Health Canada Santé Canada

Natural Health Products

DIRECTORATE

Product Licensing – A Step by Step Guide

Canada

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Our mission is to help the people of Canada maintain and improve their health.
Health Canada

Également offert en français sous le titre :
Licence d'exploitation – Un guide étape par étape

This publication is also available on the Internet at the following address: www.healthcanada.ca/nhpd

This publication can also be made available in alternate format(s) upon request.

Cat. H44-78/2004E
ISBN 0-662-38528-6

Introduction

Product Licensing: A Step-by-Step Guide provides guidance and advice on the process of licensing of natural health products in accordance with the *Natural Health Products Regulations.*

To help you understand and facilitate your submission preparation, there are two sample submissions:

- an application for a single ingredient product with a traditional claim and
- an application for a combination product with a non-traditional claim.

Examples of all the stages of the process are outlined to provide better understanding of the requirements and the process.

All natural health products that are marketed in Canada are subject to the *Food and Drugs Act.*

The regulatory requirements specific to natural health products are outlined in the *Natural Health Products Regulations*. The Regulations came into force on January 1, 2004.

For further information refer to:

- *Product Licence Guidance Document*
- *Evidence for Quality of Natural Health Products Guidance Document*
- *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document*
- *Compendium of Monographs*

All guidance documents may be found at: www.healthcanada.ca/nhpd

Overview

Licensing

The *Natural Health Products Regulations* require individuals to obtain a **product licence** before they can sell a natural health product in Canada. [*Natural Health Products Regulations*: Section 4].

To obtain a product license, individuals must submit a **product licence application** to the Natural Health Products Directorate (NHPD). The application must include sufficient data to allow NHPD to evaluate the safety, efficacy and quality of the natural health product when used under the recommended conditions of use.

Product Licence

A product licence is a document that sets out the specific product characteristics that the Natural Health Products Directorate (NHPD) has authorized for sale for the natural health product, such as its brand name or names, recommended dose, dosage form, recommended route of administration, source, the use or purpose, quantity, and, when applicable, potency of the medicinal ingredients, as well as the product number.

[*Product Licence Guidance Document*, page 4]

Product Licence Applications and Requirements

All natural health products must receive valid market authorization by the Natural Health Products Directorate (NHPD) before they can be sold in Canada. Product market authorization requires one of the following:

- reference and adherence to a natural health product monograph (published by the NHPD);
- submission of evidence of safety, efficacy, and quality of the finished product; or
- reference to one of the homeopathic pharmacopoeias listed in the Evidence for Homeopathic Medicines Guidance Document, if applicable.

There are six types of applications that may be made for a product licence which require different types of evidence are:

1. Compendial
2. Traditional Claim
3. Non-traditional Claim
4. Homeopathic
5. Transitional DIN Product
6. TPD Labelling Standard and/or Category IV Monograph

Applicants who wish to submit one set of evidence for multi product licence applications (e.g. for multiple dosage forms) may do so by submitting separate product licence applications with cross reference to the package data of the respective one.

If multiple applications are submitted together, they will be reviewed at the same time, but separate product licenses will be issued. (e.g. one licence for each dosage form). If one application is submitted after another, the applicant may cross reference the data of the previously submitted (reference) application. For the latter case, both the submission and file numbers of the reference application must be clearly stated in Part 2 E of the subsequent product licence application form.

EVIDENCE REQUIREMENTS

REQUIREMENTS	APPLICATION TYPE						
	Traditional	Non-Traditional	Homeopathic		Compendial (NHPD Monograph)	TPD Labeling Standard (LS) or Cat. IV monograph	Transitional
			specific claim	non-specific claim			
Product Licence Application Form	✔	✔	✔	✔	✔	✔	✔
Label Text	✔	✔	✔	✔	✔	✔	**Most recent version of approved label**
Evidence Summary Report	✔	✔	**NA**	**NA**	**NA**	**NA**	**NA**
References	A	B	C, D	D	E	F	
Safety Summary Report	✔	✔	**NA**	**NA**	**NA**	**NA**	**NA**
Animal Tissue Form (if applicable)	✔	✔	✔	✔	✔	✔	✔
Quality Summary Report (Finished Product Specifications)	✔	✔	✔	✔	**NA**	✔	✔

A Minimum of two traditional references (e.g., text books). Please photocopy the relevant pages, incl. cover page.

B Minimum of two pieces of evidence to support product (e.g., clinical trial) Please note that abstracts will not be accepted as key references; however they may be included as part of evidence.

C Minimum of two homeopathic references per medicinal ingredient, to support the claim

D One reference to acceptable homeopathic pharmacopoeia per medicinal ingredient

E Reference to NHPD Monograph from the Compendium of Monographs

F Reference to TPD Labeling Standards or Cat. IV monograph in a cover letter

Templates for Safety Summary Report and Evidence Summary Report can be downloaded from:

http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/templates_e.html

Applications, and General Submission

How to Submit an Application and Related Correspondence

NHPD requires submission packages for each application.

Please submit your application and all related correspondence**,** including responses to notices sent by the NHPD, should be addressed to the Submission Management Division:

Mail:

Health Canada
Health Products and Food Branch
Natural Health Products Directorate
Bureau of Product Review and Assessment
Submission Management Division
Qualicum, Tower A
2936 Baseline Rd.
AL 3302B
Ottawa, ON K1A 0K9 **Couriers:** K2H 1B3

Upon receipt of your material, the Submission Management Division will send out an acknowledgement letter by mail. This letter will state the submission and file numbers assigned to your application. These numbers should be referenced in all submission related correspondence.

If you intend to submit a binder, please ensure that the following information is included in your binder spine:

- Name of the applicant
- Proposed primary brand name of the product
- Volume number, e.g., vol. 1 of 3
- Date of submission

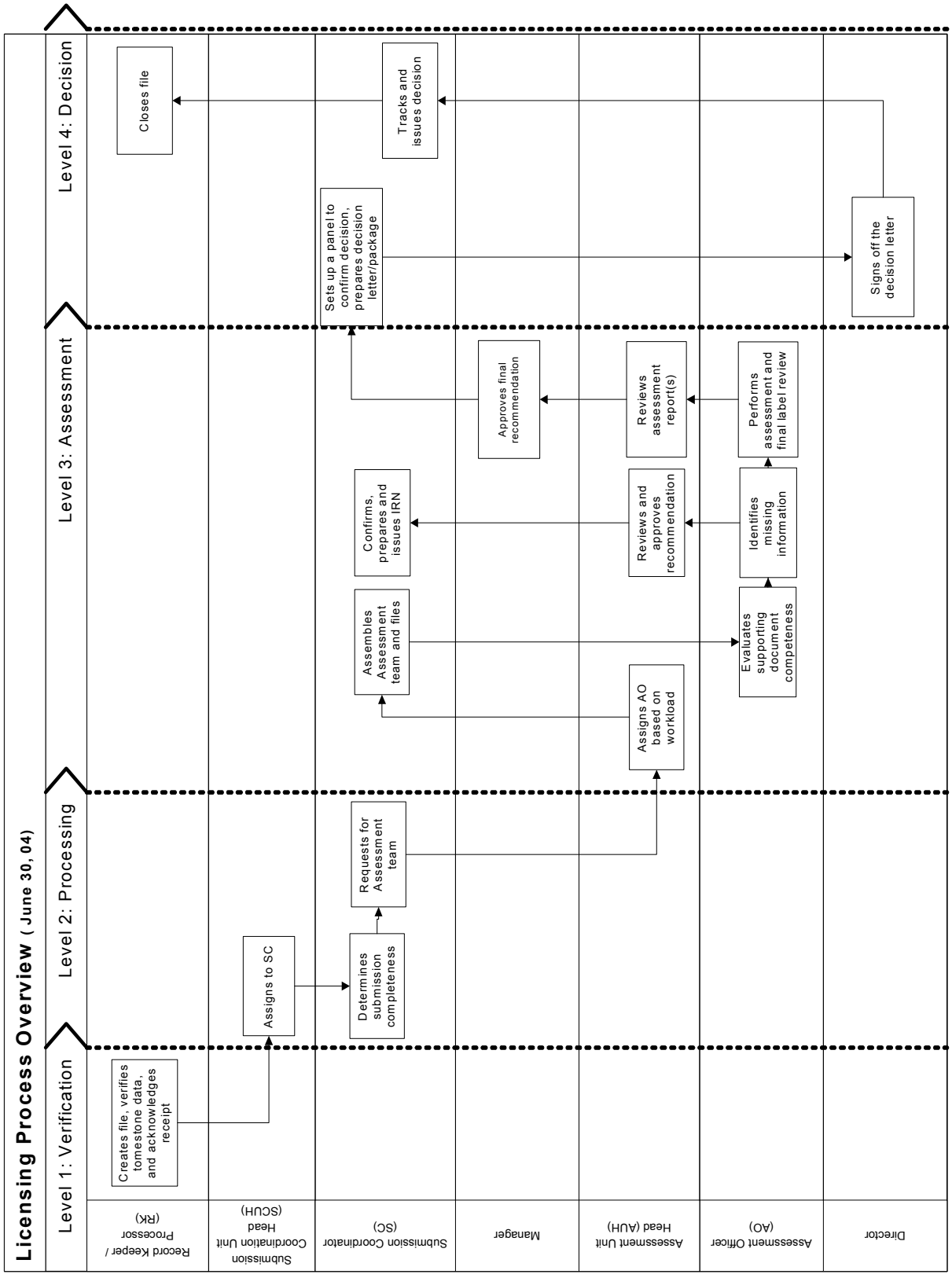
How to Submit a General Submission Inquiry

Any **inquiries** relating to submission process, requirements and/or requests for product licence applications, may be submitted by mail to the address listed above, or by e-mail or fax.

Email: submission_info@hc-sc.gc.ca
Fax: (613) 954-2877

Licensing Process

Overview



Notes:

Notes:

A. Submission Management for Non-Traditional Product Application

The Natural Health Products Directorate developed the submission management process to provide efficient, effective, and consistent service to product licence applicants.

The processes described pertain to submissions for product licences, including fundamental changes, and applications for changes to existing product licences, such as amendments and notifications.

Level 1: Verification

- NHPD verifies parts 1, 2, and 5 of the **application form** it receives for the company and contact information, and gives each application a file number (for new applications) and submission number.
- NHPD sends out an **acknowledgement notice** confirming receipt of the application. The letter lists the **company code**, **file number** and **submission number**, and notes the **date of receipt**.
- Applicants should use the file number assigned on all subsequent correspondence about the particular application.
- If NHPD notices deficiencies in the company information, these will be outlined in the acknowledgement notice. See Appendix 2 for examples of most common deficiencies at this level.
- Applicants must respond to this acknowledgement notice within 15 calendar days of the date of issue.
- If no response is received, NHPD considers the application to be withdrawn and sends a notice of withdrawal to the applicant. Applicants may re-submit withdrawn applications at a later date.

Notes:

Samples of Level 1 Submission Documentation

1. Cover Letter
2. Completed Parts 1, 2, and 5 of the Product Licence Application Form
3. Submission Receipt Acknowledgement
4. Response to the Acknowledgement Notice

Sample 1: Cover Letter

October 18, 2004

Submission Management Division
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, Ont
K1A 0K9, AL 3300C

Dear Submission Management Division:

Re: Cold Remedy

Please find enclosed two copies of our PLA and evidence for the above mentioned product.

Yours truly,

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Sample 2: Completed Parts 1, 2, and 5 of the Product Licence Application Form

Health Canada / Santé Canada

PRODUCT LICENCE APPLICATION FORM
Natural Health Products Directorate

Protected when completed

HC USE ONLY		Date/Time of Receipt
Submission Number	File Number	

Please refer to the Guide for instructions on how to complete this application. **Please Print Clearly** * - denotes Mandatory

PART 1
APPLICANT AND CONTACT INFORMATION

A. — APPLICANT OR LICENSEE (This will be the product licence holder)

Applicant/Company Name *	Company Code (If known)
Herbal Inc	

Address
Street/Suite/Land Location * 123 St Joseph Blvd.

City - Town *	Province - State *	Country *	Postal/ZIP Code *
Ottawa	Ontario	Canada	K1E 2V2

B. — CONTACT(S)

Name	Title *	Language preferred:
[X] Mr. [ ] Ms. [ ] Dr. Surname * Xu Given Name * Gus	President	[X] English [ ] French

Company Name (* if different from Applicant/Licensee)

Address same as Applicant/Licensee [X]

Street/Suite/Land Location *

City - Town *	Province - State *	Country *	Postal/ZIP Code *

Telephone No. *	Ext.	Fax No.	E-mail
613-834-1574		613-834-1575	gus@herbal.com

Contact Type *
[X] Senior Official
[ ] Contact for this Application
[ ] Representative in Canada

Name	Title *	Language preferred:
[ ] Mr. [X] Ms. [ ] Dr. Surname * Smith Given Name * Lesley	Regulatory Affairs	[X] English [ ] French

Company Name (* if different from Applicant/Licensee)

Address same as Applicant/Licensee [X]

Street/Suite/Land Location *

City - Town *	Province - State *	Country *	Postal/ZIP Code *

Telephone No. *	Ext.	Fax No.	E-mail
613-834-1577		613-834-1575	lesley@herbal.com

Contact Type *
[ ] Senior Official
[X] Contact for this Application
[ ] Representative in Canada

Name	Title *	Language preferred:
[ ] Mr. [ ] Ms. [ ] Dr. Surname * Given Name *		[ ] English [ ] French

Company Name (* if different from Applicant/Licensee)

Address same as Applicant/Licensee [ ]

Street/Suite/Land Location *

City - Town *	Province - State *	Country *	Postal/ZIP Code *

Telephone No. *	Ext.	Fax No.	E-mail

Contact Type *
[ ] Senior Official
[ ] Contact for this Application
[ ] Representative in Canada

HC/SC 9267E (12-2003) **AUSSI DISPONIBLE EN FRANÇAIS** Canada

Sample 2: Completed Parts 1, 2, and 5 of the Product Licence Application Form

PART 2
SUBMISSION TYPE

A. – PRODUCT LICENCE APPLICATION

Indicate the type of application (*select one only)

☐ Compendial ☐ Traditional claim ☒ Non-traditional claim ☐ Homeopathic ☐ Transitional DIN DIN # _____

NPN/DIN-HM # _____ (* – required for Section **B.** and **C.** only).

B. – PRODUCT LICENCE – AMENDMENT

Indicate the affected change to the NPN/DIN-HM above. (select one or more)

- ☐ Potency
- ☐ Source material of any of its medicinal ingredients
- ☐ Addition or substitution of a non-medicinal ingredient not on the NHPD List of Acceptable non medicinal ingredients
- ☐ Specification
- ☐ Deletion or modification of risk information on any labels
- ☐ Recommended dose
- ☐ Change to Animal Tissue Form(s)
- ☐ Recommended use/purpose
- ☐ Change to or from synthetically manufactured
- ☐ Recommended duration of use
- ☐ Change to manufacturing information

C. – PRODUCT LICENCE – NOTIFICATION

Indicate the type of change(s) that have been made to the NPN/DIN-HM above. (select one or more)

- ☐ Addition or substitution of any of its proposed non medicinal ingredient other than those originally authorized for the product.
- ☐ Change to the common name of any of its medicinal ingredients
- ☐ Addition of risk info on any of its labels
- ☐ Sale under a brand name other than the one(s) originally authorized for the product license
- ☐ Change to the proper name of any of its medicinal ingredients

D. – SUBMISSION CONTENT

Type of supporting documents, by volume: check type that is applicable and indicate the volume in which the document is submitted.

Number of Volumes: _____ Volume #

- ☒ **Product licence application form**
- ☐ Additional pages for Product information: #: _____
- ☐ Additional pages for Site information: #: _____
- ☐ Animal tissue form(s) #: _____ _____
- ☐ Third Party Authorization form: _____
- ☒ Label text #: _____ _____
- ☒ Evidence Summary Report: _____
- ☒ Safety Summary Report: _____
- ☒ Quality Summary Report: _____
- ☐ Other, Claim evidence: _____

E. – REFERENCE SUBMISSION

Other submission that contains the evidence to support the safety, efficacy and/or quality of this particular submission.

Submission #: _____

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Sample 2: Completed Parts 1, 2, and 5 of the Product Licence Application Form

ATTESTATION

"I attest that the natural health product that is the subject of this product license application will be manufactured, packaged, labelled, distributed and stored:

a) if the natural health product is imported, in accordance with the 'Good Manufacturing Practices' requirements as set out in Part 3 of the Natural Health Products Regulations or in accordance with requirements that are equivalent to those set out in Part 3, or

b) if the natural health product is not imported, in accordance with the 'Good Manufacturing Practices' requirements set out in Part 3 of the Natural Health Products Regulations."

Name of Authorized Senior Official (print) *	Signature *	Date *
Bob Fielding	Bob Fieldina	2 0 0 4 1 0 0 5

Sample 3: Submission Receipt Acknowledgement

Company Code 12345
File # 987655
Submission # 987655

October 20, 2004

Ms. Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Dear Ms Lesley Smith:

Re: Application Product Licence Traditional Claim
Cold Remedy
Date Received by the Natural Health Product Directorate:
2004-10-15 11:55 AM
Natural Health Products Regulation Section: 5

The Natural Health Products Directorate (NHPD), Bureau of Product Review and Assessment (BPRA), thanks you for your submission. This Correspondence will serve as acknowledgement of receipt of your submission.

Upon review of this submission, it was noted that someone other than the Senior Official has affixed their signature to the Attestation on Page 6. Please resubmit the application form only with the original signature of the Senior Official on the Attestation. Please quote the submission number 987655 on all your correspondence. Upon receipt of the Senior Official's original signature, I will be able to release your application for further processing.

Alternatively, a Designated Third Party Authorization Form may be submitted. The form can be found at http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/forms_designated_party_authorization.pdf on the Health Canada website. Should the Senior Official choose to sign and submit a Designated Third Party Authorization form, please submit the form to my attention at the address below with an original signature on the Authorization form.

The adequacy of the data submitted to the NHPD has not been fully assessed at this time and will be determined during the assessment of the submission by the assessment units. As well, a need for data to address additional data gaps may be identified during the assessment. Consequently, further information may be requested by the NHPD by means of a processing deficiency notice (PDN) or an information request notice (IRN).

If you have any questions concerning this notice, please contact the submission processor at the below co-ordinates. Please note that the File Number and Submission Number (provided at the top right corner of the title page) must be quoted on all correspondence regarding this submission.

Yours truly,

John Doe
Processor
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
phone: 613-941-1000
fax: 613-954-2877

Sample 4: Response to the Acknowledgement Notice

Company Code 12345
File # 987655
Submission # 987655

October 20, 2004

Mr John Doe
Processor
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, Ont
K1A 0K9, AL 3300C

Dear Mr John Doe:

Re: Acknowledgment Notice 987655

Please find attached a revised copy of the PLA with an attached Designated Party Authorization Form.

Yours truly,

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd
Ottawa, Ontario
Canada
K1E 2V2

Sample 4: Response to the Acknowledgement Notice

Designated Party Authorization Form

Protected when completed

Note: Only submit this document with the application when the party signing the application is a designated party acting on behalf of the applicant or licensee according to paragraph 5(b) of the *Natural Health Products Regulations.*

I Gus Xu
(The Senior Official)

authorize Bob Fielding
(Third party person)

of Fielding Inc
(Third party company name)

to file a submission with the Natural Health Products Directorate on behalf of

Herbal Inc
(Applicant/Company name)

Signature *Gus Xu*

Print Name Gus Xu

Title President

Applicant/Company name Herbal Inc.

Date October 20th, 2004

Contact Information

Surname Fielding xMr. ❑Ms. ❑Dr.

Given Name Bob

Title Senior Consultant

Language preferred x English ❑French

Street/Suite/Land Location 45 New Hampshire Dr.

City - Town Ottawa

Province - State Ontario

Country Canada

Postal/ZIP Code K1X 2C2

Telephone No.(613) 882-5463 Ext._____

Fax No. (613) 882-5462

E-mail _____

Notes:

Level 2: Processing

- NHPD checks verified application forms for completeness and to ensure that the appropriate supporting information is submitted for the type of submission in an acceptable format.
- When deficiencies are identified, NHPD issues a **processing deficiency notice (PDN**), requesting the missing information or clarification related to the completeness of the application form and supporting information. See Appendix 2 for examples of most common deficiencies at this level.
- NHPD only sends this notice once for a particular piece of information and applicants should respond to all deficiencies at once in a single, consolidated response. More than one **response** per notice will not be accepted.
- Applicants have 30 calendar days from the date the notice is issued to respond.
- When there is no response within 30 days, or inadequate response, NHPD withdraws the application and sends a notice of withdrawal to the applicant. Applicants may re-submit withdrawn applications at a later date.

Notes:

Samples of Level 2 Submission Documentation

5. Parts 3 and 4 of the Product Licence Application Form and Label Text
6. Processing Deficiency Notice (PDN)
7. Response to the PDN
8. Level 3 In-Queue Fax

Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

PART 3
SITE INFORMATION

Company Name			☐ Manufacturer SL# ____
Number, Street - Suite - PO Box			☐ Packager SL# ____
City			☐ Labeller SL# ____
			☐ Importer SL# ____
Province - State	Postal Code - ZIP Code	Country	☐ Distributor
Company Name			☐ Manufacturer SL# ____
Number, Street - Suite - PO Box			☐ Packager SL# ____
City			☐ Labeller SL# ____
			☐ Importer SL# ____
Province - State	Postal Code - ZIP Code	Country	☐ Distributor
Company Name			☐ Manufacturer SL# ____
Number, Street - Suite - PO Box			☐ Packager SL# ____
City			☐ Labeller SL# ____
			☐ Importer SL# ____
Province - State	Postal Code - ZIP Code	Country	☐ Distributor
Company Name			☐ Manufacturer SL# ____
Number, Street - Suite - PO Box			☐ Packager SL# ____
City			☐ Labeller SL# ____
			☐ Importer SL# ____
Province - State	Postal Code - ZIP Code	Country	☐ Distributor
Company Name			☐ Manufacturer SL# ____
Number, Street - Suite - PO Box			☐ Packager SL# ____
City			☐ Labeller SL# ____
			☐ Importer SL# ____
Province - State	Postal Code - ZIP Code	Country	☐ Distributor

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Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

PART 4 - PRODUCT INFORMATION

Primary Brand Name *	Other(s) if any
Cold remedy	

Was animal tissue used in the processing of this product? ** ☐ Yes ☒ No

SECTION 1 — MEDICINAL INGREDIENT(S)

Ingredient No.	A Standard or Grade	B Compendial Monograph No.	C * Proper Name	D Common Name	E * Quantity	F * Synthetic		G ** Animal Tissue	
						Yes	No	Yes	No
1.			*Echinacea angustifolia*	Echinacea	375mg		X		X
2.			*Hydrastis canadensis*	Goldenseal	45mg		X		X
3.			Ascorbic acid		20mg	X			X
4.			Zinc		5mg		X		X
5.			2-Amino-4-carbamoylbutanoic acid	L - glutamine	10mg	X			X
6.			Rutin		50mg		X		X
7.									
8.									
9.				**Deficient**					
10.									
11.									
12.									

Ingredient No.	H Potency		I * Source (if more than one enter on new line)		J Extract (if applicable)		K Method of preparation
	Amount	Constituent	Proper Name	Material	Ratio	Quantity Dried Equivalent	
1.				root	4:1	1500mg	traditional
2.	3%	berberine		root			traditional
3.				Sodium ascorbate			
4.				Zinc gluconate			
5.							
6.			*Fagopyrum esculentum*	buckwheat			
7.							
8.							
9.							
10.							
11.							
12.							

Copy as necessary
* – denotes Mandatory
** – if yes complete Animal tissue Form

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Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

SECTION 2 — PROPOSED NON-MEDICINAL INGREDIENT(S)

Ingredient No.	Proper Name	Common Name *	Purpose *	Animal Tissue Used **	
				Yes	No
1.		Cellulose	Diluent		X
2.		Corn starch	Glidant		X
3.		polyethylene glycol	Lubricant		X
4.		Magnesium stearate	Lubricant		X
5.		Titanium dioxide	Coating agent		X
6.		Gelatin (vegetable source)	Capsule Shell		X
7.					
8.					
9.					
10.					
11.					
12.					

Ingredient No	Standard or Grade	Quantity	Source (if more than one enter on new line)	
			Proper Name	Material
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				

Copy this form as necessary
** – if yes complete Animal Tissue form

HC/SC 9267E (12-2003)

Page 5 of 6

Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

Proposed Label Text

Principal Display Panel:

Cold Remedy

Product Number 8XXXXXXX

90 capsules

Other Panels:

*Echinacea angustifolia (*Echinacea) (root extract; 4:1) ..... 375 mg

Hydrastis canadensis (Goldenseal) (root extract) ..... 45 mg

(Standardized to berberine 3 %)

Ascorbic Acid (Sodium ascorbate) (synthetic) ..... 20 mg

Zinc (Zinc gluconate) ..... 5 mg

L-glutamine (synthetic) ..... 10 mg

Rutin (buckwheat) ..... 50 mg

Non-medicinal ingredients :

Cellulose, gelatin (vegetable source) Corn starch, polyethylene glycol, magnesium stearate, titanium dioxide

Use: Acts as a supportive therapy in the treatment of colds. Finally a cure for the common cold! May be used up to 7 days.

Adults: Take 2 capsules daily with food

Consult a health care practitioner prior use if you have an autoimmune-mediated or inflammatory disease such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS or HIV infection, high blood pressure, kidney disease or are taking any prescription medication.

Do not use if you are pregnant or breastfeeding.

Do not use if you have an allergy to Asteraceae / Compositae (daisy) family.

Store at room temperature.

Herbal Inc., 123 St Joseph Blvd, Ottawa, Ontario, Canada, K1E 2V2

Lot # XXXX

Expiry Date XXXX

Sample 6: Processing Deficiency Notice (PDN)

Health Canada Santé Canada

Natural Health Products Directorate
2936 Rue Baseline Rd., Basement/Sous-Sol AL3300B
Ottawa, Ontario
K1A 0K9

Company Code: 12345
File: 987655
Submission: 987655

December 20, 2004

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd
Ottawa, Ontario
Canada
K1E 2V2

Dear Ms Lesley Smith

Re: Processing Deficiency Notice
Traditional Submission - Cold Remedy

This notice is in respect of your Submission 987655, file 987655.

The application form and attachments provided with this submission have been verified by the Bureau of Product Review and Assessment for completeness and were determined to be deficient. At this time, your application is considered incomplete as per section 5 of the *Natural Health Products Regulations*. In order for the processing of your application to be completed, please submit all the following information:

1. The proper name "ascorbic acid" on the Product Licence Application is incorrect. As per Chapter 2 of the Product Licensing Guidance document, when the ingredient is a vitamin the proper name is the name set out in item 3 of Schedule 1, such as vitamin C for Ascorbic Acid. Please revise and submit the revised application form or alternatively, confirm the proper name of the ingredient in the response.
2. The proper name "rutin" on the Product Licence Application is incorrect. As per Chapter 2 of the Product Licensing Guidance document, an unambiguous chemical name is required for any ingredient other than vitamin, plant or plant material, an alga, a fungus, a bacterium, a non-human animal material or a probiotic. Please revise and submit the revised application form or alternatively, confirm the proper name of the ingredient in the response.
3. A Sub-Population Group has not been specified for this product. As per Chapter 2 of the Product Licensing Guidance Document, the Sub-Population Group(s) that the Recommended Dose is intended for must be listed in the Product Licence Application. Please revise and submit the revised application form, or confirm the sub-population group in your response.

The NHPD will retain this submission on file for 30 calendar days to enable you to address all of the deficiencies. If a written response is inadequate or is not received by the NHPD within 30 days of the date of this letter, the submission will be withdrawn. Please remember that the response to the list of deficiencies must be submitted in one consolidated package with the signature of a contact person outlined in the application form. Please note that the File Number and Submission Number (provided at the top right corner of the title page) must be quoted on all correspondence regarding this submission.

The adequacy of the data submitted to the NHPD has not been fully assessed at this time and will be determined during assessment of the submission by the Assessment Division. At this time, further information may be requested as per section 15 of the *Natural Health Products Regulations*.

Should you have any questions concerning the deficiencies identified in this notice, please contact the submission co-ordinator, Jane Jones, at the coordinates below.

Yours truly,

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
Phone: 613-941-1002
Fax: 613-954-2877

Canada

Sample 7: Response to the PDN

Company Code 12345
File # 987655
Submission # 987655

January 5, 2005

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, Ont
K1A 0K9, AL 3300C

Dear Ms. Jane Jones:

Re: PDN 987655

Please revise our Application to include the following:

1. The proper name for ascorbic acid has been changed to vitamin C and the common name to ascorbic acid.
2. The proper name for rutin has been changed to quercetin-3-rutinoside.
3. An adult sub-population.

Yours truly,

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd
Ottawa, Ontario
Canada
K1E 2V2

Sample 8: Level 3 In-Queue Fax

HEALTH CANADA
NATURAL HEALTH PRODUCTS DIRECTORATE

SANTÉ CANADA
DIRECTION DES PRODUITS DE SANTÉ NATURELS

FAX TRANSMITTAL SHEET/
FORMULAIRE DE COMMUNICATIONS PAR TÉLÉCOPIEUR

TO/À:		FROM/DE:
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PHONE NUMBER/NUMÉRO DE TÉLÉPHONE:		SENDER'S TELEPHONE NUMBER/NUMÉRO DE TÉLÉPHONE DE L'EXPÉDITEUR (E):
()		(613) / FAX: (613) 954-2877
RE/SUJET:		REFERENCE NUMBER/NUMÉRO DE RÉFÉRENCE:
NOTICE OF PLACEMENT IN ASSESSMENT (LEVEL 3) QUEUE		**N/A**

X FYI ❑ FOR REVIEW ❑ PLEASE COMMENT ❑PLEASE REPLY ❑ PLEASE RECYCLE

SUBJECT: **SUBMISSION STATUS UPDATE**
Brand Name - Sub No. 10XXXX

Please be advised that the above submission has entered Level 3 Queue for the assessment of Quality, Safety & Efficacy. Please see Chapter 4 of the Product Licensing guidance document for more information on the licensing process.

Thank you,

Submission Coordinator

Tel: (613)
Fax: (613) 954-2877

Notes:

Level 3: Assessment

When the application reaches this level, the application form and supporting information are assessed for compliance with the *Natural Health Products Regulations.*

Assessment Queues: Product Licensing

Queue #	Submission Type
1	TPD Priority Transfer
2	Transitional DINs and Homeopathic Medicines
3	Non-Compendial (except for compliance priority)
4	Compendial
5	Compliance Strategy Priority Products
6	TPD Labelling Standard and Category IV monograph

- If clarification is required for specific information in the application, an Information Request Notice is sent.
- The notice is sent by fax or mail, and applicants have 30 calendar days from the date of request to respond in writing.
- Responses should be in question-and-answer format. All clarifications must be addressed in one response.
- A response is considered complete if all clarifications or questions identified in the request are addressed.
- If no response is received, or the response is incomplete, NHPD considers the application to be withdrawn and sends a notice of withdrawal to the applicant. Applicants may re-submit withdrawn applications at a later date.
- Once the response is received, the assessment is resumed.
- The Assessment Officer prepares an assessment summary report, reviews the label text, and identifies and communicates any final deficiencies.
- A review is then conducted by the Assessment Unit Head who notifies the Submission Coordinator of the licensing recommendation.

Samples of Level 3 Submission Documentation

9. Evidence Summary Report
10. Quality Summary Report
11. Information Request Notice (IRN)
12. IRN Response

Notes:

Sample 9: Evidence Summary Report

PART 1: EVIDENCE SUMMARY REPORT (CHAPTER 8.0)
(Complete this section for each medicinal ingredient provided on the product licence application form (Part 4: Section 1) and maintain the order.)

A. RECOMMENDED USE OR PURPOSE (CLAIM)(CHAPTER 8.1)
(Check the appropriate category and provide the relevant information directly in the space provided.)

☑ Non-Traditional Use Claim(s)

Acts as a supportive therapy in the treatment of colds

Finally a cure for the common cold! → DEFICIENT

Additional Information:
(If necessary)

Not applicable

B. SEARCH STRATEGY AND LISTING OF EVIDENCE (CHAPTERS 8.2 & 8.3)
(An example is provided at the end of the template. Additional pages must be added with the relevant information captured in the appropriate table. The column headings must be maintained.)

Database 1:Natural Medicines Comprehensive Database
URL:http://www.naturaldatabase.com/
Database 2:Pubmed
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

B. SEARCH STRATEGY AND LISTING OF EVIDENCE (CHAPTERS 8.2 & 8.3)

Type of Evidence	Date of Search	Keywords	Limits	Results (#)	Relevant (#)	Rationale for Exclusion
II, IV	Aug 4 2004	*echinacea angustifolia* cold	None	43	1	Articles excluded when no abstract was available, when the language was other than English and when the abstract was not relevant.
II	Aug 4 2004	Echinacea hydrastis	None	4	2	Articles were excluded when no abstract was available and when the article was relating to the testing for hydrastine content.
IV	Aug 4 2004	Echinacea hydrastis interaction	Human	2	1	Article was excluded since no abstract was available
I	Aug 5 2004	vitamin C cold	Randomized controlled trial, human	24	2	Articles were rejected on basis of language, not relevant to cold treatment.
I	Aug 5	Vitamin C flu	None	4	2	Articles were rejected when the language was not English and were related to aging.
IV	Aug 4 2004	Vitamin C zinc cold	None	14	3	Articles were excluded on the basis of their unavailable abstract, when related to asthma, to lipoproteins and when content was not related to colds.
IV	Aug. 4 2004	Vitamin C zinc interaction	Human	21	1	Articlesrelating to asthma, zinc in infant formulas, copper and not related to nutrient interactions
IV	Aug 4 2004	Rutin vitamin C	Randomized clinical trial, human	1	1	N/A
IV	Aug 4 2004	Rutin vitamin C interaction	None	19	1	Articles were excluded when they related to other flavonoids such as lycopene, when the abstract was not available and when the language was other than English.
IV	Aug 9	rutin immune system	None	99	0	Articles were excluded when the abstract was not available, not relevant to the immune system and when the language was other than English.
	Aug 4 2004	L-glutamine immune	None	323	3	Excluded articles related to gut physiology, critically ill patients and were not relevant to the immune system, also when no abstract was available and when the language was other than English.

Sample 9: Evidence Summary Report

C. LISTING OF EVIDENCE

Type and Level of Evidence	Dosage: Dose, dosage form, frequency, and route of administration	Duration, if any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	Human; Animal; or *In vitro* (indicate below)	Design Results, and Conclusions	References
I	Encapsulated mixture of unrefined *E. purpurea* herb (25%) and root (25%) and *E. angustifolia* root (50%) taken in 1g doses, 6 times on the first day of illness and 3 times on each subsequent day for a maximum of 10 days	10 days	a) allergy b) N/A c) N/A d) N/A	Human	**Design:** Randomized, double-blinded, placebo- controlled community based trial: 148 participants with common colds of recent onset. **Results:** Compared to placebo, unrefined Echinacea provided no detectable benefit or harm in participants who had the common cold.	Barrett et al. 2002
IV	Echinacaea root, dried herb: 1g, 3 times daily orally	N/A	a) progressive systemic diseases and auto-immune conditions b) N/A c) rare cases of allergic reactions may occur, especiallyagainst Asteraceae d) parenteral use may cause chills, short-term fever reactions and nausea and vomiting (parenteral use of Echinacea is no longer approved in Germany)	Human, animal	Used to support and promote the natural powers of resistance of the body, especially in infectious conditions (influenza and colds) in the nose and throat.	Blumenthal et al. 2000
IV	Echinacea: Liquid extract (1:5, 45% ethanol), 0.5-1 ml three times daily. Tincture (1:5, 45 % ethanol) 2-4 ml three times daily	Internal use should not exceed a period of 8 successive weeks	a) should not be used in serious conditions such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDs, HIV and autoimmune disorders. Should not be administered to people with known allergy to any plant of the Asteraceae b) pregnancy, nursing c) N/A d) N/A	Human, animal	Administered orally as supportive therapy for colds and infections of the respiratory and urinary tract. Beneficial effects are thought to be from its stimulation of the immune response.	WHO 1999
IV	Echinacea: Powdered: 1g 3x/day	May be used up to 10-21 days	a) consult a health care practitioner prior use if you have rheumatoid arthritis,a progressive systemic disease, such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV infection, if you have auto-immune disorders and if you are taking immunosuppressants. b) do not use if you are pregnant or breastfeeding. Do not use if you have an allergy to Asteraceae / Compositae (daisy) family c) N/A d) N/A	Human	Acts as supportive therapy in the treatment of colds, flus, upper respiratory infections and urinary infections	NHPD published monograph Jan 19. 2004
IV	Goldenseal: dried rhizome: 0.5-1g or by decoction three times daily	N/A	a) N/A b) contraindicated in individuals with raised blood pressure, during pregnancy and lactation c) N/A d) N/A	Human, animal	Traditionally used for digestive disorders, gastritis, peptic ulceration, colitis, anorexia, upper respiratory catarrh.	Barnes et al. 2002
IV	Goldenseal: dried roots and rhizomes 0.5-1g dry, standardized extract (to 5 % hydrastine): 250-500mg, three times daily		a) pregnancy, hypertension b) pregnancy, hypertension c) N/A d) N/A	Animal and human	Has astringent action which may help in the management of infectious conditions of the gastrointestinal tract and upper respiratory tract. Based on traditional evidence, goldenseal is used to treat common cold, either alone or in combination with other herbal medicines such as echinacea.	Boon and Smith 2004

Sample 9: Evidence Summary Report

Type and Level of Evidence	Dosage: Dose, dosage form, frequency, and route of administration	Duration, if any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	Human; Animal; or *In vitro* (indicate below)	Design Results, and Conclusions	References
I	Vitamin C: 1g of vitamin C daily during winter months	60 days	a) N/A b) N/A c) N/A d) N/A	Human	**Design:** Randomized controlled trial: 168 volunteers **Results:** Compared to placebo, volunteers taking vitamin C had significantly fewer colds and shorter duration of severe symptoms of cold.	Van Straten et al 2002.
IV	Rutin N/A	N/A	a) N/A b) N/A c) N/A d) N/A	Human, animal	Rutin has been generally considered to lack toxicity. Most well-known ability to decrease capillary permeability and fragility. It is usually used in formulations with vitamin C or together with other bioflavonoids as well as rose hips, especially in the health food industry.	Leung and Foster 1996
IV	Rutin: For venous insufficiency: take 500mg of rutin twice daily. Other daily doses of 200-600mg daily	N/A	a) N/A b) pregnant woman and nursing mother should avoid using rutin supplements c) gastrointestinal such as nausea d) N/A	N/A	Rutin generally well tolerated. It may be useful in the management of venous edema, may help strengthen capillaries, protect against some toxins, have anti-inflammatory effect and may have some anticancer effects. It may prevent the oxidation of vitamin C and have some positive lipid effects.	PDR health 2004
IV	N/A	N/A	a) N/A b) N/A c) N/A d) N/A	Human and animal	Review of major roles of glutamine. It has been show to increase the phagocytic activity of neutrophils (in vitro)	Melis et al 2004
IV	N/A	N/A	a) N/A b) N/A c) N/A d) N/A	Animal and human	Immune cells utilize glutamine at high rates. Glutamine has been linked to functional activities immune cells such as proliferation, antigen presentation, cytokine production, nitric oxide production, super oxide production and phagocytosis.	Newsholme 2001

D. TYPE OF EVIDENCE (CHAPTER 8.4)

(Place a check mark in each box if the reference source was used to search for information that supports the recommended conditions of use.)

- ☐ References to traditional use
- ☐ Pharmacopoeia, Dispensatory
- ☑ Existing monographs
- ☑ Referenced texts
- ☑ Peer reviewed research articles/Journals
- ☑ Database – PubMed
- ☑ Database – Other: Natural Medicines comprehensive Database
- ☐ Previous marketing experience
- ☐ Expert opinion reports
- ☐ Other: _____

Rationale for excluding a particular source of evidence

(Provide the rationale directly in the space provided below.)

N/A

E. CRITICAL OVERVIEW (CHAPTER 8.5)

(The applicant must provide all relevant information for this section under the headings provided below. Any section that is not completed must be justified. Additional pages may be added for this section.)

A) Traditional Use
B) Non-Traditional Use
C) Pharmacology
D) Dosage and Directions

Sample 9: Evidence Summary Report

Critical Overview:

A) N/A

B) The Commission E and the WHO recognize Echinacea for its immunostimulatory properties (Blumenthal et al 2000; WHO 1999). Goldenseal is also known to be used to treat common cold alone or in combination with other herbs such as echinacea (Boon and Smith 2004). In addition, animals studies showed that an Echinacea treatment increases the antigen-specific immunoglobulins G in rats while hydrastis treatment increases the level of antigen-specific immunoglobulins M. Immunoglobulin Gand M are important for the immune response. IgM is not only the first class of antibody to appear on the surface of a developing B cell, it is also the major class secreted into the blood in the early stages of a primary antibody response. IgG is produced in large quantities during secondary immune responses (Alberts et al 2000). Goldenseal and Echinacea are widely used in traditional and non-traditional cold remedies.

For goldenseal, we have used the potency of 3% of berberine content. We used berberine as a marker of identity for goldenseal. The Unites States Pharmacopoeia 2004 reports that goldenseal products should contain not less than 2 % of hydrastine and not less than 2.5 % of berberine.

Vitamin C and zinc have been shown to reduce the duration of the cold symptoms (Douglas et al 2000; Mossad et al 1996). Van Straten et al 2002, undergone a randomized controlled trial recently and investigated the effect of 1 g of vitamin C daily during the winter months (60 days). Compared to placebo volunteers taking vitamin C had significantly fewer colds and showed a shorter duration of the cold symptoms. Reviews of the research conducted on the common cold and vitamin C conclude that large doses of vitamin C don't have a significant effect on the incidence of the common cold. However, large doses of vitamin C have been found to decrease the duration and severity of colds (Higdon 2003).

Zinc plays important role in the immune response. Despite the numerous well controlled clinical trials, the efficacy of zinc lozenges for the treatment of common cold symptoms remains unclear (Higdon 2003). Mossad et al 1996 did a randomized, double-blind placebo-controlled study to test the efficacy of zinc gluconate lozenges in reducing the duration of symptoms caused by the common cold. Employees (100) of the Cleveland Clinic who developed symptoms of the common cold within 24 hrs before enrollment. The zinc group (50) was taking one lozenge every 2 hours while awake. Lozenges contained 13.3 mg of zinc as zinc gluconate and were taken as long as the patients had cold symptoms. The placebo group was administered lozenges containing 5% calcium lactate pentahydrate. The zinc group showed that the time to resolution of all symptoms (headache, hoarseness, nasal congestion, nasal drainage and sore throat) was significantly shorter than the placebo group, 4.4 days compared to 7.6 days. Patients in the treated group had more adverse effect compared to placebo, such as nausea and bad-taste reactions (Mossad et al 1996). Another clinical trial testing the effect of zinc gluconate lozenges (23.7mg zinc) showed a decrease in the duration of the common cold and the severity of symptoms (Godfrey et al 1992). The study was conducted on 73 subjects enrolled at a cold clinic. The duration of cold symptoms for the zinc group and placebo were 4.9 and 6.1 days respectively (Godfrey et al.1992). Smith et al 1989 tested if zinc gluconate is efficacious in the treatment of acute respiratory tract infection. Lozenges contained 11.5 mg of zinc (n=57) and placebo contained sucrose octa-acetate (n=53). Patients were required to take 4 lozenges at the start and then 2 every 2 hours for seven days or 24 hours after disappearance of the last symptoms. The duration of the illness was similar in both groups, but the severity was significantly less in zinc treated subjects on days 4 to 7 of treatment.

Even though a meta-analysis (Marshall 2003) has recently concluded that the evidence of zinc lozenges for treating the common cold is inconclusive, there were few positive studies demonstrating a decrease in the duration and severity of the cold symptoms. Therefore, zinc might play a role in this combination to support the common cold therapy.

Rutin is safe and is know to be used in combination with vitamin C to decrease its oxidation (PDR health). O'Brien et al 2000, investigated the protective effect of of myricetin, quercetin and rutin against H2O2-induced DNA damage in two cell lines (Caco-2 and HepG2) and showed a similar degree of protection against DNA strand breaks in both cell lines therefore demonstrating antioxidant properties. Boyle et al 2000 conducted a clinical trial on 18 volunteers to determine the potential antioxidant effect of rutin supplementation (500 mg for up to 6 weeks). The supplementation did not induce any adverse changes in blood chemistry and liver functions. The plasma flavonoids content was increased following rutin supplementation compared to controls. Rutin has been used safely for many years and is listed in the ingredients added to food under the FDA (http://www.cfsan.fda.gov/~dms/eafus.html), however it has not been assigned for toxicological literature search. Furthermore the TGA has recently reviewed the safety of rutin and is now a substance that may be used as active ingredients (http://www.tga.health.gov.au/docs/pdf/listsubs.pdf)

Sample 9: Evidence Summary Report

L-glutamine provides nitrogen for the synthesis of purine and pyrimidime nucleotides necessary for the synthesis of new DNA and mRNA during proliferation of lymphocytes as well as for mRNA synthesis and DNA repair in macrophages (Melis et al 2004). Glutamine is an important source of energy for these white blood cells (Melis et al 2004). During severe metabolic stress the consumption of glutamine exceeds glutamine synthesis and supply from proteolysis which outcomes with a depletion of the glutamine stores (Melis et al 2004). It was established that glutamine is required by neutrophils to increase their phagocytic activity and rate of production of super oxide (Pithon-Curi et al 2003). A glutamine deficiency can make patients more prone to infections complications (Melis et al 2004). Houdijk et al 1998 conducted a clinical trial on patients with multiple trauma with an expected survival of more than 48 h. Glutamine (30.5 mg) was supplemented through enteral nutrition. It was found that severely injured patients who received glutamine-supplemented feeding had significantly less pneumonia, bacteraemia and sepsis than those from the placebo group. Boelens et al 2002 investigated the effect of glutamine enriched enteralnutrition on human leukocyte antigen (HLA-DR) and FcγR1/CD64 expression on monocytes and plasma glutamine concentration in multi trauma patients. Monocytes play a crucial role in the cellular immune response since they function both as antigen-presenting cells and as effector cells (Boelens et al 2002). The glutamine group had a higher expression of HLA-DR on monocytes on day 5 and 14 compared to controls. Therefore glutamine might play a role to improve cellular immune function and decrease the occurrence of infections in trauma patients by increasing HLA-DR expression in moncytes (Boelens et al 2002). In addition, few short term studies on intravenously infused glutamine in healthy volunteers showed no safety concerns (Buchman 2001). Some studies report that in the elderly population with dementia there might be a potential worsening of the illness; however, further studies are required for that sub-population (Buchman 2001). In the end, we can expect than during a common cold infection, the stores of glutamine would be decreased and since glutamine is important for the immune system it should be helpful to support the cold therapy.

C) See above.

D)

Medicinal ingredient	Recommended dose	Dose in combination (2 capsules daily)
Echinacea	1 g powder 3 times per day (Barnes et al 2002) = 3 g/day	1500 mg × 2 = 3000 mg or 3 g
Goldenseal	0.5-1.0 g dry 3 times daily (Boon and Smith 2004) = 1.5-3 g/day	45 mg × 2 = 90 mg or 0.09 g
Vitamin C	Minimum dose: 20 mg/day (TPD 1995) Upper limit for 19 years and older: 2000 mg/day (DRI 2000)	20 mg × 2 = 40 mg
Zinc	Upper limit for 19 years and older: 40 mg/day (DRI 2001)	5 mg × 2 = 10 mg
Rutin	500 mg (Boyle et al 2000)	50 mg × 2 =100 mg
Glutamine	30.5 mg enteral (Houdjik et al 1998; Boelens et al 2002)	10 mg × 2 = 20 mg

PART 2: SAFETY SUMMARY REPORT (CHAPTER 9.0)

(Complete this section for each medicinal ingredient provided on the product licence application form (Part 4: Section 1) and maintain the order.)

A. RISK INFORMATION

(The applicant should provide all relevant information for this section under the headings provided below. Any section that is not completed must be justified. Additional pages may be added for this section. In order to prevent duplicating the work, the applicant must decide which category best captures the risk information.)

1. Traditional Risk Information, when available:
   (This information must be from the two independent references provided in Part I(A) of the report)
2. Other Risk Information:
   A) Pre-clinical toxicology
   B) Clinical toxicology
   C) Interactions (e.g. herb-drug, herb-food, herb-laboratory tests etc.)
   D) Adverse events/reactions, side effects, cautions or warnings, contraindications
   E) Other: _____

Risk Information:

1. Traditional Risk Information, when available:N/A

2. Other Risk Information:
   A) N/A
   B) N/A

Sample 9: Evidence Summary Report

C) Please find below the list of cautions and warnings for the combination product

Medicinal ingredient	Risk information	Reference
Echinacea	Consult a health care practitioner prior use if you have an autoimmune-mediated or inflammatory disease such as tuberculosis, leucosis, collagenosis, multiple sclerosis, AIDS, HIV infection	Sparreboom et al. 2004; Werneke et al. 2004; Lee and Werth 2004
	Do not use if you have an allergy to Asteraceae / Compositae (daisy) family	Brinker 2001; Paulsen 2002
	Consult a health care practitioner if symptoms persists	NHPD monograph for Echinacea
	Do not use if you are pregnant or breastfeeding	NHPD monograph for Echinacea
Goldenseal	Consult a health care practitioner prior to use if you have high blood pressure	Boon and Smith 2004
	Consult a health care practitioner prior to use if you have kidney disease	Mills and Bone 2000; Brinker 2001
	Consult a health care practitioner prior to use if you are taking sedative drugs and/or barbiturates.	Brinker 2001; Mills and Bone 2000; Duke 1985
	Do not use if you are pregnant or breastfeeding	Boon and Smith 2004
Zinc	Consult a health care practitioner prior to use if you are taking Tetracyclines	NHPD monograph for zinc
	Zinc supplementation can cause a copper deficiency. Consult a health care practitioner if you are unsure whether or not you are taking adequate copper	DRI 2001
Rutin	No Reports known	
L-glutamine	Not Reports known	

B. SAFETY FACTORS (CHAPTER 9.1)

(For each answer, if it is "Yes," can that risk be mitigated, e.g. through reformulation, over-the-counter product labeling etc.? And such any such recommendations must be provided in the General Overview Section of the Report.)

1. Are individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring required to ensure the safety or effectiveness of the product?
2. Is the product used in treatment of a disease that is not appropriate for self-care, e.g. a serious disease easily misdiagnosed by the public?
3. Does use of the product mask other ailments or their development?
4. Does the product have known adverse effects at the recommended or therapeutic dosage level?
5. Is there a narrow margin of safety between the therapeutic and toxic doses, especially in populations such as seniors, children and pregnant or nursing women?
6. Does the product have a demonstrated potential for addiction, abuse or severe dependency that is likely to lead to harmful non-medicinal use?
7. Does the product have a therapeutic effect based on recently established pharmacological concepts, the consequences of which have not yet been fully established?
8. Have experimental data shown that the product induces toxicity in animals?If so, has it been in use long enough to establish the pattern or frequency of long term toxic effects in humans?
9. Does the product have known adverse interactions with other natural health products, drugs, or foods?
10. Is the product known to affect results of standard laboratory or other diagnostic tests?
11. Does the product contribute to, or is it likely to contribute to, the development of resistant strains of micro-organisms in humans?
12. Does the product possess a high level of risk relative to expected benefits?

Response to Safety Factors? (Additional pages may be added for this section.)

Response to Safety Factors:

1. No
2. No
3. No
4. Yes, please see general overview.
5. No
6. No
7. No
8. No
9. Yes, please see general overview.
10. No
11. No
12. No

Sample 9: Evidence Summary Report

C. ADDITIONAL SAFETY INFORMATION:
PREVIOUS MARKETING EXPERIENCE (CHAPTER 3.7)

(The applicant should provide a summary that address all the issues raised in each bullet, when applicable. If the information is not provided for an issue, the applicant must give a rationale. Additional pages may be added for this section.)

- jurisdictions where application was made for marketing authorization and the results of these applications;
- when and where the ingredient or product was approved for sale;
- statement that the product for which an application is being submitted is the same as the one previously marketed with regards to ingredients and recommended conditions of use;
- when and where the product was sold, and over what period of time;
- the date the product went on the market;
- labelling information for each jurisdiction where it was marketed;
- the date it went off the market, if applicable, and the reason it was removed; and
- the number of adverse reactions reported and a description of their nature.

Previous Marketing Experience Summary:

(Additional pages may be added for this section)

Previous Marketing Experience:

N/A

D. GENERAL OVERVIEW (CHAPTER 9.2)

(The applicant must provide an overall safety evaluation, taking into account the responses provided for the safety factors, and recommendations on how to mitigate any risk associated with the use of the medicinal ingredient and the rationale for such recommendations. Any additional information relevant to safety can also be provided. Additional pages may be added for this section.)

General Overview:

In general the combination is safe. Since there is insufficient data are available for the sub-population of pregnant and breastfeeding women, the contraindication: "Do not use if you are pregnant or breastfeeding" is included as a precaution.

Echinacea, goldenseal and zinc have many interactions with drugs such as barbiturates for goldenseal, tetracyclines for zinc and immunosuppressants for echinacea. Therefore we will include a general cautionary statement for all prescription medicines: "Consult a health care practitioner prior to use if you are taking any prescription medication."

Furthermore echinacea has known effects on progressive systemic disease and immune disorders therefore the following cautionary statement are required :
"Consult a health care practitioner prior use if you have an autoimmune-mediated or inflammatory disease such as tuberculosis, leucosis, collagenosis, multiple sclerosis, AIDS, HIV infection."

Echinacea is also reported to have potential to cause allergic reactions for subjects allergic to the Asteracea compositae family. A contraindication will be included.

Goldenseal has potential to create problems to cause nephritis therefore a cautionary statement is necessary: "Consult a health care practitioner prior to use if you have kidney disease".

Zinc supplementation is know to interact with copper and can cause copper deficiency (DRI 2001), this precaution is not necessary since the combination product will be only used during the duration of the cold therefore up to 7 days. The likelihood of zinc to cause a copper deficiency is low and the statement is not required.

L-glutamine has shown to be important for the immune system proliferation and phagocytic acitiviy. Most short term studies of intravenously infused glutamine in healthy volunteers have shown no safety concerns (Buchman 2001).

It is expected that during a cold, glutamine will assist Echinacea and goldenseal in stimulating the immune system and fighting the infection. While zinc and vitamin C will decrease the duration of the cold, rutin will prevent the oxidation of vitamin C and contribute with its antioxidant effect.

Sample 9: Evidence Summary Report

EXPERT OPINION REPORTS (CHAPTERS 2.2.2 and 3.5)
(The applicant must complete this section if they are providing evidence from this source.)

A) Rationale for using an expert opinion: **N/A**

B) Qualifications of experts:
Expert 1:
Expert 2:
Expert 3:

C) Contact information:
Expert contact information: Expert 1: Name: _____
Telephone number: _____
Email: _____
Other:

Expert contact information: Expert 2: Name: _____
Telephone number: _____
Email: _____
Other:

Expert contact information: Expert 3:Name: _____
Telephone number: _____
Email: _____
Other:

D) Summary of relevant information with corresponding references (Additional pages must be added for this section):

PART 3: REFERENCES (CHAPTER 10.0)
(The reference list must be provided in alphabetical order. The applicant must bold the entire citation for a reference to indicate when a hard copy for that reference is submitted to the NHPD. This reference must be same as the one cited in the line listing. Additional pages may be added for this section.)

REFERENCES:

1. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. Molecular Biology of the Cell. 3rd ed. New York and London: Garland Publishing; 2001.
2. **Audera C, Patulny RV, Sander BH, Douglas RM. Mega-dose vitamin C in treatment of the common cold: a randomised controlled trial. Med J Aust. 2001 Oct 1; 175(7):359-62.**
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4. Barrett BP, Brown RL, Locken K, Maberry R, Bobula JA, D'Alessio D. Treatment of the common cold with unrefined echinacea. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002 Dec 17; 137(12): 939-46.
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6. Blumenthal M, Goldberg A, Brinkmann J, editors. Herbal Medicine: Expanded Commission E Monographs. Boston (MA): Integrative Medicine Communications; 2000.
7. Boelens PG, Houdijk AP, Fonk JC, Nijveldt RJ, Ferwerda CC, Von Blomberg-Van Der Flier BM, Thijs LG, Haarman HJ, Puyana JC, Van Leeuwen PA. Glutamine-enriched enteral nutrition increases HLA-DR expression on moncytes of trauma patients. J Nutr. 2002 Sep; 132(9):2580-6.
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9. Brinker F. Herb Contraindications and Drug Interactions. 3rd ed. Sandy (OR): Eclectic Medical Publications; 2001.
10. BuchmanAL. Glutamine: commercially essential or conditionally essential?A critical appraisal of the human data. Am J Clin Nutr 2001;74:25-32.
11. **Chen SS, Gong J, Lui FT, Mohammed U. Naturally occurring polyphenolic antioxidants modulate IgE-mediated mast cell activation. Immunology. 2000 Aug;100 (4):471-80.**
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Sample 9: Evidence Summary Report

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Sample 9: Evidence Summary Report

NON-MEDICINAL INGREDIENTS (CHAPTER 7.0)
(The applicant must complete this section, when necessary, after reading the relevant chapters.)

1. Non-Medicinal Ingredients on the Acceptable List (Chapter 7.1.1)
(The applicant must check the box below, when relevant, after reading the information in the Chapter 7.1.1).

☑The non-medicinal ingredients are on the Acceptable List and within any limitations on that list. I acknowledge that I have read the requirements outlined in Chapter 7.1.1.

2. Listed Non-Medicinal Ingredients Outside the Limitations (Chapter 7.1.2)
(The applicant must provide the relevant information, when necessary, from Chapter 7.1.2 below. Additional pages may be added for this section.)

Listed Non-Medicinal Ingredients Outside the Limitations: N/A

NON-MEDICINAL INGREDIENTS (CHAPTER 7.0) continued …
(The applicant must complete this section, when necessary, after reading the relevant chapters.)

3. Non-Medicinal Ingredients NOT on the Acceptable List (Chapter 7.1.3)
(The applicant must provide the relevant information, when necessary, from Chapter 7.1.3 below. Additional pages may be added for this section.)

COMBINATION PRODUCTS (CHAPTER 12.0)
(The applicant must complete this section, when necessary, after reading the relevant chapters).

Traditional Combination (Chapter 12.2.1)
(The applicant must provide the relevant information, when necessary, from Chapter 12.2.1 below. Additional pages must be added for this section.)

Traditional Combination: **N/A**

→ DEFICIENT

COMBINATION PRODUCTS (CHAPTER 12.0) continued …
(The applicant must complete this section, when necessary, after reading the relevant chapters).

Combinations for Non-Traditional Use (Chapter 12.2.2)
(The applicant must provide the relevant information, when necessary, from Chapter 12.2.2 below. Additional pages must be added for this section.)

Combination for Non-Traditional Use:
N/A

COMBINATION PRODUCTS (CHAPTER 12.0) continued …
(The applicant must complete this section, when necessary, after reading the relevant chapters).

Additive Combinations (Chapter 12.4)
(The applicant must complete the form below with the relevant information, when necessary, after reading the information provided in Chapter 12.4. Additional pages may be added for this section.)

The additive form is not required since all ingredients act differently.

Sample 10: Quality Summary Report

Quality Summary Report

Cold Remedy

Date of Preparation:
2004-09-01

Sample 10: Quality Summary Report

Finished Product Specifications for Cold Remedy

Test Parameters	Test	Test Method	Tolerances
Identity	Appearance	Visual	White and yellow capsules
	Qualitative test	HPLC	Conforms to reference material
	Disintegration	USP	Not more than 30 mins.
Purity	Contaminating fungus (yeast and mould)	USP<2021>	< 1000 / g
	Total Aerobic Count	USP <2021>	< 3000 / g
	Total Heavy Metals		20 ppm
	Solvents	USP	Conforms to ICH limits

Deficiencies:

a. Name of the test method and tolerance limits for *Eschericia coli, Salmonella* spp. and *Staphylococcus aureus*

b. The name of the test method used and tolerance limits for pesticides

c. Name of method used for quantification of the finished product

d. Name of the test method and tolerances for arsenic, cadmium, lead and total mercury

Sample 11: Information Request Notice (IRN)

Health Canada Santé Canada

Natural Health Products Directorate
AL: 3300B, Qualicum, 2936 Baseline Road
Ottawa, Ontario K1A 0K9

Company Code: 12345
File Number: 987655
Submission Number: 987655

November 15, 2004

Ms. Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd
Ottawa, Ontario
Canada
K1E 2V2

Dear Ms. Smith:

Re: Information Request Notice
Non-traditional Combination Cold Remedy

This is in response to your submission 987655, file 987655.

The application and evidence provided with this submission have been assessed for quality and have been determined to be deficient. At this time, NHPD requires further information in order to properly assess your submission. As per section 15 of the *Natural Health Products Regulations, please submit all the following information:*

1. The source material for rutin is incorrect; "buckwheat" is not considered an adequate description of the source material, as it is not the part of the plant used. According to Part 5 of the *Natural Health Products Regulations, a* description of the source material of each medicinal ingredient contained in the product is required on the Product License Application and label. Please provide the part of the plant used, and indicate that it will be provided on both the PLA and label.
2. According to Chapter 5.4.3 of the Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document, the second half of the claim: "Finally, a cure for the common cold !" is misleading and the evidence provided does not support this part of the claim. Please revise the claim by removing "Finally, a cure for the common cold!" such as the claim reads; "Acts as a supportive therapy in the treatment of colds". Please submit revised Product Licence Application or confirm in your response, and provide revised label text.
3. The rationale for the combination must be provided in the evidence summary report, as per Chapter 12 of the Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document. Please include rationale for the combination in your response.
4. Please provide a revised copy of Finished Product Specification which should include the following information:
    a. Name of the test method and tolerance limits for *Eschericia coli, Salmonella spp. and Staphylococcus aureus.* have not been provided in the specifications. As per Chapter 2.2.1 of the Evidence for Quality of Finished Natural Health Products guidance document microbial limits should be included in the specifications.
    b. Name of the test method and tolerance limits for pesticides in Cold Remedy are required as per Chapter 2.2.2 of the Evidence for Quality of Finished Natural Health Products guidance document. Please include this in the specifications.
    c. Please provide the name of the method used for quantification (e.g. HPLC, GC) of the finished product, as per Chapter 2.2.2 of the Evidence for Quality of Finished Natural Health Products guidance document Please provide the tolerance limits for each medicinal ingredient.
    d. Please provide the name of the test method and tolerances for arsenic, cadmium, lead and total mercury in Cold Remedy, as per Chapter 2.2.2 of the Evidence for Quality of Finished Natural Health Products guidance document.

The NHPD will retain this submission on file for 30 calendar days in order for all of the deficiencies to be addressed. If a written response is inadequate or is not received by the NHPD within 30 days of the date of this letter, the submission will be withdrawn. Please remember that the response to the list of deficiencies must be submitted in one consolidated package and numbered accordingly. In responding to these issues, please quote the submission number and file number in your response.

If you have any questions concerning the information requested for this submission, please contact the submission co-ordinator at the co-ordinates below.

Yours truly,

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
Phone: 613-941-1002
Fax: 613-954-2877

Canada

Sample 12: IRN Response

Company Code 12345
File # 987655
Submission # 987655

January 25, 2005

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, Ont
K1A 0K9, AL 3300C

Dear Ms. Jane Jones:

Re: Information Request Notice
Non-Traditional Cold Remedy

Please find attached our revised Application including the following:

1. The source material for rutin has been updated.
2. The claim has been changed to “Acts as a supportive therapy in the treatment of common colds”.
3. The rationale for the combination has been submitted.
4. Please review the attached new copy of Finished Product Specification.

Yours truly,

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd
Ottawa, Ontario
Canada
K1E 2V2

Sample 12: IRN Response

PART 4 - PRODUCT INFORMATION

Primary Brand Name *	Other(s) if any		
Cold remedy			

Was animal tissue used in the processing of this product? ** ☐ Yes ☒ No

SECTION 1 — MEDICINAL INGREDIENT(S)

Ingredient No.	A Standard or Grade	B Compendial Monograph No.	C * Proper Name	D Common Name	E * Quantity	F * Synthetic		G ** Animal Tissue	
						Yes	No	Yes	No
1.			*Echinacea angustifolia*	Echinacea	375 mg		X		X
2.			*Hydrastis canadensis*	Goldenseal	45 mg		X		X
3.			Vitamin C	Ascorbic Acid	20 mg	X			X
4.			Zinc		5 mg		X		X
5.			2-amino-4-carbamoylbutanoic acid	L-glutamine	10 mg	X			X
6.			Quercetin 3-rutinoside	Rutin	50 mg		X		X
7.									
8.									
9.									
10.									
11.									
12.									

Ingredient No.	H Potency		I * Source (if more than one enter on new line)		J Extract (if applicable)		K Method of preparation
	Amount	Constituent	Proper Name	Material	Ratio	Quantity Dried Equivalent	
1.				root	4:1	1500 mg	Traditional
2.	3%	berberine		root			Traditional
3.				Sodium ascorbate			
4.				Zinc gluconate			
5.							
6.			*Fagopyrum esculentum*	seed			
7.							
8.							
9.							
10.							
11.							
12.							

Copy as necessary
* – denotes Mandatory
** – if yes complete Animal tissue Form

Sample 12: IRN Response

SECTION 3 — RECOMMENDED CONDITIONS OF USE

Recommended Use or Purpose *

Acts as a supportive therapy in the treatment of colds

*May be used up to 7 days.

Dosage Form (one only) *	Duration of Use (if any)	Sterile *	Route of Administration *
Capsules	See *	☐ Yes ☒ No	Oral

Recommended Dose (repeat for each sub-population group)

Sub-population group *	Amount *	Dosage Unit *	Frequency	Directions of Use
Adults	2	Capsules	daily	Take with food

Risk Information

Cautions and Warnings *

Consult a health care practitioner prior use if you have an autoimmune-mediated or inflammatory disease such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS or HIV infection
Consult a health care practitioner prior to use if you have high blood pressure.
Consult a health care practitioner prior to use if you have kidney disease.
Consult a health care practitioner prior to use if you are taking other medication.
Consult a health care practitioner prior to use if you are taking any prescription medication.

Contra-Indications *

Do not use if you are pregnant or breastfeeding.
Do not use if you have an allergy to Asteraceae / Compositae (daisy) family.

Known Adverse Reactions

ATTESTATION

"I attest that the natural health product that is the subject of this product license application will be manufactured, packaged, labelled, distributed and stored:

a) if the natural health product is imported, in accordance with the 'Good Manufacturing Practices' requirements as set out in Part 3 of the Natural Health Products Regulations or in accordance with requirements that are equivalent to those set out in Part 3, or

b) if the natural health product is not imported, in accordance with the 'Good Manufacturing Practices' requirements set out in Part 3 of the Natural Health Products Regulations."

Name of Authorized Senior Official (print) *	Signature *	Date *
Bob Fielding	*Bob Fielding*	2 0 0 5 0 1 2 0

HC/SC 9267E (12-2003) **Page 6 of 6**

Sample 12: IRN Response

Rationale for combination:

COMBINATION PRODUCTS (CHAPTER 12.0) continued...
(The applicant must complete this section, when necessary, after reading the relevant chapters.)

Combinations for Non-Traditional Use (Chapter 12.2.2)
(The applicant must provide the relevant information, when necessary, from Chapter 12.2.2 below. Additional pages must be added for this section.)

Combination for Non-Traditional Use:
In the Cold Remedy combination all ingredients support the claim at a different level. Echinacea and goldenseal are known from their traditional and non-traditional use to help the immune system during the common cold. Furthermore studies have observed that vitamin C and zinc decrease the duration and severity of the symptoms of the cold. Rutin is widely known as an antioxidant. Rutin prevents the oxidation of vitamin C. Glutamine has been recognized to play a role in the immune system. Although supporting scientific evidence for glutamine is weak, it is expected that glutamine's role in immune proliferation will positively influence the ability of Echinacea and goldenseal to stimulate the immune system and hence fight cold infections. Note that our combination contains many ingredients at sub-therapeutic levels, but since echinacea is at its full therapeutic level, we are confident that the product will be a supportive therapy for colds. With respect to safety, all the ingredients in the product are safe at the recommended conditions of use and any safety concerns are mitigated with appropriate advisory information (e.g. Cautions/warnings and contraindications) on the label.

Sample 12: IRN Response

Principal Display Panel:

Cold Remedy

Product Number 8XXXXXXX

90 capsules

Other Panels:

Echinacea angustifolia (Echinacea) (root extract; *4:1*)..... *375 mg*

Hydrastis canadensis (Goldenseal) (root extract) ..... *45* mg

(Standardized to 3 % berberine)

Vitamin C (Ascorbic acid from Sodium ascorbate) (synthetic) ..... *20* mg

Zinc (Zinc gluconate)..... *5* mg

L-glutamine (synthetic)..... *10* mg

Rutin (*Fagopyrum esculentum; seed)* ..... *50* mg

Non-medicinal ingredients :

Cellulose, gelatin (vegetable source) Corn starch, polyethylene glycol, magnesium stearate, titanium dioxide

Use: Acts as a supportive therapy in the treatment of colds. May be used up to 7 days.

Adults: Take 2 capsules daily with food

Consult a health care practitioner prior use if you have an autoimmune-mediated or inflammatory disease such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS or HIV infection, high blood pressure, kidney disease or are taking any prescription medication.

Do not use if you are pregnant or breastfeeding.

Do not use if you have an allergy to Asteraceae / Compositae (daisy) family.

Store at room temperature

Herbal Inc., 123 St Joseph Blvd, Ottawa, Ontario, Canada, K1E 2V2

Lot # XXXX

Expiry Date XXXX

Sample 12: IRN Response

Quality Summary Report

Cold Remedy

Date of Preparation:
2004-09-01

Sample 12: IRN Response

Test Parameters	Test	Test Method	Tolerances
Identity	Appearance	Visual	White and yellow capsules
	Qualitative test	HPLC	Conforms to reference material
	Disintegration	USP	Not more than 30 mins.
Purity	Contaminating fungus (yeast and mould)	USP<2021>	< 1000 / g
	Total Aerobic Count	USP <2021>	< 3000 / g
	Escherichia coli	USP <2021>	Absent
	Salmonella spp.	USP <2021>	Absent
	Staphylococcus aureus	USP <2021>	Absent
	Arsenic	ICP-MS	<0.14 mcg /kg b.w. / day
	Cadmium	ICP-MS	<0.09 mcg /kg b.w. / day
	Lead	ICP-MS	<0.29 mcg /kg b.w. / day
	Total mercury	ICP-MS	<0.29 mcg /kg b.w. / day
	Pesticides	USP	Conforms to USP limits
	Solvents	USP	Conforms to ICH limits
HPLC Quantity	Echinacea	HPLC	80-120%
	Goldenseal	HPLC	80-120%
	Vitamin C	HPLC	90-145%
	Zinc	ICP-MS	80-120%
	Glutamine	HPLC	80-120%
	Rutin	HPLC	80-120%

Level 4: Decision

- Product licence submissions are accepted or refused based on the requirements set out in the *Natural Health Products Regulations* Section 7.
- When NHPD deems a product licence submission to have met those requirements, it issues a **product licence.**
- NHPD will refuse to issue a product licence when:
    - it finds the product likely to result in injury to health of consumer;
    - the applicant does not provide additional information requested; or
    - the information submitted is false or misleading.
- When a product licence application is refused, NHPD sends the applicant a notice stating the reasons for refusal.

Note: If the product had previously been issued a DIN under the *Food and Drug Regulations, the NHPD product number will be the* same 8-digit number as was previously assigned.

- Within 30 days after the day on which the notice is sent, the applicant may request that NHPD reconsider this refusal.
- When a request for reconsideration is received, NHPD must give the applicant an opportunity to be heard about the refusal, after which NHPD may reconsider the initial refusal and decide whether to issue the product licence.
- When the decision is made to uphold the refusal to issue a product licence, NHPD sends the applicant a final notice stating the reason for refusal.

Product Licence

- A **product licence** authorizes the licensee to sell a natural health product, according to the provisions of the Natural Health Products Regulations.
- As per section 14, the licence sets out information relating to the natural health product.
- It is the applicant's responsibility to ensure that the product being sold is that which was approved by NHPD. The licensee must notify NHPD, within 60 days of the licence being issued, if the information on the product licence is incorrect.
- If the licence is incorrect, the licensee should send NHPD a letter outlining:
    - the submission and file numbers;
    - the product licence number;
    - which information is incorrect;
    - where in the evidence, submitted in the application, does it support the correction.

Samples of Level 4 Submission Documentation

13. Product Licence Issuance
14. Product Licence

Notes:

Sample 13: Product Licence Issuance

Company Code	12345
File #	987655
Submission #	987655

February 1st, 2005

Mr Bob Fielding
Senior Consultant
45 New Hampshire Drive
Ottawa, Ontario
Canada
K1X 2C2

Dear Mr Fielding,

Re: Product Licence Issuance NPN 80000000
Non-Traditional, Cold Remedy

The Natural Health Products Directorate (NHPD) has conducted an assessment of your submission and has considered the product to be in compliance pursuant to section 7 of the *Natural Health Products Regulations.* Please note that any labels used in the marketing of this product must reflect the information outlined on the product licence and must comply with the labelling requirements as per Part 5 of the Regulations.

Please find enclosed a copy of the Product Licence thereby authorizing the sale of the product described therein.

Please note as per sections 11, 12 and 13 of the *Natural Health Products Regulations*, changes made in respect of a licenced product, require an amendment, notification or a new product licence. Please see the Product Licensing Guidance Document for further information and the applicable requirements.

Please note that as per Part 5, Section 87 of the *Natural Health Products Regulations* (Labelling and Packaging), you are responsible for ensuring that the label text is translated correctly into French.

If you have any questions concerning the information on the licence, please submit a "Request for Correction to the Product Licence" using the form found in Appendix 5 of the Product Licensing Guidance Document or contact the Submission Coordinator, Jane Jones, of the Submission Management Division. Please note that the File Number (provided at the top right corner of the title page) and Product Number must be quoted on all future correspondence regarding this product.

Yours truly,

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
Phone: 613-941-1002
Fax: 613-954-2877

encl.: Product licence
c.c: Lesley Smith

Sample 14: Product Licence

Product Licence
Licence de mise en marché

Product Number/*Numéro de produit*: **80000000**

Brand Name/*Marque nominative*: **Cold Remedy**

Issued to:
Name of licensee/*Nom du titulaire*: Herbal Inc.
Address(e): 123 St Joseph
Ottawa, Ontario
Canada
K1E 2V2

Authorized for the following/*Authorizé pour ce qui suit*:
Dosage form/*Forme posologique*: capsule
Recommended route of administration/*Voie d'administration recommandée*: oral
Recommended dose/*Dose recommandée*: Adults: 2 capsules, daily
Recommended duration of use/*Durée d'ulitisation recommandée*:
May be used up to 7 days.
Recommended use or purpose/*Usage ou les fins recommandés:* Acts as a supportive theray in the treatment of common colds

Medicinal Ingredient/*Ingrédients médicinaux*		**Quantity/ dosage unit** *Quantité par unité posologique*	Extract Ratio/*Ratio D'éxtraction*	Potency/ *Activité*	Source Material/ *Matière d'origine*
Proper Name/*Nom propre*	Common Name/ *Nom Usuel*				
Echinacea angustifolia	Echinacea	375 mg	4:1	n/a	root
Hydrastis canadensis	Goldenseal	45 mg	n/a	3% berberine	root
Vitamin C	Vitamin C	20 mg	n/a	n/a	Sodium ascorbate Synthetic
Zinc	zinc	5 mg	n/a	n/a	zinc gluconate
2-amino-4-carbamoylbutanoic Acid	L-glutamine	10 mg	n/a	n/a	synthetic
Quercetin 3-rutinoside	Rutin	50 mg	n/a	n/a	*Fagopyrum esculentum* seed

This licence is issued by the Minister of Health under the authority of section 7 of the Natural Health Products Regulations. Sale of the described natural health product, including any changes thereto pursuant to section 11 of the Regulations, is subject to the Food and Drugs Act and to the Natural Health Products Regulations.
Cette licence est délivrée par la ministre de la Santé en vertu de l'article 7 du Règlement sur les produits de santé naturels. La vente du produit de santé naturel décrit dans la présente, y compris toute modification afférente au sens de l'article 11 du Règlement, est assujettie à la Loi sur les aliments et drogues et au Règlement sur les produits de santé naturels.

Issued/*délivrée le:* January 31, 2005	Revised/Amended/*Modifiée le*: N/A

Director General/*Directeur Générale*
NHPD/*DPSN*

B. Submission Management for Traditional Product Application

Level 1: Verification

For more information about level 1, see page 11.

Notes

Samples of Level 1 Submission Documentation

1. Cover Letter
2. Completed Parts 1, 2, and 5 of Product Licence Application Form
3. Acknowledgement
4. Response to the Acknowledgement Notice

Sample 1: Cover Letter

October 18, 2004

Submission Management Division
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, Ont
K1A 0K9, AL 3300C

Dear Submission Management Division:

Re: Chinese Remedy
Please find enclosed two copies of our PLA and evidence for the above mentioned product.

Yours truly,

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Sample 2: Completed Parts 1, 2, and 5 of Product Licence Application Form

Health Canada / Santé Canada

PRODUCT LICENCE APPLICATION FORM
Natural Health Products Directorate

Protected when completed

HC USE ONLY		Date/Time of Receipt
Submission Number	File Number	

Please refer to the Guide for instructions on how to complete this application. Please Print Clearly * - denotes Mandatory

PART 1
APPLICANT AND CONTACT INFORMATION

A. — APPLICANT OR LICENSEE (This will be the product licence holder)

Applicant/Company Name *	Company Code (If known)
Herbal Inc	

Address
Street/Suite/Land Location * 123 St Joseph Blvd.

City - Town *	Province - State *	Country *	Postal/ZIP Code *
Ottawa	Ontario	Canada	K1E 2V2

B. — CONTACT(S)

Name	Title *	Language preferred:
[X] Mr. [ ] Ms. [ ] Dr. Surname * Xu Given Name * Gus	President	[X] English [ ] French

Company Name (* if different from Applicant/Licensee)

Address same as Applicant/Licensee [X]

Street/Suite/Land Location *

City - Town *	Province - State *	Country *	Postal/ZIP Code *

Telephone No. *	Ext.	Fax No.	E-mail
613-834-1574		613-834-1575	gus@herbal.com

Contact Type *
[X] Senior Official
[ ] Contact for this Application
[ ] Representative in Canada

Name	Title *	Language preferred:
[ ] Mr. [X] Ms. [ ] Dr. Surname * Smith Given Name * Lesley	Regulatory Affairs Agent	[X] English [ ] French

Company Name (* if different from Applicant/Licensee)

Address same as Applicant/Licensee [X]

Street/Suite/Land Location *

City - Town *	Province - State *	Country *	Postal/ZIP Code *

Telephone No. *	Ext.	Fax No.	E-mail
613-834-1577		613-834-1575	lesley@herbal.com

Contact Type *
[ ] Senior Official
[X] Contact for this Application
[ ] Representative in Canada

Name	Title *	Language preferred:
[ ] Mr. [ ] Ms. [ ] Dr. Surname * Given Name *		[ ] English [ ] French

Company Name (* if different from Applicant/Licensee)

Address same as Applicant/Licensee [ ]

Street/Suite/Land Location *

City - Town *	Province - State *	Country *	Postal/ZIP Code *

Telephone No. *	Ext.	Fax No.	E-mail

Contact Type *
[ ] Senior Official
[ ] Contact for this Application
[ ] Representative in Canada

Sample 2: Completed Parts 1, 2, and 5 of Product Licence Application Form

PART 2
SUBMISSION TYPE

A. – PRODUCT LICENCE APPLICATION

Indicate the type of application (*select one only)

☐ Compendial ☒ Traditional claim ☐ Non-traditional claim ☐ Homeopathic ☐ Transitional DIN DIN # _____

NPN/DIN-HM # _____ (* – required for Section **B.** and **C.** only).

B. – PRODUCT LICENCE – AMENDMENT

Indicate the affected change to the NPN/DIN-HM above. (select one or more)

☐ Potency
☐ Source material of any of its medicinal ingredients
☐ Addition or substitution of a non-medicinal ingredient not on the NHPD List of Acceptable non medicinal ingredients
☐ Specification
☐ Deletion or modification of risk information on any labels
☐ Recommended dose
☐ Change to Animal Tissue Form(s)
☐ Recommended use/purpose
☐ Change to or from synthetically manufactured
☐ Recommended duration of use
☐ Change to manufacturing information

C. – PRODUCT LICENCE – NOTIFICATION

Indicate the type of change(s) that have been made to the NPN/DIN-HM above. (select one or more)

☐ Addition or substitution of any of its proposed non medicinal ingredient other than those originally authorized for the product.
☐ Change to the common name of any of its medicinal ingredients
☐ Addition of risk info on any of its labels
☐ Sale under a brand name other than the one(s) originally authorized for the product license
☐ Change to the proper name of any of its medicinal ingredients

D. – SUBMISSION CONTENT

Type of supporting documents, by volume: check type that is applicable and indicate the volume in which the document is submitted.

Volume #

Number of Volumes: _____

☒ **Product licence application form**
☐ Additional pages for Product information: #: _____
☐ Additional pages for Site information: #: _____
☐ Animal tissue form(s) #: _____ _____
☐ Third Party Authorization form: _____
☒ Label text #: _____ _____
☒ Evidence Summary Report: _____
☒ Safety Summary Report: _____
☒ Quality Summary Report: _____
☐ Other, Claim evidence: _____

E. – REFERENCE SUBMISSION

Other submission that contains the evidence to support the safety, efficacy and/or quality of this particular submission.

Submission #: _____

HC/SC 9267E (12-2003) **Page 2 of 6**

Sample 2: Completed Parts 1, 2, and 5 of Product Licence Application Form

ATTESTATION

"I attest that the natural health product that is the subject of this product license application will be manufactured, packaged, labelled, distributed and stored:

a) If the natural health product is imported, in accordance with the 'Good Manufacturing Practices' requirements as set out in Part 3 of the Natural Health Products Regulations or in accordance with requirements that are equivalent to those set out in Part 3, or

b) If the natural health product is not imported, in accordance with the 'Good Manufacturing Practices' requirements set out in Part 3 of the Natural Health Products Regulations."

Name of Authorized Senior Official (print) *	Signature *	Date *
Bob Fielding	Bob Fielding	2 0 0 4 1 0 1 5

Sample 3: Submission Receipt Acknowledgement

Company Code 12345
File # 987654
Submission # 987654

October 20, 2004

Ms. Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Dear Ms Lesley Smith:

Re: Application Product Licence Traditional Claim
Chinese Remedy
Date Received by the Natural Health Product Directorate:
2004-10-15 11:55 AM
***Natural Health Products Regulation* Section: 5**

The Natural Health Products Directorate (NHPD), Bureau of Product Review and Assessment (BPRA), thanks you for your submission. This Correspondence will serve as acknowledgement of receipt of your submission.

The adequacy of the data submitted to the NHPD has not been fully assessed at this time and will be determined during the assessment of the submission by the assessment units. As well, a need for data to address additional data gaps may be identified during the assessment. Consequently, further information may be requested by the NHPD by means of a processing deficiency notice (PDN) or an information request notice (IRN).

If you have any questions concerning this notice, please contact the submission processor at the below co-ordinates. Please note that the File Number and Submission Number (provided at the top right corner of the title page) must be quoted on all correspondence regarding this submission.

Yours truly,

John Doe
Processor
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
phone: 613-941-1000
fax: 613-954-2877

Sample 4: Response to the Acknowledgement Notice

Company Code	12345
File #	987655
Submission #	987655

October 20, 2004

Mr John Doe
Processor
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C

Dear Mr John Doe:

Re: Acknowledgment Notice 987655

Please find attached a revised copy of the PLA with an attached Designated Party Authorization Form.

Yours truly,

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Level 2: Processing

For more information about Level 2, see page 21.

Notes:

Samples of Level 2 Submission Documentation

5. Parts 3 and 4 of the Product Licence Application Form and Label Text
6. Processing Deficiency Notice (PDN)
7. Response to the PDN
8. Level 3 In-Queue Fax

Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

PART 3
SITE INFORMATION

Company Name			☐ Manufacturer SL# ______ ☐ Packager SL# ______ ☐ Labeller SL# ______ ☐ Importer SL# ______ ☐ Distributor
Number, Street - Suite - PO Box			
City			
Province - State	Postal Code - ZIP Code	Country	
Company Name			☐ Manufacturer SL# ______ ☐ Packager SL# ______ ☐ Labeller SL# ______ ☐ Importer SL# ______ ☐ Distributor
Number, Street - Suite - PO Box			
City			
Province - State	Postal Code - ZIP Code	Country	
Company Name			☐ Manufacturer SL# ______ ☐ Packager SL# ______ ☐ Labeller SL# ______ ☐ Importer SL# ______ ☐ Distributor
Number, Street - Suite - PO Box			
City			
Province - State	Postal Code - ZIP Code	Country	
Company Name			☐ Manufacturer SL# ______ ☐ Packager SL# ______ ☐ Labeller SL# ______ ☐ Importer SL# ______ ☐ Distributor
Number, Street - Suite - PO Box			
City			
Province - State	Postal Code - ZIP Code	Country	
Company Name			☐ Manufacturer SL# ______ ☐ Packager SL# ______ ☐ Labeller SL# ______ ☐ Importer SL# ______ ☐ Distributor
Number, Street - Suite - PO Box			
City			
Province - State	Postal Code - ZIP Code	Country	

HC/SC 9267E (12-2003) **Page 3 of 6**

Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

PART 4 -
PRODUCT INFORMATION

Primary Brand Name *	Other(s) if any		

Was animal tissue used in the processing of this product? ** ☐ Yes ☐ No

SECTION 1 — MEDICINAL INGREDIENT(S)

Ingredient No.	A Standard or Grade	B Compendial Monograph No.	C * Proper Name	D Common Name	E * Quantity	F * Synthetic		G ** Animal Tissue	
						Yes	No	Yes	No
1.				Astragalus, Huang qi	1 g		X		X
2.									
3.									
4.									
5.									
6.									
7.									
8.									
9.				Deficient					
10.									
11.									
12.									

Ingredient No.	H Potency		I * Source (if more than one enter on new line)		J Extract (if applicable)		K Method of preparation
	Amount	Constituent	Proper Name	Material	Ratio	Quantity Dried Equivalent	
1.							traditional
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							

Copy as necessary
* – denotes Mandatory
** – if yes complete Animal tissue Form

HC/SC 9267E (12-2003)

Page 4 of 6

Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

SECTION 2 — PROPOSED NON-MEDICINAL INGREDIENT(S)

Ingredient No.	Proper Name	Common Name *	Purpose *	Animal Tissue Used **	
				Yes	No
1.		Lactose	Capsule diluent		X
2.		Hydroxypropyl cellulose	Coating agent		X
3.		Microcrystalline cellulose	Capsule diluent		X
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					

Ingredient No.	Standard or Grade	Quantity	Source (if more than one enter on new line)	
			Proper Name	Material
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				

Copy this form as necessary
** – if yes complete Animal Tissue form

HC/SC 9267E (12-2003)

Page 5 of 6

Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

SECTION 3 — RECOMMENDED CONDITIONS OF USE

Recommended Use or Purpose *

Used in Traditional Chinese Medicine to tonify the lungs and is used for symptomatic relief in frequent colds

*For prolonged use consult a Traditional Chinese Medicine practitioner

Dosage Form (one only) *	Duration of Use (if any)	Sterile *	Route of Administration *
Capsule	See *	☐ Yes ☒ No	Oral

Recommended Dose (repeat for each sub-population group)

Sub-population group *	Amount *	Dosage Unit *	Frequency	Directions of Use
Adults	3	Capsules	3 times a day	N/A

Risk Information

Cautions and Warnings *

Consult a health care practitioner if you have an auto-immune disorder.

Contra-Indications *

Do not use if you are pregnant or breastfeeding.

Known Adverse Reactions

N/A

ATTESTATION

"I attest that the natural health product that is the subject of this product license application will be manufactured, packaged, labelled, distributed and stored:

a) if the natural health product is imported, in accordance with the 'Good Manufacturing Practices' requirements as set out in Part 3 of the Natural Health Products Regulations or in accordance with requirements that are equivalent to those set out in Part 3, or

b) if the natural health product is not imported, in accordance with the 'Good Manufacturing Practices' requirements set out in Part 3 of the Natural Health Products Regulations."

Name of Authorized Senior Official (print) *	Signature *	Date *
		y y y y m m d d

HC/SC 9267E (12-2003)

Page 6 of 6

Sample 5: Parts 3 and 4 of the Product Licence Application Form and Label Text

Proposed Label Text

Principal Display Panel:

Chinese Remedy

Product Number 8XXXXXXX

90 capsules

Other Panels:

*Astragalus membranaceus (*Astragalus, Huang qi) (dried root powder)….1g

Non-medicinal ingredients :

Lactose

Hydroxypropyl cellulose

Microcrystalline Cellulose

Use: Used in Traditional Chinese Medicine to tonify the lungs and is used for symptomatic relief in frequent colds.

Adults: Take 3 capsules, 3 times a day. For prolonged use consult a Traditional Chinese Medicine practitioner

Consult a health care practitioner if you have an auto-immune disorder.

Do not use if you are pregnant or breastfeeding.

Store at room temperature.

Herbal Inc., 123 St. Joseph Blvd, Ottawa, Ontario, Canada, K1E 2V2

Lot # XXXX

Expiry Date XXXX

Sample 6: Processing Deficiency Notice (PDN)

Natural Health Products Directorate
2936 Rue Baseline Rd., Basement/Sous-Sol AL3300B
Ottawa, Ontario
K1A 0K9

Company Code:12345
File: 987654
Submission: 987654

December 20, 2004

Ms Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd
Ottawa, Ontario
Canada
K1E 2V2

Dear Ms Lesley Smith

Re: Processing Deficiency Notice
Traditional Submission - Chinese Remedy

This notice is in respect of your Submission 987654, file 987654.

The application form and attachments provided with this submission have been verified by the Bureau of Product Review and Assessment for completeness and were determined to be deficient. At this time, your application is considered incomplete as per section 5 of the *Natural Health Products Regulations.* In order for the processing of your application to be completed, please submit all the following information:

1. The proper name for Astragalus, Huang qi was not provided. As per Chapter 2 of the Product Licensing guidance document, the proper name for all medicinal ingredients must be provided. As this ingredient is a plant, the proper name is the Latin name of its genus and, if any, its specific epithet. Please provide NHPD with the proper name for this ingredient.
2. The source material for Astragalus, Huang qi has not been indicated. As per Chapter 2 of the Product Licensing guidance document, it is required that the source material be provided for all medicinal ingredients. Please indicate the part of the plant used in this submission.
3. The submission package did not fulfill all the submission requirements. As per Chapter 3 of the Product Licensing guidance document, each type of application has specific submission requirements. For this traditional product licence application, 2 traditional references are required, as well as a listing of the search strategy used for this product. Please provide this data in your response.

The NHPD will retain this submission on file for 30 calendar days to enable you to address all of the deficiencies. If a written response is inadequate or is not received by the NHPD within 30 days of the date of this letter, the submission will be withdrawn. Please remember that the response to the list of deficiencies must be submitted in one consolidated package with the signature of a contact person outlined in the application form. Please note that the File Number and Submission Number (provided at the top right corner of the title page) must be quoted on all correspondence regarding this submission.

The adequacy of the data submitted to the NHPD has not been fully assessed at this time and will be determined during assessment of the submission by the Assessment Division. At this time, further information may be requested as per section 15 of the *Natural Health Products Regulations.*

Should you have any questions concerning the deficiencies identified in this notice, please contact the submission co-ordinator, Jane Jones, at the coordinates below.

Yours truly,

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
Phone: 613-941-1002
Fax: 613-954-2877

Sample 7: Response to the PDN

Company Code	12345
File #	987654
Submission #	987654

January 5, 2005

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, Ont
K1A 0K9, AL 3300C

Dear Ms. Jane Jones:

Re: PDN 987654

Please revise our Application to include the following:

The proper name for Astragalus, Huang qi is *Astragalus membranaceus*

The source material for Astragalus, Huang qi is the root.

Please find attached a copy of the evidence to support this product.

Yours truly,

Ms. Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd
Ottawa, Ontario
Canada
K1E 2V2

Sample 8: Level 3 In-Queue Fax

HEALTH CANADA
NATURAL HEALTH PRODUCTS DIRECTORATE

SANTÉ CANADA
DIRECTION DES PRODUITS DE SANTÉ NATURELS

FAX TRANSMITTAL SHEET/
FORMULAIRE DE COMMUNICATIONS PAR TÉLÉCOPIEUR

TO/À:		FROM/DE:
COMPANY/ORGANIZATION:		DATE:
FAX NUMBER/NUMÉRO DE TÉLÉCOPIEUR:		PAGE(S) INCLUDING COVER/PAGE(S) INCLUANT LA PAGE COUVERTURE:
()		1
PHONE NUMBER/NUMÉRO DE TÉLÉPHONE:		SENDER'S TELEPHONE NUMBER/NUMÉRO DE TÉLÉPHONE DE L'EXPÉDITEUR (E):
()		(613) / FAX: (613) 954-2877
RE/SUJET:		REFERENCE NUMBER/NUMÉRO DE RÉFÉRENCE:
NOTICE OF PLACEMENT IN ASSESSMENT (LEVEL 3) QUEUE		**N/A**

X FYI ❑ FOR REVIEW ❑ PLEASE COMMENT ❑PLEASE REPLY ❑ PLEASE RECYCLE

SUBJECT: **SUBMISSION STATUS UPDATE**
Brand Name - Sub No. 10XXXX

Please be advised that the above submission has entered Level 3 Queue for the assessment of Quality, Safety & Efficacy. Please see Chapter 4 of the Product Licensing guidance document for more information on the licensing process.

Thank you,

Submission Coordinator

Tel: (613)
Fax: (613) 954-2877

Notes:

Level 3: Assessment

For more information about Level 3, see page 31.

Notes:

Samples of Level 3 Submission Documentation

10. Evidence Summary Report
11. Quality Summary Report
12. Information Request Notice (IRN)
13. IRN Response

Sample 9: Evidence Summary Report

PART 1: EVIDENCE SUMMARY REPORT FOR TRADITIONAL PRODUCTS

(Refer to Part 4, Section 3.0 of the Product License Application)

A. RECOMMENDED USE OR PURPOSE (CLAIM)

(Provide the references that support the traditional use claim).

References:

1. **Bensky D, Gamble A. Chinese Herbal Medicine: Materia Medica. Seattle (WA): East and Press, Inc; 1993**
   [Hard copy provided]

2. **Pharmacopoeia of The People's Republic of China. Vol 1. Beijing (China): Chemical Industry Press; 1997.**
   [Hard copy provided]

3. **WHO monographs on selected medicinal plants vol.1: Radix Astragali. World Health Organization. Geneva; 1999.**
   [Hard copy provided]

4. Upton RH. American Herbal Pharmacopoeia and Therapeutic Compendium. Astragalus Root. Santa Cruz (CA): American Herbal Pharmacopoeia; 1999.

B. RECOMMENDED DOSE

(Provide the references that support the recommended daily dose.)

References: References 1, 2, and 3 indicated above support the recommended daily dose.

PART 2: SAFETY SUMMARY REPORT FOR TRADITIONAL PRODUCTS

(Complete this section for each medicinal ingredient provided on the product licence application form (Part 4: Section 1) and maintain the order.)

A. RISK INFORMATION

(Provide the rationale for the safety of the combination if applicable and references that support the risk information provided in Section 3.0 of the Product License Application.)

Traditional Combination Rationale: Not applicable

References: References 1, 2, 3, and 4 provided the relevant risk information.

B. SEARCH STRATEGY and LINE LISTING

(An example is provided at the end of the template. Additional pages must be added with the relevant information captured in the appropriate table. The column headings must be maintained.)

***Note:** The intent of the search strategy is to gather recent/current risk information (when available) on the traditional product.*

The intent of the listing is to summarize the information related to the recommended conditions of use based on the relevant articles discovered by the search strategy or from references for which hard-copies are not being submitted to the NHPD.

Database 1: Pubmed; limit: human; subset: toxicology
URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

SEARCH STRATEGY

Type of Evidence	Date of Search	Keywords	Limits	Results (#)	Relevant (#)	Rationale for Exclusion
I, IV	July 27 2004	astragalus	Human toxicology	31	1	Articles were excluded on the basis of the disease paradigm such as cancer, selenium toxicity or hepatitis. Articles in Chinese were also excluded.
IV	July 27 2004	Astragalus membranaceus	Human toxicology	14	0	Articles in Chinese were also excluded. Articles were excluded if cancer and hepatitis were investigated.
IV	July 27 2004	Astragalus immune	human	16	0	Articles in Chinese were excluded. Articles were excluded if organ rejection and hepatitis were investigated.

Sample 9: Evidence Summary Report

LISTING OF EVIDENCE

Type and Level of Evidence	Dosage: Dose, dosage form, frequency, and route of administration	Duration, if any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	Human; Animal; or *In vitro* (indicate below)	Design Results, and Conclusions	References
IV	N/A	N/A	a) N/A b) N/A c) N/A d) Very safe and doses as high as 100 g/kg of the raw herb have been given to rats with no adverse effects. The LD 50 of Astragalus is approximately 40g/kg when administered by intraperitoneal injection	N/A	Much of the pharmacological research is focused on its immune stimulating properties.	Sinclair S. Chinese Herbs: A clinical Review of Astragalus, Ligusticum and Schizandrae. Altern. Med. Rev.1998; 3(5):338-344.
V	One dropperful of tincture is taken two to three times per day. The dried root is taken in dosage of 1 to 4g three times per day.	N/A	a) N/A b) N/A c) N/A d) N/A	Human	It is believed to function as a warming tonic for increased resistance to cold. Help to replenish vital energy (qi), aiding the body in overcoming fatigue and weakness. Toxicity very low and known to be used for centuries.	Peirce A. Practical Guide to Natural Medicines. New York (NY): The Stonesong Press, Inc; 1999.
V	9-30 g daily. Decoction 0.5-1L daily (up to 120 g of whole root/L of water)	N/A	a) May not be appropriate for the treatment of autoimmune disease or following organ transplant. b) N/A c) N/A d) N/A	Human	Tonifies spleen lung and vital qi. Widely used as a immune modulator. Very safe.	Upton RH. American Herbal Pharmacopoeia and Therapeutic Compendium. Astragalus Root. Santa Cruz (CA): American Herbal Pharmacopoeia; 1999.
V	10-30 g per day of the dried root by decoction; 4-8 ml per day of the 1:2 liquid extract	May be used long term for most applications but is contraindicated during acute infections.	a) N/A b) Contraindicated for acute infections and pregnancy. c) N/A d) N/A	Human	In traditional Chinese medicine used to tonify the Qi and blood. Some of its actions are immunostimulant, tonic and adpatogenic	Mills S, Bone K. Principles and Practice of Phytotherapy. Modern Herbal Medicine. London (UK): Churchill Livingstone; 2000.

Sample 9: Evidence Summary Report

C. SAFETY FACTORS

(For each answer, if it is "Yes," can that risk be mitigated, e.g. through reformulation, over-the-counter product labeling etc.? And such any such recommendations must be provided in the General Overview Section of the Report.)

1. Are individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring required to ensure the safety or effectiveness of the product?
2. Is the product used in treatment of a disease that is not appropriate for self-care, e.g. a serious disease easily misdiagnosed by the public?
3. Does use of the product mask other ailments or their development?
4. Does the product have known adverse effects at the recommended or therapeutic dosage level?
5. Is there a narrow margin of safety between the therapeutic and toxic doses, especially in populations such as seniors, children and pregnant or nursing women?
6. Does the product have a demonstrated potential for addiction, abuse or severe dependency that is likely to lead to harmful non-medicinal use?
7. Does product have a therapeutic effect based on recently established pharmacological concepts, the consequences of which have not yet been fully established?
8. Have experimental data shown that the product induces toxicity in animals? If so, has it been in use long enough to establish the pattern or frequency of long term toxic effects in humans?
9. Does the product have known adverse interactions with other natural health products, drugs, or foods?
10. Is the product known to affect results of standard laboratory or other diagnostic tests?
11. Does the product contribute to, or is it likely to contribute to, the development of resistant strains of micro-organisms in humans?
12. Does the product possess a high level of risk relative to expected benefits?

Response to Safety Factors? (Additional pages may be added for this section.)

Response to Safety Factors:

1. No
2. No
3. No
4. Yes. Upton 1999 (reference 4) reported that astragalus might not be appropriate for the treatment of autoimmune disease or following organ transplant (immunosuppressive drugs). A caution will appear on the label concerning auto-immune disorder. Bensky and Gamble 1993 (reference 1) contraindicate astragalus in cases of exterior excess, qi stagnation, damp obstruction, food stagnation, yin deficiency with heat signs or skin lesions either in their early stages or where there is heat toxin, this contraindication refers to its traditional use. The risk will be mitigated by the following contraindication: "According to traditional Chinese medicine, do not use in cases of exterior excess, qi stagnation, damp obstruction, food stagnation, yin deficiency with heat signs or skin lesions either in their early stages or where there is heat toxin"
5. No, since no data are available for pregnant and breastfeeding women, a contraindication will be included for that population.
6. No
7. No
8. No
9. No
10. No
11. No
12. No

NON-MEDICINAL INGREDIENTS (NMIs)

(NMIs used in this product are provided in 2.0 of the Product License Application)

☑ I acknowledge that all the NMIs are on the Acceptable List and within any limitations on that list.

Additional information is required for NMIs not on the Acceptable List or not within the limitations. Refer to Chapters 7.0 of the Evidence for Safety and Efficacy for Finished Natural Health Products Guidance Document and provide the relevant information with the submission.

Sample 10 Quality Summary Report

ABC Laboratory

Item name: *Astragalus membranaceus* (capsule)
Item Number: 01-234
Formula Version: 1 **Date:** March 30, 2004
Specific Version: 2 **Date:** April 30, 2004

Prepared by: Analyst **Date:** July 30, 2004
Approved by: Supervisor / Manager **Date:** July 30, 2004

Test	Method	Label Claim	Parameters Excess	Limits
Physical Tests				
Description	Organoleptic			
Quantity/Potency				
Astragalus membranaceus	01.04.800	1.0g	90-110%	
Purity				
Yeast and Mould (Contaminating fungus)	USP <2021>		NMT 300 cfu/g	
Total Aerobic Count	USP <2021>		NMT 3,000 cfu/g	
E. coli			Absent	
Salmonella spp.			Absent	
S. aureus			Absent	
Arsenic	ICP-MS		< 0.14 mcg / kg b.w./day	
Cadmium	ICP-MS		< 0.09 mcg/ kg b.w./day	
Lead	ICP-MS		< 0.29 mcg / kg b.w./day	
Total mercury	ICP-MS		< 0.29 mcg / kg b.w./day	

Sample 11: Information Request Notice (IRN)

Health Canada / Santé Canada

Natural Health Products Directorate
AL: 3300B, Qualicum, 2936 Baseline Road
Ottawa, Ontario K1A 0K9

Company Code: 12345
File Number: 987654
Submission Number: 987654

January 24, 2005

Ms. Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Dear Ms. Smith:

Re: Information Request Notice
Traditional -Chinese Remedy

This is in response to your submission 987654, file 987654.

The application and evidence provided with this submission have been assessed for quality and have been determined to be deficient. At this time, NHPD requires further information in order to properly assess your submission. As per section 15 of the *Natural Health Products Regulations, please submit all the following information:*

1. The risk information provided in your Product License Application and label is insufficient. As per section 5(f) of the Natural Health Products Regulations, the applicant is required to include recommended conditions of use on its Product License Application. According to your safety summary report, astragalus should not be used in case of exterior excess, qi stagnation, damp obstruction, food stagnation, yin deficiency with heat signs or skin lesions either in early stages or where there is heat toxin. Because of the traditional claim, known traditional contraindications should be included on your Product License Application and label. Please add the following cautionary statement on your Product License Application and label: "According to Traditional Chinese Medicine, do not use in cases of exterior excess, qi stagnation, damp obstruction, food stagnation, yin deficiency with heat signs or skin lesions either in their early stages or where there is heat toxin." Please confirm that this will be added to both the Product License Application and the label.
2. Please provide a revised copy of the Finished Product Specifications which should include the following information:
    a. The name of the test method and tolerance limits for the dissolution of the capsules, as per Section 3.1 of the *Evidence for Quality of Finished Natural Health Products Guidance Document.* Disintegration times are applied for natural health products intended to be swallowed whole whether uncoated and plain coated tablets or hard and soft gelatin capsules. Applicants are expected to comply with these tablet disintegration times as tested by the official method DO-25.
    b. The name of the test method and tolerance limits for heavy metals i.e., Lead, Arsenic, Mercury and Cadmium in the product as per Chapter 2.2.2 of the *Evidence for Quality of Finished Natural Health Products Guidance Document* must be provided.
    c. The product is plant based, therefore the name of the test method and tolerance limits for pesticides in the product as per Chapter 2.2.2 of the *Evidence for Quality of Finished Natural Health Products Guidance Document* must be provided. If not, provide a scientific rationale to justify the omission of this test.
    d. Please provide a brief description and/or name of the house test method "01.04.800".

The NHPD will retain this submission on file for 30 calendar days in order for all of the deficiencies to be addressed. If a written response is inadequate or is not received by the NHPD within 30 days of the date of this letter, the submission will be withdrawn. Please remember that the response to the list of deficiencies must be submitted in one consolidated package and numbered accordingly. In responding to these issues, please quote the submission number and file number in your response.

If you have any questions concerning the information requested for this submission, please contact the submission co-ordinator at the co-ordinates below.

Yours truly,

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
Phone: 613-941-1002
Fax: 613-954-2877

Sample 12: IRN Response

Company Code 12345
File # 987654
Submission # 987654

January 25, 2005

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C

Dear Ms. Jane Jones:

Re: Information Request Notice
Traditional -Chinese Remedy

Please find attached our revised Application including the following:

1. The contraindication: "According to Traditional Chinese Medicine, do not use in cases of exterior excess, qi stagnation, damp obstruction, food stagnation, yin deficiency with heat signs or skin lesions either in their early stages or where there is heat toxin" is now included in the Product Licence Application and revised label. See attached.
2. Please review the attached new copy of Finished Product Specification with details on the disintegration of the tablet, test for pesticides. As for the house method number "01.04.800.01", a brief description of the Standard Operating Procedures for the Method for Reporting Amount by Input is provided in a separate binder.

Yours truly,

Ms. Lesley Smith
Regulatory Affairs Agent
Herbal Inc.
123 St. Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Sample 12: IRN Response

SECTION 3 — RECOMMENDED CONDITIONS OF USE

Recommended Use or Purpose *

Used in Traditional Chinese Medicine to tonify the lungs and is used for symptomatic relief in frequent colds.

* For prolonged use consult a Traditional Chinese Medicine practitioner

Dosage Form (one only) *	Duration of Use (if any)	Sterile *	Route of Administration *
capsule	See *	☐ Yes ☒ No	Oral

Recommended Dose (repeat for each sub-population group)

Sub-population group *	Amount *	Dosage Unit *	Frequency	Directions of Use
Adults	3	capsules	3 times a day	N/A

Risk Information

Cautions and Warnings *

Consult a health care practitioner if you have an auto-immune disorder.

Contra-Indications *

Do not use if you are pregnant or breastfeeding.

According to Traditional Chinese Medicine, do not use in cases of exterior excess, qi stagnation, damp obstruction, food stagnation, yin deficiency with heat signs or skin lesions either in their early stages or where there is heat toxin.

Known Adverse Reactions

n/a

ATTESTATION

"I attest that the natural health product that is the subject of this product license application will be manufactured, packaged, labelled, distributed and stored:

a) if the natural health product is imported, in accordance with the 'Good Manufacturing Practices' requirements as set out in Part 3 of the Natural Health Products Regulations or in accordance with requirements that are equivalent to those set out in Part 3, or

b) if the natural health product is not imported, in accordance with the 'Good Manufacturing Practices' requirements set out in Part 3 of the Natural Health Products Regulations."

Name of Authorized Senior Official (print) *	Signature *	Date *
Gus Xu	*Gus Xu*	2004 10 15

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Page 6 of 6

Sample 12: IRN Response

Proposed Label Text

Principal Display Panel:

Chinese Remedy

Product Number 8XXXXXXX

90 capsules

Other Panels:

*Astragalus membranaceus (*Astragalus, Huang qi) (dried root powder) ….1g

Non-medicinal ingredients :

Lactose

Hydroxypropyl cellulose

Microcrystalline Cellulose

Use: Used in Traditional Chinese Medicine to tonify the lungs and is used for symptomatic relief in frequent colds.

Adults:Take 3 capsules, 3 times a day. For prolonged use consult a Traditional Chinese Medicine practitioner.

Consult a health care practitioner if you have an auto-immune disorder.

Do not use if you are pregnant or breastfeeding.

According to Traditional Chinese Medicine, do not use in cases of exterior excess, qi stagnation, damp obstruction, food stagnation, yin deficiency with heat signs or skin lesions either in their early stages or where there is heat toxin.

Store at room temperature.

Herbal Inc., 123 St Joseph Blvd, Ottawa, Ontario, Canada, K1E 2V2

Lot # XXXX

Expiry Date XXXX

Sample 12: IRN Response

Finished Product Specification

Item name: *Chinese remedy*
Item Number: 01-234
Formula Version: 1 **Date:** March 30, 2004
Specific Version: 2 **Date:** April 30, 2004

Prepared by: Analyst **Date:** July 30, 2004
Approved by: Supervisor / Manager **Date:** July 30, 2004

Test	Test Method	Tolerance Limits
Physical Tests		
Description	Organoleptic	characteristics to item
Disintegration	USP<701>	Not more than 30 minutes
Quantity/Potency		
Astragalus membranaceus	(01.04.800 see description)	90-110%
Purity		
Yeast and Mould (Contaminating fungus)	USP <2021>	NMT 300 cfu/g
Total Aerobic Count	USP <2021>	NMT 3,000 cfu/g
E. coli	USP <2021>	Absent
***Salmonella* spp.**	USP <2021>	Absent
S. aureus	USP <2021>	Absent
Arsenic	ICP-MS	< 0.14 mcg / kg b.w./day
Cadmium	ICP-MS	< 0.09 mcg/ kg b.w./day
Lead	ICP-MS	< 0.29 mcg / kg b.w./day
Total mercury	ICP-MS	< 0.29 mcg / kg b.w./day
Pesticides	USP <561>	conforms to USP limits

Notes:

Level 4: Assessment

For more information about Level 4, see page 55.

Notes:

Samples of Level 4 Submission Documentation

13. Product Licence Issuance
14. Product licence

Sample 13: Product Licence Issuance

Company Code 12345
File # 987655
Submission # 987655

February 1st, 2005

Mr Bob Fielding
Senior Consultant
45 New Hampshire Drive
Ottawa, Ontario
Canada
K1X 2C2

Dear Mr Fielding,

Re: Product Licence Issuance NPN 80000000
Non-Traditional, Cold Remedy

The Natural Health Products Directorate (NHPD) has conducted an assessment of your submission and has considered the product to be in compliance pursuant to section 7 of the *Natural Health Products Regulations.* Please note that any labels used in the marketing of this product must reflect the information outlined on the product licence and must comply with the labelling requirements as per Part 5 of the Regulations.

Please find enclosed a copy of the Product Licence thereby authorizing the sale of the product described therein.

Please note as per sections 11, 12 and 13 of the *Natural Health Products Regulations*, changes made in respect of a licenced product, require an amendment, notification or a new product licence. Please see the *Product Licensing Guidance Document* for further information and the applicable requirements.

Please note that as per Part 5, Section 87 of the *Natural Health Products Regulations* (Labelling and Packaging), you are responsible for ensuring that the label text is translated correctly into French.

If you have any questions concerning the information on the licence, please submit a "Request for Correction to the Product Licence" using the form found in Appendix 5 of the *Product Licensing Guidance Document* or contact the Submission Coordinator, Jane Jones, of the Submission Management Division. Please note that the File Number (provided at the top right corner of the title page) and Product Number must be quoted on all future correspondence regarding this product.

Yours truly,

Jane Jones
Product Licencing Submission Co-ordinator
Natural Health Products Directorate
2936 Baseline Rd.
Ottawa, ON
K1A 0K9, AL 3300C
Phone: 613-941-1002
Fax: 613-954-2877

encl.: Product licence
c.c: Lesley Smith

Sample 13: Product Licence Issuance

Product Licence
Licence de mise en marché

Product Number/*Numéro de produit*: **80000000**

Brand Name/*Marque nominative*: **Chinese Remedy**

Issued to:
Name of licensee/*Nom du titulaire*: Herbal Inc.
Address(e): 123 St Joseph Blvd.
Ottawa, Ontario
Canada
K1E 2V2

Authorized for the following/*Authorizé pour ce qui suit*:
Dosage form/*Forme posologique*: capsule
Recommended route of administration/*Voie d'administration recommandée*: oral
Recommended dose/*Dose recommandée*: Adults: 3 capsules, three times a day
Recommended duration of use/*Durée d'ulitisation recommandée*: For prolonged use consult a Traditional Chinese Medicine practitioner
Recommended use or purpose/*Usage ou les fins recommandés*:
Used in Traditional Chinese Medicine to tonify the lungs and is used for symptomatic relief in frequent colds.

Medicinal Ingredient/*Ingrédients médicinaux*		**Quantity/ dosage unit** *Quantité par unité posologique*	**Extract Ratio/***Ratio D'éxtraction*	**Potency/** *Activité*	**Source Material/** *Matière d'origine*
Proper Name/*Nom propre*	**Common Name/** *Nom Usuel*				
Astragalus membranaceus	Astragalus, Huang qi	1 g	n/a	n/a	dried root powder

This licence is issued by the Minister of Health under the authority of section 7 of the Natural Health Products Regulations. Sale of the described natural health product, including any changes thereto pursuant to section 11 of the Regulations, is subject to the Food and Drugs Act and to the Natural Health Products Regulations.
Cette licence est délivrée par la ministre de la Santé en vertu de l'article 7 du Règlement sur les produits de santé naturels. La vente du produit de santé naturel décrit dans la présente, y compris toute modification afférente au sens de l'article 11 du Règlement, est assujettie à la Loi sur les aliments et drogues et au Règlement sur les produits de santé naturels.

Issued/*délivrée le*: **January 31, 2005**	**Revised/Amended/***Modifiée le*: **N/A**

Director General/*Directeur Générale*
NHPD/*DPSN*

Appendices

Appendix 1: Annotated Product Licence Application Form

PART 1: APPLICANT AND CONTACT INFORMATION
The **Applicant or Licensee** is the company whose name the application is filed and the product licence will be issued.

Contacts refers to the contact people specific to the product licence application.

Applicant/Company Name: Legal name of the applicant. Do not abbreviate the company name.

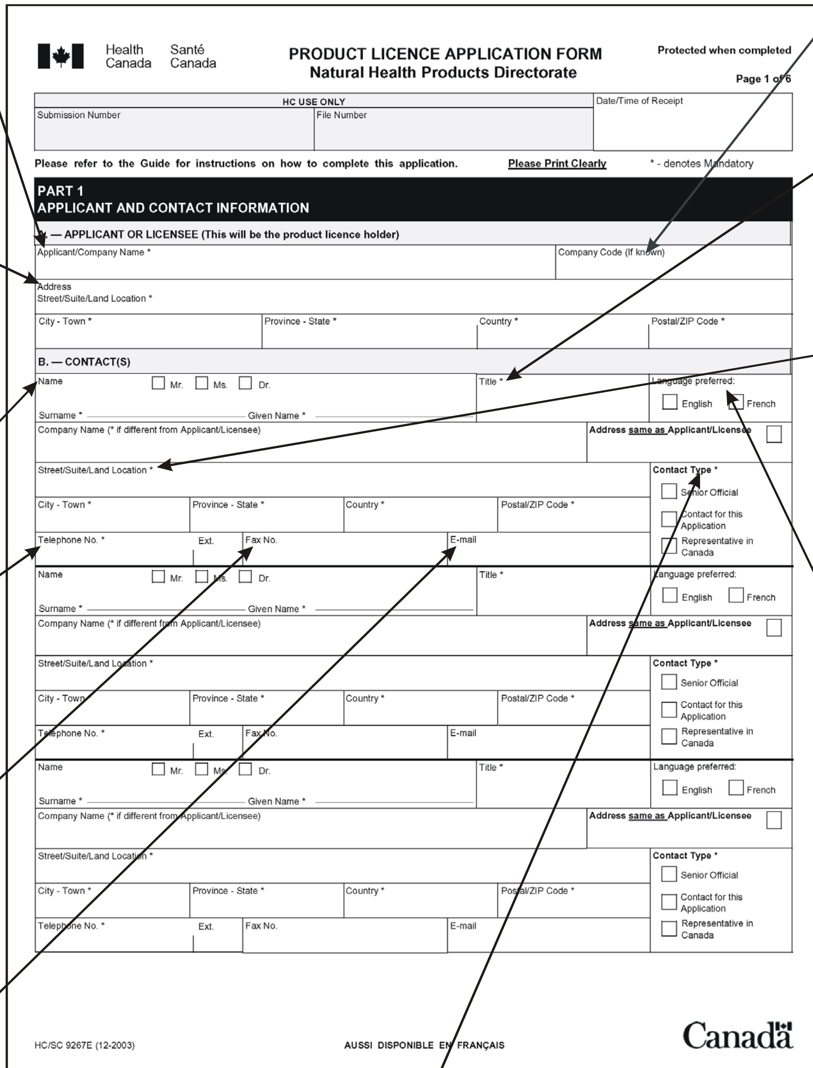
Address: City address for the company making the application. If a P.O. Box is used, the address must also be provided.

Name: Name of the contact person.

Telephone Number: Phone number (with area code and extension) for this contact person.

Fax Number: Number (with area code) to which facsimiles may be sent for this contact person.

Email: Electronic mailing address for this contact person.



Health Canada / Santé Canada

PRODUCT LICENCE APPLICATION FORM
Natural Health Products Directorate

Protected when completed

Page 1 of 6

HC USE ONLY		Date/Time of Receipt
Submission Number	File Number	

Please refer to the Guide for instructions on how to complete this application. Please Print Clearly * - denotes Mandatory

PART 1
APPLICANT AND CONTACT INFORMATION

A. — APPLICANT OR LICENSEE (This will be the product licence holder)

Applicant/Company Name * | Company Code (If known)

Address
Street/Suite/Land Location *

City - Town * | Province - State * | Country * | Postal/ZIP Code *

B. — CONTACT(S)

Name ☐ Mr. ☐ Ms. ☐ Dr. | Title * | Language preferred: ☐ English ☐ French
Surname * Given Name *
Company Name (* if different from Applicant/Licensee) | Address same as Applicant/Licensee ☐
Street/Suite/Land Location * | Contact Type * ☐ Senior Official ☐ Contact for this Application ☐ Representative in Canada
City - Town * | Province - State * | Country * | Postal/ZIP Code *
Telephone No. * | Ext. | Fax No. | E-mail

Name ☐ Mr. ☐ Ms. ☐ Dr. | Title * | Language preferred: ☐ English ☐ French
Surname * Given Name *
Company Name (* if different from Applicant/Licensee) | Address same as Applicant/Licensee ☐
Street/Suite/Land Location * | Contact Type * ☐ Senior Official ☐ Contact for this Application ☐ Representative in Canada
City - Town * | Province - State * | Country * | Postal/ZIP Code *
Telephone No. * | Ext. | Fax No. | E-mail

Name ☐ Mr. ☐ Ms. ☐ Dr. | Title * | Language preferred: ☐ English ☐ French
Surname * Given Name *
Company Name (* if different from Applicant/Licensee) | Address same as Applicant/Licensee ☐
Street/Suite/Land Location * | Contact Type * ☐ Senior Official ☐ Contact for this Application ☐ Representative in Canada
City - Town * | Province - State * | Country * | Postal/ZIP Code *
Telephone No. * | Ext. | Fax No. | E-mail

HC/SC 9267E (12-2003) AUSSI DISPONIBLE EN FRANÇAIS Canada

Company Code: Code assigned by Health Canada, if known.

Title: Title and designation of this contact, e.g., Director of Research.

Address: Address to which mail should be sent to reach this contact person.

Language Preferred: Language of preference for correspondences to this contact person.

Contact Type: Check boxes as applicable, e.g., if the senior official is also the representative in Canada, only one "contact" box needs to be completed, with a check mark for "senior official" box and "representative in Canada" box.

- **Senior Official:** Principal contact person; **not** the contact person for product specific questions, but the person who represents the company. This should be a senior person in the company such as a CEO or director. This is the same person for all product licence applications submitted to NHPD from your organization.
- **Contact for this Application:** Contact person for product specific questions. This may be an employee of the applicant company, or one contracted from another company on behalf of the applicant.
- **Representative in Canada:** Contact to whom Health Canada should direct regulatory mail. This is required if the Senior Official's address is not Canadian.
- **Note:** Although a representative in Canada is always required, any contact with a Canadian address may act as the representative in Canada.

Appendix 1: Annotated Product Licence Application Form

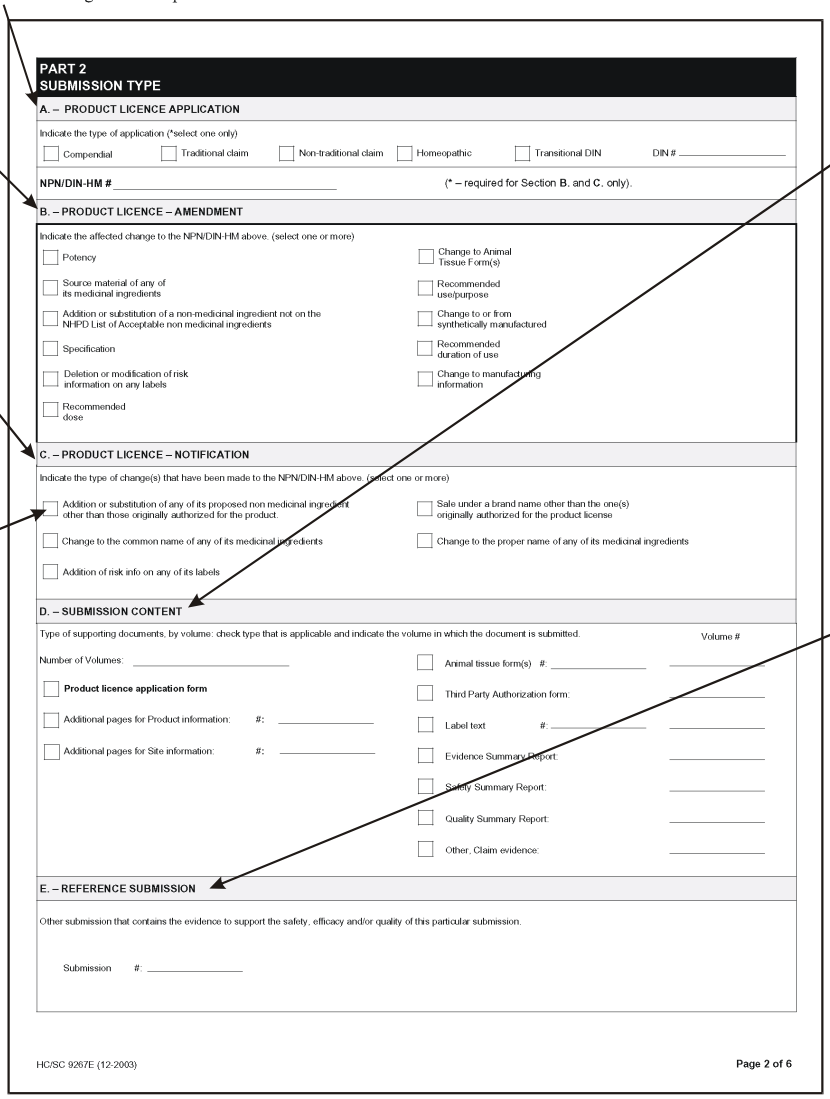
PART 2 - SUBMISSION TYPE
A: PRODUCT LICENSE APPLICATION
For further information on these types of applications, refer to Chapter 3 of the *Product Licencing Guidance Document.*

- **Compendial:** An application for a product that has one or more medicinal ingredients contained in a monograph for a single or combination of medicinal ingredient(s) in the NHPD *Compendium of Monographs*.
- **Traditional Claim:** An application for a product whose use is supported by two or more independent traditional references.
- **Non-Traditional Claim:** An application for a product which does not fit any other application categories.
- **Homeopathic:** An application for a product in which all the ingredients are homeopathic.
- **Transitional DIN:** An application for a product which has a valid **Drug Identification Number** (DIN). Include the DIN assigned to this product.

B: Product License Amendment
If the subject submission is to amend an already existing product licence, please place a checkmark beside the applicable amendment(s) listed.

C: Product Licence Notification
If the subject submission is to notify NHPD of changes to a product licence, please place a checkmark in the applicable changes listed.

- The new ingredient must also be on the Acceptable List (see the *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document*).



PART 2
SUBMISSION TYPE

A. – PRODUCT LICENCE APPLICATION

Indicate the type of application (*select one only)

☐ Compendial ☐ Traditional claim ☐ Non-traditional claim ☐ Homeopathic ☐ Transitional DIN DIN # _____

NPN/DIN-HM # _____ (* – required for Section B. and C. only).

B. – PRODUCT LICENCE – AMENDMENT

Indicate the affected change to the NPN/DIN-HM above. (select one or more)

☐ Potency
☐ Source material of any of its medicinal ingredients
☐ Addition or substitution of a non-medicinal ingredient not on the NHPD List of Acceptable non medicinal ingredients
☐ Specification
☐ Deletion or modification of risk information on any labels
☐ Recommended dose
☐ Change to Animal Tissue Form(s)
☐ Recommended use/purpose
☐ Change to or from synthetically manufactured
☐ Recommended duration of use
☐ Change to manufacturing information

C. – PRODUCT LICENCE – NOTIFICATION

Indicate the type of change(s) that have been made to the NPN/DIN-HM above. (select one or more)

☐ Addition or substitution of any of its proposed non medicinal ingredient other than those originally authorized for the product.
☐ Change to the common name of any of its medicinal ingredients
☐ Addition of risk info on any of its labels
☐ Sale under a brand name other than the one(s) originally authorized for the product license
☐ Change to the proper name of any of its medicinal ingredients

D. – SUBMISSION CONTENT

Type of supporting documents, by volume: check type that is applicable and indicate the volume in which the document is submitted. Volume #

Number of Volumes: _____

☐ **Product licence application form**
☐ Additional pages for Product information: #: _____
☐ Additional pages for Site information: #: _____
☐ Animal tissue form(s) #: _____ _____
☐ Third Party Authorization form: _____
☐ Label text #: _____ _____
☐ Evidence Summary Report: _____
☐ Safety Summary Report: _____
☐ Quality Summary Report: _____
☐ Other, Claim evidence: _____

E. – REFERENCE SUBMISSION

Other submission that contains the evidence to support the safety, efficacy and/or quality of this particular submission.

Submission #: _____

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D: Submission Content
Number of Volumes: Number of volumes (binders) included in the submission, if applicable.

Type of Supporting Documents: Number of pages attached and volume, if applicable, in which they can be found.

E: Reference Submission: If previous submission made relates to the application, include, where applicable, the submission number.

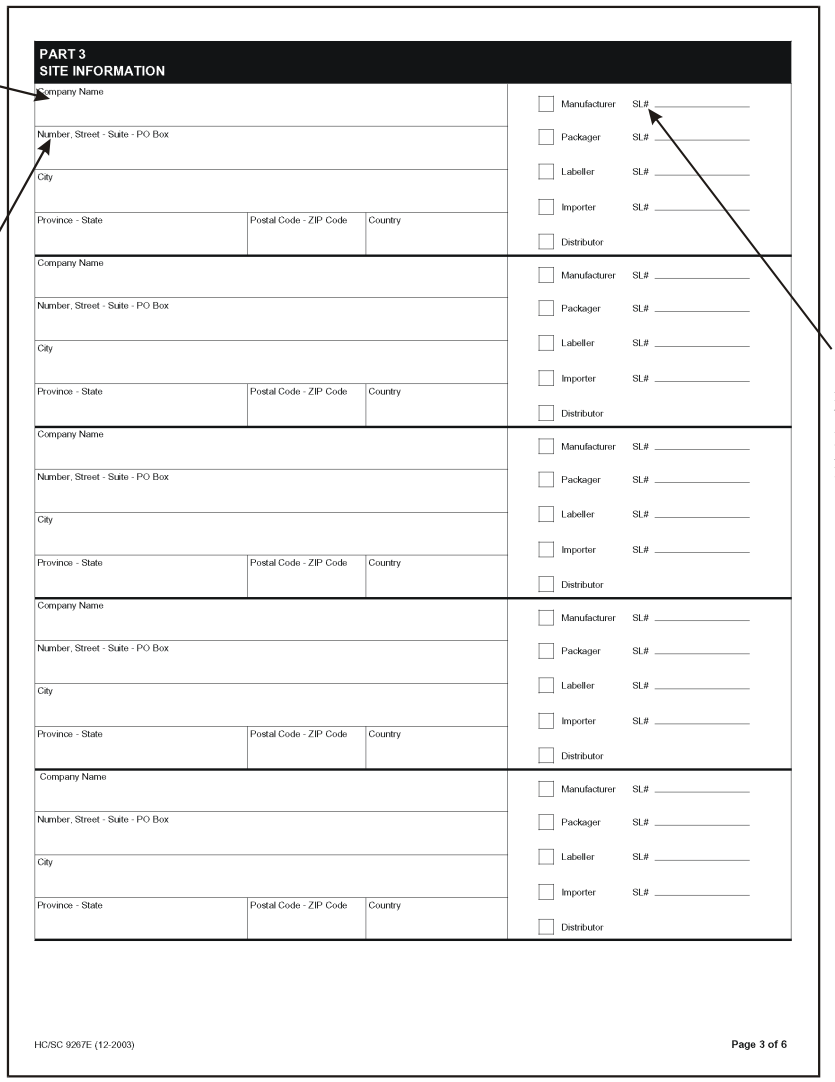
Appendix 1: Annotated Product Licence Application Form

PART 3: SITE INFORMATION
Site information relates to the sites which are involved in the production of the product.

A location may be licensed to manufacture, package, label, import and/or distribute. For each company name, check all activities which are conducted by that company.

Company Name: The company that owns the site.

Address: The address of the company, **not** the site at which the activity is taking place.



PART 3
SITE INFORMATION

Company Name
Number, Street - Suite - PO Box
City
Province - State | Postal Code - ZIP Code | Country
Manufacturer SL# _____
Packager SL# _____
Labeller SL# _____
Importer SL# _____
Distributor

(Repeated for 5 companies)

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Page 3 of 6

Site licence number: If site licence number is not available, leave it blank.
Note: Distributors do not require a site licence.

Note: If there is not sufficient room on the form to complete the information for all companies involved in the production of the product, please attach separate sheets, using the same format and providing the same information as requested in the application. State the number of additional pages.

Appendix 1: Annotated Product Licence Application Form

PART 4 - PRODUCT INFORMATION
Primary Brand Name: If the product will be sold under more than one brand name, choose one as the primary brand name. Include this name in correspondence with NHPD.

Others: Additional brand names under which the product will be sold should also be listed.

Was animal tissue used in the processing of this product?: If animal tissue was used in processing the product, but is not in the final product, this must be declared, and the animal tissue form completed.

SECTION 1 - MEDICINAL INGREDIENT(S)

A: Standard or Grade: If the ingredient conforms to a particular standard, state that standard here.

B: Compendial Monograph No.: If the application cites a NHPD monograph, specify the NHPD monograph number.

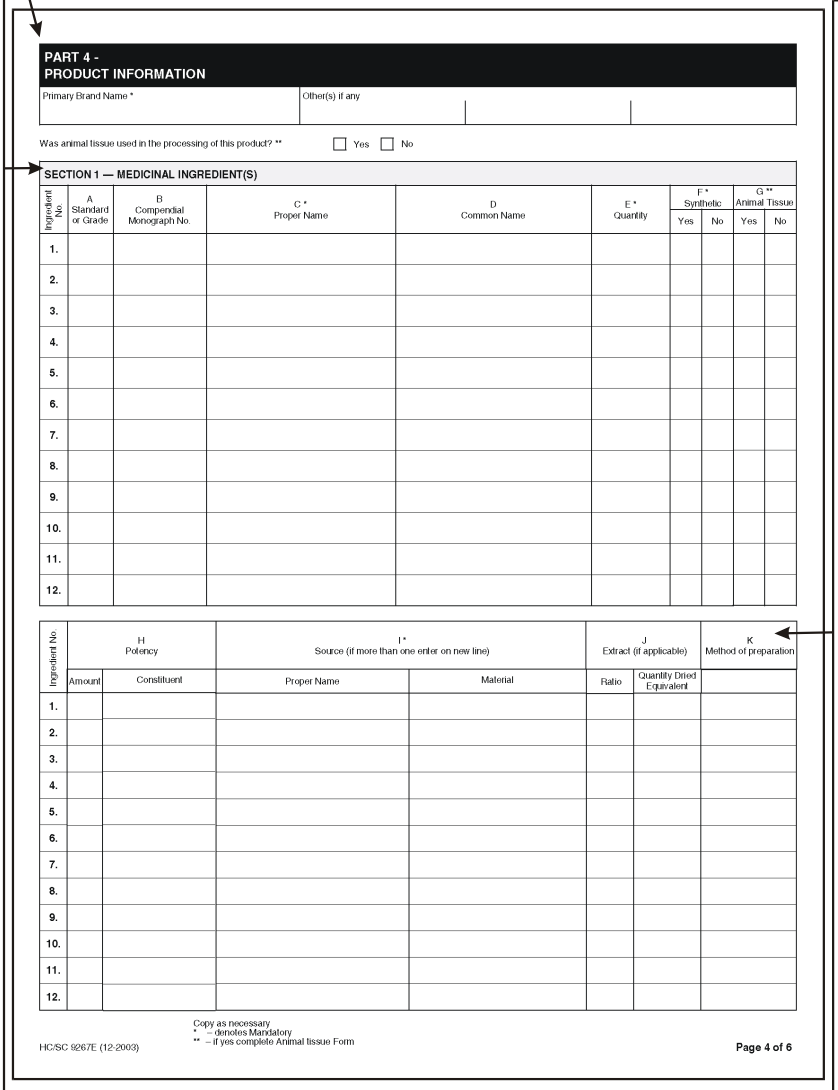
C: Proper Name: Proper name of the ingredient.

D: Common Name: Common name of the ingredient which will appear on the label. Common name and proper name may be the same, e.g., *Vitamin C*. If so, leave common name blank.

E: Quantity: Quantity of the specified medicinal ingredient per dosage unit.*
Example: For a 500mg tablet.
Quantity: 500 mg

F: Synthetic: Indicate if ingredient has been synthetically manufactured. Additional information may be required of synthetic products; consult the *Evidence of Quality for Natural Health Products* for information.

G: Animal Tissue: Indicate if the ingredient is derived from animal sources. If yes, complete the animal tissue form Appendix 4 of the *Product Licencing Guidance Document*.



PART 4 - PRODUCT INFORMATION

Primary Brand Name * | Other(s) if any

Was animal tissue used in the processing of this product? ** ☐ Yes ☐ No

SECTION 1 — MEDICINAL INGREDIENT(S)

Ingredient No.	A Standard or Grade	B Compendial Monograph No.	C * Proper Name	D Common Name	E * Quantity	F * Synthetic Yes	F * Synthetic No	G ** Animal Tissue Yes	G ** Animal Tissue No
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
9.									
10.									
11.									
12.									

Ingredient No.	H Potency Amount	H Potency Constituent	I * Source (if more than one enter on new line) Proper Name	I * Source (if more than one enter on new line) Material	J Extract (if applicable) Ratio	J Extract (if applicable) Quantity Dried Equivalent	K Method of preparation
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							

Copy as necessary
* – denotes Mandatory
** – if yes complete Animal tissue Form

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* If the ingredient is an extract or tincture, this is the amount of extract including the unit measure contained in each dosage unit.
For homeopathic products, this is the dilution/potency of the ingredient. Only the most concentrated dilution should be included in this field.

H: Potency: Potency of homeopathic products should not be declared here, but as quantity **[E]**.
Amount: Amount of standardized component; usually a percentage.
Constituent: The component to which the amount applies.
Example: 5% hyperforin

I: Source: Origin of the ingredient. There may be multiple sources for an ingredient. If so, list each source on a separate line.
Proper Name - Required only in the case of isolates, probiotics and essential fatty acids and is the proper name of the source.
Material - Required in all cases. See explanatory chart in Appendix 2.

J: Extracts (if applicable):
- **Ratio -** Ratio for extracts and tinctures should be denoted as: crude material : preparation.
- **Quantity dried equivalent -** Completed only in the case of an extract or tincture; amount of crude ingredient used in the extract.

K: Method of Preparation: Indicate if the method of preparation is a traditional method of preparation (see the *Evidence for Safety and Efficacy Guidance Document*) or a non-traditional method.

Appendix 1: Annotated Product Licence Application Form

PART 4 - PRODUCT INFORMATION - CONTINUED
SECTION 2: PROPOSED NON-MEDICINAL INGREDIENTS
There are two basic categories of non-medicinal ingredients to consider: those from the List of Acceptable Non-medicinal Ingredients and those not from the List (refer to the *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document*).

Proper Name: Proper name of the non-medicinal ingredient is required for ingredients not on the List mentioned above.

Common Name: Common name of the ingredient is always required.

Standard or Grade: Standard to which the ingredient conforms is required only if a claim to a standard or grade is being made.

Quantity: Quantitative listing of the ingredient per dosage unit is only required if the ingredient is not on the List mentioned above or when the ingredient does not meet the limitations specified in the List.

Purpose: Use or function of the ingredient is always required. (A sample list of purposes can be found in Appendix 6 to the *Product Licencing Guidance Document*)

Animal Tissue Used: If the ingredient is derived from animal sources, an animal tissue form must be completed.

Source: Origin of the ingredient and should be listed as described above for medicinal ingredients.

SECTION 2 — PROPOSED NON-MEDICINAL INGREDIENT(S)

Ingredient No.	Proper Name	Common Name *	Purpose *	Animal Tissue Used **	
				Yes	No
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					

Ingredient No.	Standard or Grade	Quantity	Source (if more than one enter on new line)	
			Proper Name	Material
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				

Copy this form as necessary
** – if yes complete Animal Tissue form

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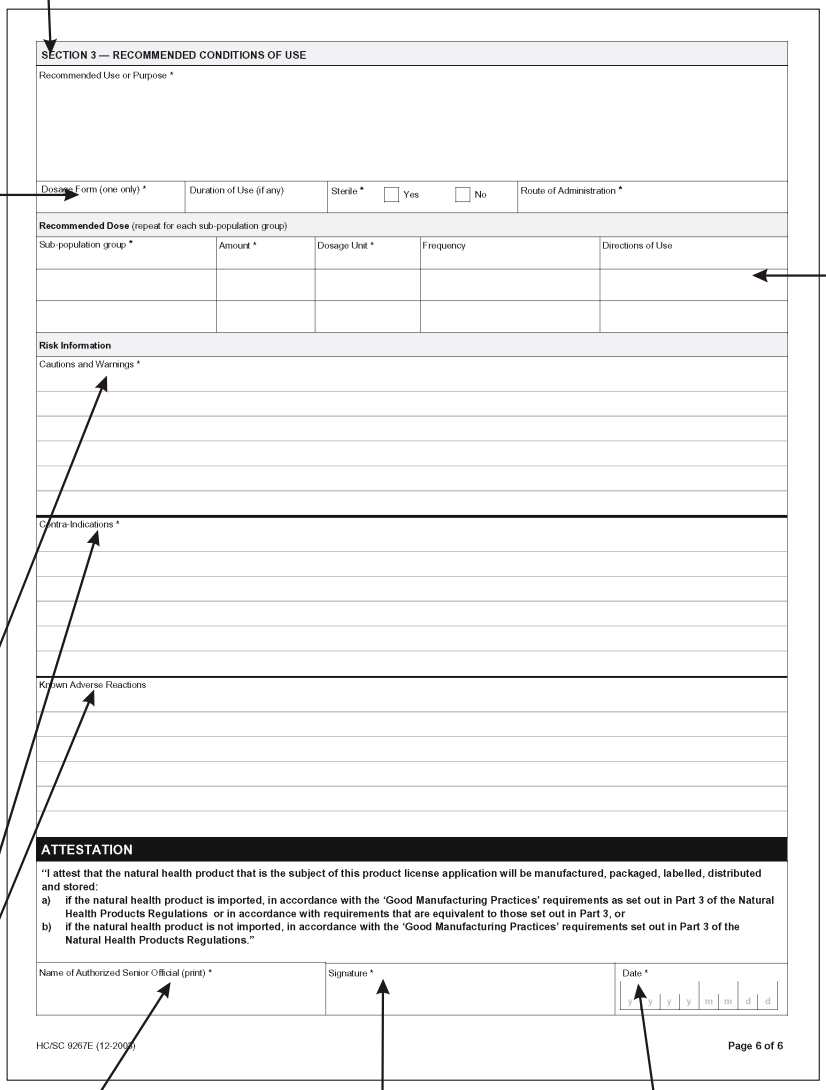
Note: The information required by section 5 of the *Natural Health Product Regulations* for non-medicinal ingredients includes common name, purpose and animal tissue information. However, to prevent delay in assessment, additional information is likely to required by NHPD under section 15 of the *Natural Health Product Regulations* and it is encouraged that the applicant submit this information at the time of initial submission.

Appendix 1: Annotated Product Licence Application Form

PART 4 - PRODUCT INFORMATION - CONTINUED
SECTION 3: RECOMMENDED CONDITIONS OF USE
Recommended Use or Purpose: Claim to be listed on the label.



SECTION 3 — RECOMMENDED CONDITIONS OF USE

Recommended Use or Purpose *

Dosage Form (one only) * | Duration of Use (if any) | Sterile * ☐ Yes ☐ No | Route of Administration *

Recommended Dose (repeat for each sub-population group)

Sub-population group *	Amount *	Dosage Unit *	Frequency	Directions of Use

Risk Information

Cautions and Warnings *

Contra-Indications *

Known Adverse Reactions

ATTESTATION

"I attest that the natural health product that is the subject of this product license application will be manufactured, packaged, labelled, distributed and stored:
a) if the natural health product is imported, in accordance with the 'Good Manufacturing Practices' requirements as set out in Part 3 of the Natural Health Products Regulations or in accordance with requirements that are equivalent to those set out in Part 3, or
b) if the natural health product is not imported, in accordance with the 'Good Manufacturing Practices' requirements set out in Part 3 of the Natural Health Products Regulations."

Name of Authorized Senior Official (print) * | Signature * | Date * (y y y y m m d d)

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Dosage Form: Form of the finished product. Refer to Appendix 3 of the *Product Licencing Guidance Document* for list of dosage forms.

Duration of Use: Time frame in which it is safe, causing no major health concerns, to consume the product. If no duration of use, please indicate.

Sterile: Indicate if the product is to be sold as a sterile product

Route of Administration: Route by which the product is delivered, e.g., oral, topical, nasal. Only one route may be chosen. Refer to Appendix 3 of the *Product Licencing Guidance Document* for route of administration. **Note:** for all products, including homeopathic products, one product licence will be issued per route of administration.

Risk Information
Risk information to be listed on the label

Cautions and Warnings: All cautionary and warning statements associated with this product

Contra-indications: All contra-indications associated with this product.

Known Adverse Reactions: All known adverse reactions associated with this product.

Recommended Dose Sub-population group: Group to which the product is targeted. Most often this is "adult," if there are additional doses, list them as well.
Example: children, seniors

Amount & Dosage Unit: Quantity of product to be taken at one time.
Example: 3 tablets
Amount: 3
Dosage Unit: tablets
For non-discrete dosage forms, dosage unit should be 5ml (teaspoon) or 15ml (tablespoon). The product may be labelled using teaspoon, but the application must show metric equivalent.
Example:
Label: 2 teaspoons
Amount: 2
Dosage Unit: 5 ml

Frequency: How often the product should be taken.
Example: 3 times a day.

Directions of Use: Additional information which may aid consumer in using the product more effectively.
Example: Take on a full stomach.

Name of Authorized Signing Official: The person authorized to sign this application. If different than that of the Senior Official Applicant, a Third Party form must be included in the application.

Signature: The signature of the person listed as authorized signing official.

Date: The date on which the application was completed and signed.

Appendix 2: Most Common Deficiencies by Submission Level

Level 1:

1. *Applicant did not name a Senior Official on the application.*
   NHPD requires a senior official to be named on all applications. The senior official should be the same person for all applications made to NHPD, as this is the person who will represent the company. The senior official is also the person who should be signing the application form (unless a Designated Party Authorization form is included).

2. *Applicant did not name a Contact for the Application on the application.*
   NHPD requires a contact for the Application to be included in any Product Licence Application submission. This is the technical contact person to whom all questions regarding the submission will be sent. This contact person can vary from submission to submission.

3. *An American Applicant did not name a Representative in Canada.*
   NHPD requires a Representative in Canada to be named on the Product Licence Application form, as this is the person to whom regulatory mail will be sent. The Representative in Canada can be anyone (consultant, lawyer, etc.) with a Canadian address.

4. *Submission did not contain the Submission Content indicated on Page 2.*
   NHPD requires that a description of the data included in the submission package be detailed. This allows for NHPD to account for all of the information submitted.

5. *The Attestation was not signed*.
   NHPD requires that the Product License Application form be signed by the Senior Official or a Designated Third Party. This signature is an indication that the company agrees to the attestation found at the end of the Product Licence Application form.

6. *The attestation was signed by someone other than the Senior Official and a Designated Third Party Application form was not submitted.*
   NHPD requires that the application form be signed by the Senior Official of the applicant company as they are responsible for this application. If the Senior Official decides not to sign, but to designate someone else as able to sign on their behalf, a Designated Third Party Application form must be submitted.

Appendix 2: Most Common Deficiencies by Submission Level

Level 2:

1. *Non-traditional evidence not provided*
   The complete set of requirements for non-traditional claim submissions has not been met. In addition to the Product License Application, you must submit safety summary, evidence summary and quality summary reports. Please refer to Chapter 3.2.2 of the *Product Licensing Guidance Document*.
   - Many applicants supply only the Product Licence Application and label text, but not the supporting evidence.

2. *Attesting to an unpublished monograph*
   As NHPD has not yet published a monograph for 'Vitamin C', the safety summary, evidence summary, and quality summary report must be submitted. Please refer to the *Evidence for Quality of Finished Natural Health Products* and *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Documents*.
   - Applicants should ensure that the monographs which they attest to are monographs that are currently published. Applicants may opt to attest to TPD Category IV Monographs, if applicable.

3. *Attesting to multiple monographs for a combination product*
   'Glucosamine & Chondroitin' is a combination product. For medicinal ingredients of which the NHPD published monographs for, one may reference the appropriate monograph for the evidence of the safety and efficacy of the individual ingredients. However, all other requirements for combination products still apply. Please see chapter 12 of the *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document*.
   - Please note that it is necessary to provide evidence supporting the combination if the two ingredients have individual monographs.

4. *Proper names are not provided*
   For all medicinal ingredients, it is required that the proper name be provided, ie. Latin binomial, IUPAC name, or as listed on Schedule 1. Please refer to chapter 2 of the *Product Licensing Document* for further information.
   - The proper name is rarely provided in its correct form (i.e. IUPAC or Latin binomial).

5. *Did not provide source material*
   For all medicinal ingredients, it is required that the source material be provided. Please provide the source material for each medicinal ingredient.
   - Frequently the source material is not provided or provided incorrectly. Often, potency, source material, and medicinal ingredient are confused, and this is usually identified by Submission Coordinators.

6. *Animal tissue used in processing*
   It is required that all animal tissue used in the product as an ingredient or in the processing must be indicated (with completed Animal Tissue Form) to address any safety concerns when dealing with potential animal-borne diseases. The question regarding animal tissue use in the processing of the product does NOT refer to the medicinal or non-medicinal ingredients (ie., the capsule is considered a non-medicinal ingredient NOT as part of the processing) but rather to the manufacturing of the finished product or intermediary.

Appendix 2: Most Common Deficiencies by Submission Level

7. *Correct use of extract information*
   If the product is an extract, the extract information must be supplied to assist in the determination of safe dosage levels. When supplying the extract information, both the **extract ratio** and **crude dried equivalent** (amount of material from which the ingredient was extracted) must be supplied.
   - The quantity of the medicinal ingredient is the amount of extract per dosage unit.

   Crude dried material : extract

   ie., For a Tincture - 1:5 (1 gram of crude dried material to make 5 mL of extract)

   For a Powder - 5:1 (5 grams of crude dried material to make 1 gram extract)