the Product Licence Application form.	*Ensure the proposed label text includes all relevant information and that it is consistent with what was provided in the Product Licence Application form. Review Part 5, Section 87-97 of the* Natural Health Products Regulations *or the Labelling guidance document* for further information.

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SITE LICENSING INFORMATION:

No new information to report this month.

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COMPLIANCE CORNER:

No new information to report this month.

To learn more about Health Canada's compliance approach for natural health products, please refer to the *Compliance Policy for Natural Health Products*. You may also wish to read the December 2005 issue of the *NHPD Monthly Communiqué*.

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CLINICAL TRIAL INFORMATION:

No new information to report this month.

To learn more about clinical trials for natural health products, please refer to the following guidance document: *Clinical Trials for Natural Health Products*.

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POLICY AND REGULATORY AFFAIRS:

No new information to report this month.

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RESEARCH INFORMATION:

No new information to report this month.

Learn more about the *Natural Health Products Research Program*.

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OTHER INFORMATION:

Applicants Encouraged to Withdraw Non-Active Submissions

Applicants are encouraged to inform the NHPD of any inactive submissions which should be withdrawn from the submission review process so that the NHPD can focus on active submissions. Upon receipt of this request from the senior official or designated party, the NHPD will issue a "Notice of Withdrawal by Applicant". Requests to withdraw submissions at any level of review should be directed to the address below. The cover letter should clearly state the submission number, company code and that the submission(s) are being withdrawn.

Submission Management Division
Natural Health Products Directorate
2936 Baseline Road, Qualicum Tower A
AL 3302B
Ottawa, Ontario
K1A 0K9 (Couriers: K2H 1B3)

Fax: 613-954-2877

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Submitting New Licence Applications or Responses sent by Courier

The NHPD on a daily basis receives a number of new licence applications, responses to Processing Deficiency Notices (DPN), and responses to Information Request Notices (IRNs) by courier. New applications and responses sent by courier should be sent to the following address:

Health Canada
Health Products and Food Branch
Natural Health Products Directorate
Bureau of Product Review and Assessment
Submission Management Division
Basement, Qualicum, Tower A
2936 Baseline Road
AL 3300C
Ottawa, Ontario
K2H 1B3

If the incorrect postal code is used, the submission or response is directed elsewhere within Health Canada prior to be being received by the Natural Health Products Directorate that can cause delays or, in rare occasions, items can get lost in transit between Health Canada's central mail room and the NHPD's offices. As per the March 2006 Communiqué, the NHPD strongly encourages all applicants to submit applications and replies to deficiency/information requests by courier. Replies to deficiency/information requests should also be sent to the attention of the applicable Processor or Submission Coordinator as identified on the Acknowledgment Letter, Processing Deficiency Notice, or Information Request Notice.

Submitting Unsolicited Information at the Assessment Level (Level 3)

At this time, unsolicited information is accepted by the NHPD at the processing and screening levels (levels 1 and 2) of the four-level review process. **However, unsolicited information submitted at the assessment level (Level 3) is not acceptable if the assessment has begun.** Please note that changes that require an amendment or notification can be made once a license is received for the application. For further information regarding Amendments and Notifications, refer to Chapter 6 of the *Product Licensing guidance document*.

Due to the large number of applications now residing in queue at the assessment level, applicants are encouraged to contact their Submission Coordinator prior to submitting an unsolicited change to determine whether the change will be accepted at this stage of the review. Applicants who are not certain who the Submission Coordinator is for their application may contact the NHPD's general inquiries line at **1-888-774-5555** or send an e-mail to **NHPD_DPSN@hc-sc.gc.ca** to obtain the name and telephone number of their Submission Coordinator.

Responses to Information Request Notices

When responding to an Information Request Notice (IRN), applicants should note that only those pages (i.e. - the Product Licence Application form, the label, and the finished product specifications) that have been changed as a result of the request should be provided in the response package. Providing additional copies of pages already on file, which do not require correction or clarification, can delay the processing of an Information Request Notice response.

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Applicants to Refrain from Sending Faxes Greater Than 30 Pages in Length

The NHPD receives a large number of faxes in response to information requests on a daily basis, some of which are in excess of 80 pages. Extremely long faxes cause congestion and compromise the reliability of faxes being received in their entirety, thus increasing the time required to process the information submitted. As per the August 2006 issue of the NHPD Monthly Communiqué, the NHPD strongly encourages all applicants to submit responses to information requests by courier or mail when the response is greater than 30 pages in length.

Applicants should note that more than one response per Processing Deficiency Notice (PDN) or Information Request Notice (IRN) will not be accepted. Therefore, a response consisting of 30 or more pages should be sent by courier rather than multiple faxes.

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