Health Canada Santé Canada

NATURAL HEALTH PRODUCTS PROGRAM

SUMMATIVE EVALUATION

Final Report

Approved by

Executive Committee
Finance, Evaluation and Accountability (EC-FEA)
Health Canada

November 10, 2010

Canada

TABLE OF CONTENTS

Natural Health Products Program – Summative Evaluation
Management Action Plan

This Management Action Plan has been developed by participating organizations [i.e., Natural Health Products Directorate (NHPD), Marketed Health Products Directorate (MHPD), and the Health Products and Food Branch Inspectorate (HPFBI)] in response to the recommendations made in the Natural Health Products Program (NHPP) Summative Evaluation Report. *All responsibility for reporting on key activities rests at the director general level.*

Recommendations	Response	Key Activities	Responsible Manager	Time Frame
R1. The NHPP should continue to be implemented in Health Canada but detailed plans and timelines should be developed to evolve and improve the Program in line with the evaluation findings. Thus, in consultation with the Health Products and Food Branch (HPFB), the Directors General Natural Health Products Program Coordinating Committee (DGCC) should determine whether:				
• The NHPP pre-market evaluation process should be streamlined by considering whether regulatory borders are still appropriate, especially in the areas of functional foods with health claims and cosmetics, and should clarify the classification of which products should be regulated under the Natural Health Products Regulations (NHPR).	Agree	NHPD will use a risk-based approach, including the use of tools that have already been developed [e.g., the classification document for products within the cosmetic-drug interface and the classification document for products within the food-Natural Health Product (NHP) interface] to address those consumer products that cross regulatory borders. For food-like NHPs, NHPD and the Food Directorate (FD) are developing policies for addressing those products. Regulatory Modernization, an overarching principle now underway across the Branch, will affect the regulatory landscape and impact product divisions and classifications such as these.	Director General, Natural Health Products Directorate (NHPD), Health Products and Food Branch (HPFB), Health Canada (HC)	Review of major categories of products at the cosmetic-drug interface will be completed in accordance with the Action Plan by March 2011. Proposed regulatory resolution for food-NHP interface will be completed by March 2012.

Recommendations	Response	Key Activities	Responsible Manager	Time Frame
• NHP-specific monitoring and surveillance and compliance activities should be enhanced and change from responsive to proactive, without compromising MHPD and HPFBI's ability to complete these activities for other product lines. Proactive monitoring and surveillance and compliance activities could use a risk analysis to choose targeted products, such as weight loss products, products from countries that have had a history of adulteration, contamination and substitution, or products that have non-compliant labels.	Agree	In order to develop a more proactive surveillance system, MHPD is focusing on the regulatory pharmacovigilance tool of Annual Summary Reports (ASRs) on a risk-based approach i.e., safety issues have been identified. After successful implementation of this approach, Market Authorization Holders (MAHs) will be requested to submit the most current ASR to MHPD for evaluation for products with an identified safety concern. MHPD will continue to request additional safety data (ASRs) from MAHs based on detected safety issues. The ASRs, requested in Periodic Update Safety Report (PSUR) format will be reviewed according to standardized SOPs and templates, aligning with other product lines. Any recommendation(s) and/or deficiencies identified in the PSUR reviews will be communicated to NHPD and MAHs.	Director General, Marketed Health Products Directorate (MHPD), HPFB, HC	The use of mandated ASRs is ongoing. An update will be provided by March 2012 on the use of this pharmacovigilance tool, and any additional voluntary post-market commitments by MAH(s).
		Health Canada will implement proactive monitoring of the Canada Vigilance database using piloted targeted monitoring strategies for all product types, including NHPs.	Director General, MHPD, HPFB, HC	Four piloted strategies to be implemented by March 2012.
		HPFBI will continue to include NHPs in the scope of the current annual compliance monitoring program (CMP). HPFBI will explore the feasibility of establishing an NHP-specific compliance monitoring program.	Director General, Health Products and Food Branch Inspectorate (HPFBI), HPFB, HC	The next CMP will be completed by March 2012 and will include NHPs.
In addition, a certain percentage of sites could be randomly inspected since findings show that smaller manufacturers comply mainly out of fear of penalties.	Agree.	HPFBI will participate with NHPD to develop an inspection program that is based on a Risk-Based Approach to Site Licensing (RBA-SL). HPFBI will explore the feasibility of including a random inspection component.	Director General, HPFBI, HPFB, HC	RBA-SL in place by March 2015.
• Additional expertise specific to NHPs, as recommended in interviews with researchers, international partners as well as larger companies and their associations, should be developed as a means to enhance post-market evaluation.	Agree	The Program will develop a training plan.	Director General, NHPD, HPFB, HC	A training plan will be developed by September 2011.
R2. NHPD should work with relevant Provincial/Territorial bodies (government and non-governmental) to ensure coordinated and comprehensive application of NHPR across Canada. This would involve: • Developing an agreement and/or process designed to allow NHP/Traditional Chinese Medicine (TCM) or other practitioners to have access to regulated 'professional use only products';		The Program acknowledges that complementary and alternative health care practice sectors (including TCM in ON and BC) are moving towards being regulated under provincial regulatory frameworks, thereby impacting the utilization of products used in those fields. The Program will explore potential product/practice interface areas.	Director General, NHPD, HPFB, HC	The PAC will address the three bullets by March 2012.

Recommendations	Response	Key Activities	Responsible Manager	Time Frame
• Leveraging information from the practitioner communities; and, • Developing an integrated action plan for the sale of safe, effective and quality NHPs (with an emphasis on TCMs) in Canada.	Agree	The Program will explore existing committees within the health portfolio/public health councils as potential bodies to examine F/P/T issues such as this. NHPD has transitioned its NHP Advisory Committee to the new Program Advisory Committee (PAC). The PAC is comprised of representatives from health professional areas (including TCM) as well as provincial regulatory bodies. This Committee will provide advice, feedback and recommendations related to the NHP regulatory framework to the appropriate level of Program governance.		
R3. NHPD, with support from MHPD and HPFBI, should develop a comprehensive education and outreach strategy to enhance and extend activities that target and provide information to consumers (i.e., regarding general awareness of the NHPP, and risks and benefits of using NHPs), manufacturers and the retail sector (i.e., regarding compliance promotion).	Agree	The NHPP Working Group TOR will be modified with the addition of coordinating promotional activities for the Program. Within the confines of NHPD's budget, NHPD has and will continue to develop and implement the Stakeholder Focus Plan; this provides information on NHPs to stakeholders (including industry, consumers, health care professionals and retailers) via workshops, webinars, distribution of NHPD information sheets, newspaper articles and video. NHPD will build on this work and develop and post on the Web NHP-related awareness material that is aimed at the consumer, e.g., lexicon of terms, information sheets on NHP labelling and risk information. HPFBI will develop compliance promotion material (manufacturers, importers, retailers, etc.) which will be distributed during compliance verification activities.	Director General, NHPD, HPFB, HC Director General, HPFBI, HPFB, HC	An updated TOR will be ready by March 2011. Education and outreach activities targeted to consumers will be completed by March 2012. Development of HPFBI compliance promotion materials will be completed by March 2011.

Recommendations	Response	Key Activities	Responsible Manager	Time Frame
This strategy should include the development of an online information sharing mechanism that clearly communicates the risks and benefits of certain NHPs to consumers and industry. This mechanism should also provide information on issues of non-compliance. To that effect, reports on compliance investigations and regulatory warning letters should be made available to the public, to raise awareness of all the compliance activities of the Branch - for transparency and educational purpose as well as incentive to industry to comply with regulations. In interviews, partners such as consumer organizations, professional associations and the scientific community have indicated their willingness to assist the NHPP in this process.	Agree.	NHPD, MHPD, and HPFBI, in conjunction with the Office of Consumer and Public Involvement (OCAPI) and the Regions and Programs Branch (RAPB) will continue to develop Education / Outreach strategies, as part of the mandate of the NHP Program Working Group. Outreach activities by the NHP Program partners will be tracked by the NHPP Working Group, within the confines of the NHPP Landscape. In addition, MHPD will continue to develop outreach strategies to promote and increase education of AR reporting across Canada, including for NHPs. This outreach will be done in collaboration with the regions, and will involve various stakeholders (e.g., healthcare practitioners, academia, poison control centers, MAHs). MHPD will also develop a fact sheet on the need and mechanism for AR reporting for Naturopathic Doctors.	Director General, NHPD, MHPD, HPFB, HC	Completed in March 2012.
		A "Compliance Transparency Initiative" (CTI) will continue to be explored to address posting of non-compliances on the Health Canada (HC) website.	Director General, HPFBI, HPFB, HC	HPFBI will begin meetings to address CTI by March 2011.
R4. NHPD, in consultation with MHPD and HPFBI, should task the PAC to: • Analyze the existing Standard of Evidence (SOE) requirements for all product application streams and propose solutions for low-risk and novel products without abandoning the efficacy principle; and, • Develop guidance materials and tools that can assist industry (particularly small- to medium-sized companies) in meeting SOE requirements for non-traditional products (with assistance from the Clinical Trials Division and Monograph Group).	Agree	The PAC completed an analysis of SOEs and a report was developed in January 2010. NHPD has responded to the resulting recommendations and is actioning recommendations as appropriate. The PAC will address bullets one and two. The complete list of PAC recommendations and Program responses can be found on the following website: http://www.hc-sc.gc.ca/ dhp-mps/prodnatur/activit/com/soe-rep-npr-rap-fin-eng.php. In particular, the recommendations and responses #2, 4, 5 and 27 address the bullets under R4.	Director general, NHPD, HPFB, HC	Report recommendations will be addressed by March 2012. Bullets one and two will be addressed by March 2013.
R5. NHPD, in consultation with HPFBI, should develop a strategy and approach for introducing a site inspection element to the NHPP site licensing process to verify that facilities are manufacturing NHPs in accordance with the Good Manufacturing Practices (GMPs) referenced in their application packages. This exercise should also find a long term solution to address the terms and conditions of Mutual Recognition Agreements (MRAs).	Agree	NHPD, in consultation with HPFBI, is currently developing an inspection program for GMPs based on RBA-SL. Once developed, this program may include a random inspection component.	Director General, NHPD, HPFB, HC	RBA-SL is currently underway and a pilot project will be completed by March 2012.
		NHPD, in consultation with HPFBI, will discuss with the Department of Foreign Affairs and International Trade Canada (DFAIT) the need, if any, for MRAs for NHPs.	Director General, NHPD, HPFB, HC	MRA discussions with DFAIT to be held by March 2013.

Recommendations	Response	Key Activities	Responsible Manager	Time Frame
R6. MHPD, with HPFBI and NHPD, should improve the Program's surveillance, assessment and monitoring activities by targeting resources to: • Facilitate an active adverse reaction (AR) reporting program; and,	Agree	In order to facilitate an active AR program, MHPD will build on a project that has been underway for the past 3 years with the University of Alberta. This pilot project was designed to enhance the reporting rates for adverse events of NHPs. The feasibility of any new project/ activities under SONAR will be assessed and based on available resources. In order to facilitate an active AR project, a 3 year pilot project investigating the use of data collected by Canadian poison control centers will be initiated. Two centers will be chosen based on the population density, cultural diversity, and the use of NHPs.	Director General, MHPD, HPFB, HC	The University of Alberta project will be completed in March 2012. Centers will be selected and contracts will be finalised by March 2011; the Canadian PCC pilot project is expected to run over a 3 year period, starting from the date of the finalised and signed contracts.
• Assess the effectiveness of risk communications in terms of meeting their intended purpose	Agree	A Strategy document and Performance Measurement and Evaluation Plan (PMEP) are being developed to take a structured approach for evaluating the effectiveness of health product risk communications.	Director, General, MHPD, HPFB, HC	The Strategy document and PMEP are targeted to be finalized by Dec 2011.
R7. HPFBI, with input from MHPD and NHPD, should improve the Program's compliance and enforcement activities by: • Developing an ongoing monitoring program for sites; and, • Implementing active compliance promotion.	Agree	See **R1**, **R3** and **R5** For key activities.	Director General, HPFBI, HPFB, HC	See **R1**, **R3** and **R5** for timelines.
R8. NHPD, with the concentration of NHP experts in the Department, should be formally acknowledged as the Program lead (i.e., Champion) and be given the appropriate authority to execute Program leadership, on a consensus basis, with MHPD and HPFBI, through the DGCC. Specific responsibilities should include designing and developing a series of documents that can shape the Program's direction and guide its activities (see **R9**). Consideration should be given to having Assistant Deputy Minister (ADM) participation on the DGCC to build consensus (via active ADM engagement or a separate dispute resolution mechanism) among the	Agree	NHPD has been acknowledged by the ADM as the Program lead, i.e., NHPD is currently leading the development of the Program Strategic Plan. An open invitation to the ADM will be extended. It is accepted that NHPD should be the Program Lead, and work with the partner Directors General (DGs) within the accepted Terms of Reference (ToR) of the applicable DGCC. The current initiative within HPFB to implement a "Program Approach" is intended to review these and other related Program-wide issues regarding planning and reporting.	Director General, NHPD, HPFB, HC	Immediate implementation.

	Recommendations	Response	Key Activities	Responsible Manager	Time Frame
	implementing organizations and ensure that NHP-specific activities are targeted towards achieving an agreed set of objectives and desired outcomes that are cognizant of each organization's mandate, approaches and resource limitations.				
R9.	In consultation with HPFB, the DGCC should develop an **integrated Program plan** (medium- to long-term) and approach to planning activities, monitoring performance and reporting to HC Executives. This task should include the development of a set of strategic objectives and priorities to guide all Program activities funded under the latest funding approval.	Agree	The DGCC will evaluate the need to establish a NHPP planning operational committee consisting of operational members from each of the Program areas. This committee, or an existing body (e.g., NHPP Working Group), will develop annual operating plans, establish performance monitoring and reporting and develop a risk profile for the Program.	Director General, NHPD, HPFB, HC	Integrated Program Plan with strategic objectives and priorities in place by March 2011.
	The DGCC **should develop a corporate risk profile** that identifies and prioritizes the Program's existing risks and their accompanying risk drivers. Once completed, the corporate risk profile should serve as a starting point for identifying Program priorities, allocating Program resources, and developing mitigation measures to address risks that may impede the NHPP's ability to achieve its anticipated outcomes.	Agree	The Program is already moving toward a program approach to many of the planning and reporting activities (i.e., Strategic Plan, quarterly reporting). The Program will build on current efforts and work towards a Program risk profile.	Director General, NHPD, HPFB, HC	Corporate risk profile in place by March 2011.
	The DGCC should **develop Terms of reference (TOR)** to establish an Operational Committee that is responsible for: developing an annual operational plan aligned with an integrated Program plan (for approval by the DGCC); an approach and framework for Program-wide performance reporting; and, financial tracking of Program resources (planned and spent). The Operational Committee should also be responsible for leading initiatives to develop baseline and performance data in order to better understand NHP use and their effects on public health and sector compliance.	Agree	The DGCC will develop language in the Program's TOR for the formation of an Operational Committee. The Program agrees with the suggestions of the third paragraph. Performance data will be collected to report on key activities and progress toward targets across the Program.	Director General, NHPD, HPFB, HC	NHPP TOR (addressing this recommendation) in place by March 2011. An NHPP Operational Committee comprised of working level members from NHPD, MHPD and HPFBI in place by March 2011. Performance data identification and collection in place by March 2012 for all key Program activities.
	Finally, the DGCC should provide the direction to develop a formal plan for introducing an ongoing internal work exchange program (at the technical and management levels) designed to share information and experiences across the Program.	Agree	HC will build on its existing exchange activities and investigate the possibility of formalizing the process through the development of guiding principles and criteria for an internal work exchange program.	Director General, NHPD, HPFB, HC	Guiding principles and criteria for an internal work exchange program developed by March 2011.

Health Canada
Santé Canada

NATURAL HEALTH PRODUCTS PROGRAM

Summative Evaluation

Final Report

May 2010

Canada

Prepared by:
Stratos Inc.
1404-1 Nicholas Street
Ottawa, Ontario
K1N 7B7

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACRONYMS USED IN THIS REPORT

AAFC	Agriculture and Agri-Food Canada
AC	Advisory Committee (Evaluation)
ADM	Assistant Deputy Minister
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
ASC	Advertising Standards Canada
BCTHS	Bureau of Clinical Trials and Health Sciences
BEC	Branch Executive Committee
CA	Causality Assessment
CAM	Complementary and Alternative Medicine
CARN	Canadian Adverse Reaction Newsletter
CBSA	Canada Border Services Agency
CFIA	Canadian Food Inspection Agency
CPM	Chinese Propriety Medicine
CVS	Canada Vigilance System
DEC – FEA	Departmental Executive Committee – Finance, Evaluation and Accountability since then renamed Finance, Evaluation and Accountability (FEA)
DG	Director General
DGCC	Director General Natural Health Products Program Coordinating Committee
DIN	Drug Identification Number
DIN-HM	Homeopathic Medicine Number
DPD	Drug Products Database
DS	Dietary Supplements
EAC	Expert Advisory Committee
EAG	Evaluation Advisory Group
EC	European Community
EU	European Union
FCPA	Food and Consumer Products Association
FD	Food Directorate
FDA	*Food and Drugs Act*
FTE	Full Time Equivalent
GMP	Good Manufacturing Practice
HC	Health Canada
HHE	Health Hazard Evaluations
HPFB	Health Products and Food Branch
HPFBI	Health Products and Food Branch Inspectorate
HRA	Health Risk Assessments
IAS	Issue Analysis Summaries
IIRD	Internal information Request Database
IS	Incident System
ISR	Information Summary Report
LNHPD	Licensed Natural Health Products Database
MAC	Management Advisory Committee
MAH	Market Authorization Holders

MedDRA	Medical Dictionary for Regulatory Activities
MHPD	Marketed Health Products Directorate
MOU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
NAPRA	National Association of Pharmacy Regulatory Authorities
ND	Doctor of Naturopathic Medicine
NHP	Natural Health Products
NHPD	Natural Health Products Directorate
NHPD-RMC	Natural Health Products Directorate Risk Management Committee
NHPP	Natural Health Products Program
NHPPwg	Natural Health Products Program Working Group
NHPR	*Natural Health Products Regulations*
NHP-SAS	Natural Health Products - Submission Approval System Database
NPN	Natural Product Number
OAG	Office of the Auditor General
PAA	Program Activity Architecture
PAC	Program Advisory Committee
PACCB	Public Affairs, Consultation and Communications Branch
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PLA	Product Licence Application
PMRS	Program Management and Reporting System
RAPB	Regions and Programs Branch
RIAS	Regulatory Impact Analysis Statement
RMAF	Results-based Management and Accountability Framework
S.T.E.P.S.	Standardized Claims for NHPs and Pre-Cleared Information; Transparency and Openness; Electronic Solutions; Process Improvements; Service Delivery
SA	Signal Assessment
SAP	Systems Applications and Products
SOE	Standards of Evidence
SOP	Standard Operating Procedure
StatCan	Statistics Canada
TBS	Treasury Board Secretariat
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TOR	Terms of Reference
TPD	Therapeutic Products Directorate
TWS	Tracking Workflow System
UK	United Kingdom
UN	United Nations
US	United States of America
USFDA	United States Food and Drugs Administration
WCFN	Western Canadian Functional Food Natural Health Products Network
WHO	World Health Organization

ACKNOWLEDGEMENTS

The evaluation team would like to thank the numerous individuals who provided assistance to this project, including:

- ✓ Health Canada personnel from the Departmental Performance Measurement and Evaluation Directorate and the Office of Evaluation at the Policy, Planning and International Affairs Directorate of HPFB who provided coordination, support and oversight for the delivery of this evaluation;
- ✓ Personnel from the Natural Health Products Directorate, the Marketed Health Products Directorate and the Health Products Food Branch Inspectorate who participated in the interview process and provided detailed insights and comments crucial to the development of this report; and
- ✓ Program partners and stakeholders whom provided their insights on the accomplishments and challenges in implementing the Natural Health Products Program.

EXECUTIVE SUMMARY

BACKGROUND

An independent summative evaluation of the Natural Health Products Program (NHPP) in Health Canada (HC) was undertaken from May 2009 to February 2010. The objectives of the evaluation were to:

- Assess the key areas of relevance and performance (design, effectiveness, efficiency and economy); and,
- Highlight Program evolution and achievements over time, along with lessons learned and challenges experienced.

The scope of the evaluation included Program delivery from April 1st, 1999, to March 31st, 2008, with a focus on program activities to implement the *Natural Health Products Regulations (*NHPR*)*, which came into effect on January 1, 2004. Recent developments and other issues arising from the period April 1, 2008 to present were also considered and documented when evidence was submitted by Program staff. From an organization and process perspective, the scope of the evaluation included the activities and outputs of all HC organizations involved in program delivery, as well as cross-organizational governance and administrative support structures. The focus of the evaluation was not on the effectiveness of various NHPs, but rather on the effectiveness of Health Canada's NHPP.

OVERVIEW OF THE PROGRAM

HC is responsible for regulating NHPs for sale in Canada with the ultimate outcome of ensuring Canadians have ready access to NHPs that are safe[1], effective and of high quality while respecting freedom of choice and philosophical and cultural diversity. The NHPP derives its authority from the *Food and Drugs Act* and the NHPR, which are a part of the Government's response to the 1999 House of Commons Standing Committee on Health's report. Under the NHPR, NHPs are defined as: vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines (such as traditional Chinese medicines), probiotics and other products (like amino acids and essential fatty acids) that are manufactured, sold or represented for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans, restoring or correcting organic functions in humans or modifying organic functions in humans (such as modifying those functions in a manner that maintains or promotes health).

The NHPP is implemented by three separate organizations in HC: the Natural Health Products Directorate (NHPD), the Marketed Health Products Directorate (MHPD) and the Health Products and Food Branch Inspectorate (HPFBI) with the Regions. NHPD is responsible for implementation of the regulations, including pre-market, risk-benefit assessments of product and

[1] Assuring safety means striking an appropriate balance between risk and benefit of NHPs. Absolute safety is unachievable by any regulator.

site applications and authorization of clinical trials. MHPD is responsible for post-market safety surveillance, risk communications and regulatory oversight of advertising. HPFBI, in partnership with the Regions and Programs Branch (RAPB), is responsible for compliance and enforcement activities, such as compliance verification and investigations, compliance monitoring including recall monitoring, border integrity activities, analysis of NHP samples, and compliance promotions and outreach activities. When the NHPR came into force in January 2004, full funding for implementation by these organizations was not provided for through a separate Budget plan initiative; however, in 2008, funding provided for these activities totalled $82.45M over five years ($16.49M annually).

EVALUATION FINDINGS AND CONCLUSIONS

The following report details the evaluation findings by key question, provides a comparison of Canada's approach to regulating NHPs to other key countries, and integrates the findings from three case studies. Overall, the evaluation concluded the following:

In terms of **relevance**:

1. There is a continued need to assure the safety, efficacy and quality of NHPs in Canada, and HC is the appropriate organization to regulate NHPs.
2. The NHPP takes a broad-based approach, which may be over-regulating products and under-emphasizing post-market verification.

In terms of performance related to **effectiveness**:

3. The NHPP has developed national standards for NHPs; however some gaps exist within the current regulatory framework.
4. There is international interest in Canada's regulatory approach.
5. There is insufficient evidence to assess if the NHPP has increased awareness and knowledge of the risks and benefits of NHPs.
6. The licensing of NHPs in Canada assures that those NHPs available on the market with Natural Product Number (NPN) or Drug Identification Number – Homeopathic Medicine (DIN-HM) are safe, of high quality and effective, if taken as directed.
7. NHPD efforts have focused on developing process improvements to address the NHP backlog. Greater attention to the existing Standards of Evidence (SOE) for efficacy and the Program's approach to issuing site licences is required.
8. Surveillance, assessment and monitoring activities have informed NHP regulatory decision making, but to a limited extent.
9. MHPD, and more broadly the NHPP, is challenged in its ability to fully understand the risks associated with NHP use in Canada.
10. Compliance and enforcement activities are largely complaint driven and the degree of NHP sector compliance with the NHPR is not known.

11. HPFBI successfully addresses NHP complaints but has not developed a regular and ongoing compliance promotion element to its NHP-related activities.

12. While there are extensive working relationships and collaborations across the Program, the NHPP has not developed a fully integrated internal approach to program planning, delivery, and reporting.

13. NHPD has made good use of its resources to work with partners and stakeholders to improve the understanding of pre-market processes and activities.

14. The degree to which Canadians make informed decisions on NHPs is not known, and the NHPP has yet to implement a broad outreach campaign to Canadians.

15. The NHPP has demonstrated that its activities can reduce Canadians' exposure to health risks, but there is no objective evidence to assess the extent of health benefits derived from the Program.

16. Canada is generally viewed as a responsible participant internationally, with the majority of domestic and international stakeholders providing favourable reviews of the Canadian system.

17. The NHPP has demonstrated that it can be a responsive and evidence-based system, but the evaluation was unable to determine if it is cost effective and/or sustainable.

18. At this early stage, it is difficult to determine if the NHPP has increased health benefits and/or decreased NHP-related illnesses among Canadians.

In terms of performance related to **organizational delivery, efficiency and economy**:

19. While a Results-based Management and Accountability Framework (RMAF) has been developed, and organizations routinely report on Program outputs at the organizational level, there is no integrated Program-wide performance measurement and reporting.

20. The evaluation was unable to assess the appropriateness of NHP allocations vs. spending.

21. The NHPP was designed with an early and appropriate emphasis on pre-market activities and alternate delivery modes or shifts are only now being considered.

EVALUATION RECOMMENDATIONS (R)

In response to the findings and conclusions, it is recommended that:

R1. The NHPP should continue to be implemented in Health Canada but detailed plans and timelines should be developed to evolve and improve the Program in line with the evaluation findings. Thus, in consultation with Health Products and Food Branch, the Director General Natural Health Products Program Coordinating Committee (DGCC) should determine whether:

- The NHPP pre-market evaluation process should be streamlined by considering whether regulatory borders are still appropriate, especially in the areas of functional foods with health claims and cosmetics, and should clarify the classification of which products should be regulated under the NHPR.

- NHP-specific monitoring and surveillance and compliance activities should be enhanced and change from responsive to proactive, without compromising MHPD and HPFBI's ability to complete these activities for other product lines. Proactive monitoring and surveillance and compliance activities could use a risk analysis to choose targeted products, such as weight loss products, products from countries that have had a history of adulteration, contamination and substitution, or products that have non-compliant labels. In addition, a certain percentage of sites could be randomly inspected since findings show that smaller manufacturers comply mainly out of fear of penalties.
- Additional expertise specific to NHPs, as recommended in interviews with researchers, international partners and larger companies and their associations, should be developed as a means to enhancing post-market evaluation.

R2. NHPD should work with relevant Provincial/Territorial bodies (government and non-governmental) to ensure coordinated and comprehensive application of NHPR across Canada. This would involve:

- Developing an agreement and/or process designed to allow NHP/TCM or other practitioners to have access to regulated 'professional use only products';
- Leveraging information from the practitioner communities; and,
- Developing an integrated action plan for the sale of safe, effective and quality NHPs (with an emphasis on TCMs) in Canada.

R3. NHPD, with support from MHPD and HPFBI, should develop a comprehensive education and outreach strategy to enhance and extend activities that target and provide information to consumers (i.e., regarding general awareness of the NHPP, and risks and benefits of using NHPs), manufacturers and the retail sector (i.e., regarding compliance promotion).

R4. NHPD, in consultation with MHPD and HPFBI, should task the Program Advisory Committee to:

- analyze the existing standard of evidence (SOE) requirements for all product application streams and propose solutions for low-risk and novel products without abandoning the efficacy principle; and
- develop guidance materials and tools that can assist industry (particularly small- to medium-sized companies) in meeting SOE requirements for non-traditional products (with assistance from the Clinical Trials Division and Monograph Group).

R5. NHPD, in consultation with HPFBI, should develop a strategy and approach for introducing a site inspection element to the NHPP site licensing process to verify that facilities are manufacturing NHPs in accordance with the Good Manufacturing Practices (GMPs) referenced in their application packages. This exercise should also find a long term solution to address the terms and conditions of Mutual Recognition Agreements (MRAs).

R6. MHPD, with HPFBI and NHPD, should improve the Program's surveillance, assessment and monitoring activities by targeting resources to:

- facilitate an active adverse reaction reporting program; and
- assess the effectiveness of risk communications in terms of meeting their intended purpose.

R7. HPFBI, with input from MHPD and NHPD, should improve the Program's compliance and enforcement activities by:

- developing an ongoing monitoring program for sites; and
- implementing active compliance promotion.

R8. NHPD, with the concentration of NHP experts in the Department, should be formally acknowledged as the Program lead (i.e. Champion) and be given the appropriate authority to execute Program leadership, on a consensus basis, with MHPD and HPFBI, through the DGCC. Specific responsibilities should include designing and developing a series of documents that can shape the Program's direction and guide its activities (see Recommendation 9). Consideration should be given to having Assistant Deputy Minister (ADM) participation on the DGCC to build consensus (via active ADM engagement or a separate dispute resolution mechanism) among the implementing organizations and ensure that NHP-specific activities are targeted towards achieving an agreed set of objectives and desired outcomes that are cognizant of each organization's mandate, approaches and resource limitations.

R9. In consultation with HPFB, the DGCC should develop an integrated program plan (medium to long-term) and approach to planning activities, monitoring performance and reporting to HC Executives. This task should include the development of a set of strategic objectives and priorities to guide all Program activities funded under the latest funding approval.

The DGCC should develop a corporate risk profile that identifies and prioritizes the Program's existing risks and their accompanying risk drivers. Once completed, the corporate risk profile should serve as a starting point for identifying Program priorities, allocating Program resources, and developing mitigation measures to address risks that may impede the NHPP's ability to achieve its anticipated outcomes.

The DGCC should develop Terms of Reference (TOR) to establish an Operational Committee that is responsible for: developing an annual operational plan aligned with an integrated Program plan (for approval by the DGCC); an approach and framework for Program-wide performance reporting; and, financial tracking of Program resources (planned and spent). The Operational Committee should also be responsible for leading initiatives to develop baseline and performance data in order to better understand NHP use and their effects on public health and sector compliance.

Finally, the DGCC should provide the direction to develop a formal plan for introducing an ongoing internal work exchange program (at the technical and management levels) designed to share information and experiences across the Program.

1 INTRODUCTION TO THE EVALUATION

1.1 Background to the Evaluation

This evaluation was undertaken in response to a request from Health Canada (HC) to conduct an independent and objective summative evaluation of the relevance and performance of the Natural Health Products Program (NHPP). This evaluation was conducted in accordance with the Strategic Five-Year Plan for Evaluations prepared by the Health Products and Food Branch (HPFB) and approved by the Departmental Executive Committee – Finance, Evaluation and Accountability [DEC – FEA, since renamed Finance, Evaluation and Accountability (FEA)], which seeks to address the Treasury Board Secretariat's accountability requirements and provide senior management with a sound basis of information for making well informed decisions regarding program performance and success.

This evaluation was designed to:

- assess the key areas of relevance and performance (design, effectiveness, efficiency and economy) for the NHPP;
- highlight achievements and lessons learned as well as any challenges that were experienced; and
- address the accountability requirements of the commitments to the Treasury Board Secretariat (TBS), as well as the broad needs of senior management on the performance of the NHPP to assist senior management in making decisions about the Program.

This document contains the results of the "Evaluation of the Natural Health Products Program" and is organized into four main sections:

Section 1 outlines the purpose and objectives of the evaluation, and includes a summary of the evaluation methodology, and;

Section 2 provides a detailed overview the NHPP;

Section 3 presents the result of the international benchmarking exercise that compares the NHPP to other world systems; and

Section 4 documents the evaluation findings, conclusions and recommendations by each evaluation question.

1.2 Evaluation Objectives and Scope

Evaluation Objectives
The objectives of this evaluation were to:

- Assess the key areas of relevance and performance (design, effectiveness, efficiency and economy) for the NHPP; and,
- Highlight the Program's evolution and achievements over time, along with lessons learned and challenges that were experienced.

The evaluation is summative, that is, there was an emphasis on addressing the ability of the NHPP to provide results that can demonstrate the successful achievement of the Program's immediate to long-term and ultimate outcomes as described in the Program's logic model, as well as the efficiency and economy of the Program's activities and processes.

To build the necessary evidence to comment on the evaluation's objectives, the evaluation focussed on answering a number of key questions that apply to the Program as a whole and the activities of the Natural Health Products Directorate (NHPD), Marketed Health Products Directorate (MHPD), and Health Products and Food Branch Inspectorate (HPFBI). The key questions assessed by the evaluation included[2]:

Section A - Program Relevance:

A1. Is there a continued need for the NHPP as it is defined?

Section B – Immediate Outcomes:

B1. To what extent has the NHPP contributed to the development of national and international standards and regulatory approaches for NHPs?

B2. To what extent has the NHPP increased awareness and knowledge of risks and benefits of NHPs?

B3. To what extent has the assessment of applications for licensing/approval increased the availability of safe and effective NHPs for Canadians?

B4. To what extent have surveillance, assessment and monitoring activities enhanced the knowledge of NHPs' risks and benefits to inform regulatory decisions?

B5. To what extent have compliance and enforcement activities increased adherence to Acts, regulations and guidelines?

Section C – Intermediate Outcomes:

C1. To what extent has the NHPP contributed to the development of an integrated approach (nationally and internationally) for implementation of its priorities and activities?

C2. To what extent do Canadians make informed decisions and choose and use NHPs with confidence as a result of Program activities?

[2] In accordance with the guidance presented in the TBS' Policy on Evaluation, Section A refers to Relevance whereas Sections B – E focus on Performance.

C3. To what extent has a reduced exposure of Canadians to health risks been achieved as a result of NHPP activities?

Section D – Long-term Outcomes:

D1. To what extent is Canada viewed as a responsible participant and scientific expert in an international context regarding NHPs as a result of Program activities?

D2. To what extent has a sustainable, cost-effective, responsive and evidence-based regulatory system for the people of Canada been achieved as a result of NHPP activities?

D3. To what extent have health benefits increased and NHP-related illnesses decreased as a result of NHPP activities?

Section E - Economy and Efficiency

E1. To what extent has the NHPP designed and implemented a Performance Measurement strategy?

E2. Was the amount allotted/spent appropriate for the scope of the NHPP?

E3. In view of the current delivery structures, are there any alternate delivery structures that could be considered and in which areas?

Each evaluation question was supported by a series of evaluation indicators. Collectively these questions and indicators were part of the evaluation framework.

Scope

The evaluation focused on program delivery from April 1st, 1999, to March 31st, 2008. Recent developments and other issues arising from the period April 1, 2008, to present were also considered and documented in some cases. The purpose of the extended timeframe is to assess the historical evolution of the Program and to understand the full impact of the Program both before and after regulations.

From an organizational and process perspective, the scope of the evaluation included:

- The activities and outputs of cross-organizational governance and administrative support structures; and
- The activities and outputs of NHPD, MHPD and HPFBI, individually and collectively, to support Program delivery and decision making.

The focus of the evaluation was not on the effectiveness of various natural health products (NHPs), but rather on the effectiveness of HC's NHPP - its key successes and issues encountered, the impact of key Program areas, overall Program management, and the ongoing need for and relevance of the Program. The evaluation did not address how the provinces and territories oversee the sale and practice of NHPs in their respective jurisdictions.

1.3 Evaluation Approach and Methodology

The evaluation was summative in nature. It measured progress towards achieving results, and the performance of the current NHPP. The evaluation activities were designed and executed so that the evaluation questions and indicators could be addressed by completing multiple lines of inquiry.

The evaluation was "evidence based". That is, its conclusions and recommendations were based on objective, quantitative and qualitative evidence to the fullest extent possible. Where possible, findings and conclusions were drawn from documented evidence; however, information obtained from interviews was incorporated into the evaluation to provide context for formulating findings and conclusions when documented evidence was not available.

The evaluation was conducted in accordance with the Evaluation Work Plan prepared by Stratos Inc. The major phases of the evaluation included:

Phase I: Evaluation Planning
This phase of the evaluation consisted of developing an Evaluation Work Plan that met the requirements of the Evaluation Framework for the NHPP. During this phase, the evaluation team worked closely with the Evaluation Advisory Group (EAG)[3] to develop the appropriate evaluation instruments to collect evidence from multiple sources and perspectives. This phase included the development of:

- Evidence collection templates to ensure a common and consistent approach to collecting evidence across the evaluation team;
- A framework for completing an international benchmarking exercise used to compare the NHPP to other regulatory approaches applied in Australia, the European Union, Singapore, the United States of America and the World Health Organization;
- Interview guides to facilitate the interview process with key informants, Program partners and Program stakeholders; and
- A framework for conducting three case studies designed to develop a deeper understanding of Program activities and processes, and the achievement of results.

Phase II: Evidence Collection and Review
The methodological approach for the evaluation incorporated multiple lines of inquiry, both qualitative and quantitative in nature. An overview of each line of inquiry is presented below.

[3] The EAG consisted of representatives from the Departmental Performance Measurement and Evaluation Directorate and the Office of Evaluation at the Policy, Planning and International Affairs Directorate of HPFB.

1. Review of Program Documentation, Academic Publications, and NHPP Internal and External Databases

This phase of the evaluation focussed on collecting and analyzing information from multiple sources to better understand NHP regulatory frameworks in Canada and elsewhere, as well as the specific activities completed by each NHPP organization at HC. This phase included the completion of three major tasks:

Literature Review and International Benchmarking Exercise

The evaluation team conducted a literature review on the subject of NHPs and the NHPR (or equivalent legislation related to herbal products, dietary supplements, vitamins, etc.) in Canada and in four selected countries, as well as the World Health Organization (WHO). The literature review focussed on the herbal regulatory systems in Canada, the United States of America and the European Union (EU), and to a lesser degree on Singapore and Australia, and the WHO.

The literature review focussed on peer reviewed materials, which included resources available through HC's library (including the Cochrane Reviews) as well as from tools and databases, such as Pubmed, Web of Science, government websites and WHO documents. The review of key literature sources was supplemented by a series of key informant interviews (by phone, email, Skype, etc.) to further investigate and collect information about NHP regulatory systems and legislative approaches.

Using Canada's NHP definition as a benchmark, the evaluation team conducted an analysis that compared the placement of products under different regulatory systems to the existing system applied in Canada.

Review of Program Documentation

The evaluation team reviewed all of the documentation in an extensive catalogue of information specific to each partner organization as well as HPFB submitted by the Project Authority. Over 700 pieces of documentation were reviewed. The documentation provided a substantive base of information related to each organization's relevant authorities, key activities, and processes as they relate to the NHPP. The inclusion/exclusion of information within the document analysis tables was based on relevancy to the evaluation questions and associated indicators.

Review of Relevant Internal and External Databases

The evaluation team also completed a review of relevant databases to obtain an appreciation of the Program's performance measurement history, as well as its ability to maintain accurate and reliable records of information for public and non-public use. The databases reviewed are presented below in **Table 1**.

Table 1 - Internal and External Databases Reviewed as part of the evaluation

Database	Administrator	Internal or External
Natural Health Products - Submission Approval System Database (NHP-SAS)	NHPD	Internal
Licensed Natural Health Products Database (LNHPD)	NHPD	External
Drug Products Database (DPD)	TPD	External
Canada Vigilance System (CVS)	MHPD	External
Coordination Compliance Information Management (CCIM) & Internal information Request Database (IIRD)	NHPD	Internal
Incident System (IS)	HBFBI	Internal
Program Management and Reporting System (PMRS)	HBFBI	Internal
Systems Applications and Products (SAP)	NHPD	Internal
Ingredients database	NHPD	External
Tracking Workflow System (TWS)	NHPD	Internal
Site licences database (part of TWS)	NHPD	Internal

A summary of the findings from the review of Program Documentation, Academic Publications, and NHPP Internal and External Databases was prepared (Technical Report #1) and submitted to the EAG and the NHP Evaluation Advisory Committee (AC)[4] for review and comment.

2. Design and Development of Three Case Studies

Three case studies were completed with the aim of providing an in-depth understanding of how the various mandated and supporting activities of the NHPP translate into practice, and how specific initiatives have led to the demonstrable achievement of the Program's expected outcomes. Where possible, the case studies sought to address key accomplishments and challenges in implementing the NHPP, as well as any lessons learned.

The evaluation team worked in conjunction with EAG to develop criteria to select three case study topics. Six topics were presented to the EAG and three were selected based on the following criteria:

- ✓ Ability for the case study topic to be aligned directly with one or more of the questions presented in the evaluation framework;
- ✓ Ability to speak directly to engaged individuals and obtain access to key documentation;
- ✓ Ability for the case studies to be reflective of the NHPP and the NHPR;

[4] The Advisory Committee (AC) was composed of the Director Generals from NHPD, MHPD and HPFBI, the Regional Director of the Western Region, the Director of Departmental Performance Measurement and Evaluation Directorate and the Manager of the Office of Evaluation within HPFB.

- ✓ Ability to demonstrate a range of views from multiple partners and stakeholders on a particular process, issue, or product;
- ✓ At least one case study reports on how a product flows through the NHPP regulatory system;
- ✓ At least one case study highlights how the completion of an explicit activity has led to an outcome in the logic model;
- ✓ At least one case study focuses on an issue such as public safety, efficacy, etc.; and,
- ✓ Ability to identify and highlight best practices and critical success factors or challenges and weaknesses associated with NHP processes and activities.

Three case study topics were selected:

- The NHPD Monograph-based registration stream;
- How NHPD established ranges for vitamin and mineral dosing; and,
- HC's approach to managing the potential risks associated with the use of Black Cohosh.

The evaluation team relied primarily on two sources of data for the case studies:

- Interviews with Program staff (7) from the relevant NHPP organizations and, where applicable, with external stakeholders from industry (3) and other NHP regulatory authorities (1); and,
- Program and web-based documents and, where possible, scholarly publications with an emphasis on peer reviewed journal articles.

Case studies findings were summarized (Technical Report #2) and submitted to the EAG and the AC for review and comment.

3. Interviews with Key Informants, Partners and Stakeholders[5]

HC's Departmental Performance Measurement and Evaluation Directorate and the HPFB's Office of Evaluation provided the evaluation team with a list of key informants. The evaluation team reviewed the list and, using Program knowledge and coordinator input, selected individuals and groups who could provide relevant information within the time/budget allotted to interviews.

[5] Key informants are HC employees who are knowledgeable about the NHP Program. They include employees of NHPD, MHPD and HPFBI as well as government regulators. Partners are organizations that assist in the implementation of the Program or that have parallel regulatory programs that deal with NHPs. These include Federal/Provincial/Territorial partners, international government organizations and HC enforcement agencies. Stakeholders are those that receive the benefits or the effects of the Program.

The evaluation team and EAG agreed on a list of 113 individuals from three target groups:

Group 1: **Health Canada organizations responsible for implementing the Natural Health Product Regulations (NHPR)**

- Senior Program Managers at NHPD, MHPD, and HPFBI (i.e., Senior Executive Director, Directors and Managers) involved with NHPP in headquarters, the laboratories and the regional centres; and
- Program staff and policy analysts in NHPD, MHPD and HPFBI working on the Program in headquarters, the laboratories and the regional centres.

Group 2: Partner Organizations that have a NHP regulatory relationship with HC

- Departments of Health and Agriculture at the Provincial level;
- Organizations within HC [e.g., Therapeutic Products Directorate (TPD)] and other federal departments consulted for the delivery of the NHPP activities [e.g., Agriculture and Agri-food Canada (AAFC); Public Health Agency of Canada (PHAC); and, the Canadian Food Inspection Agency (CFIA)];
- National associations [e.g., Canadian Association of Professional Regulatory Affairs, Canadian Medical Association and National Association of Pharmacy Regulatory Authorities (NAPRA)]; and,
- International government regulators [e.g., United States Food and Drug Administration (USFAD), European Medicines Agency (EMEA), etc.].

Group 3: Stakeholder Organizations

- Industry/Manufacturers (large and small) and retail associations (e.g., the Canadian Health Food Association, Canadian Spice Association, American Herbal Products Association, and selected companies);
- Academia (e.g., representatives from the Universities of Guelph and Toronto);
- International and science-based organizations (e.g., World Health Organization);
- Members of NHPP Committees (e.g., Advisory committees);
- National Health Products Research Program participants;
- Consumer/patient groups; and,
- Healthcare practitioners.

The evaluation team worked in consultation with the Project Authority to develop interview guides specific to each group. The interview guide for Group 1 was further developed into guides specific to NHPD, MHPD and HPFBI managers/directors and NHPD, MHPD and HPFBI Program staff.

The evaluation team contacted individuals by e-mail and/or phone up to three times to schedule an interview. If no response was obtained, or if scheduling was not possible within the required timeframe, an interview guide was sent to the interviewee for a written response to be completed and submitted to the evaluation team's assistant project manager. Three populated interview guides were submitted to the evaluation team in response to this request.

Interviews were completed between October 13th and November 25th. A total of 107 interviews were completed, broken down by:

- 25 in NHPD;
- 11 in MHPD;
- 24 in HPFBI;
- 1 in HPFB;
- 14 Partners; and
- 32 Stakeholders

Individuals were interviewed by applying three interview methods (**Table 2**) and using the interview guides. All interview participants were told that evaluation findings would be non-attributable to allow them to speak freely in the interview.

Table 2 - Methods for Conducting the Key Informant Interviews

Interview Method	Key Informant	Approximated Time to Complete Interview	Total Interviewed
One-on-one, in person or by telephone	Director-level and above	@ 1 hour	63 individuals Completed by Team Leads
Group, in-person interviews (where staff are working on similar Program aspects)	HC staff-level and partners	@ 1-2 hours	6 individuals (2 groups) Completed by Team Leads and Evaluators
Group telephone interviews	HC staff-level, partners & stakeholders	@ 1-2 hours	38 individuals (14 phone interviews) Completed by Team Leads and Evaluators

Interview findings were developed by aggregating individual interview notes into a number of theme areas that followed the structure of the approved interview guides.
Interview findings were summarized (Technical Report #3) and submitted to the EAG and the AC for review and comment.

4. Corroboration of evidence and evaluation findings and conclusions

Evidence obtained from each line of inquiry was summarized in a series of three Technical Reports, as noted above, that were submitted to the EAG for review and comment. In addition to this review, the EAG distributed each Technical Report to the AC for the purpose of reviewing the evaluation team's findings as well as to provide an opportunity to comment on any errors or omissions.

The evaluation team held an internal meeting to discuss the relevance of the evidence collected from each task and to address any inconsistencies found in the information provided by the EAG and the NHP Evaluation AC. A summary of the preliminary findings for each evaluation question and indicator was prepared and recorded in an evidence collection summary template.

The evaluation conclusions were developed in consultation with the EAG. A draft set of conclusions and recommendations was presented to the EAG to test tone, accuracy and the connectivity between evaluation findings and evaluation conclusions.

1.4 Limitations

The findings and conclusions presented in this report are based on both quantitative and qualitative evidence gathered throughout the evaluation process. The key limitations associated with the research methods applied during the evaluation are noted below.

1. Availability of documentation to accurately reflect achievements and results for the full scope of the evaluation.

Documentation to confirm what activities were completed, what results were achieved, and why key decisions were made before and immediately after the NHPR came into force was not able to address all evaluation issues and questions. As a result the evaluation team had to rely also on key informant interviewees to better understand specific events, perspectives, and key decisions (e.g., what stakeholders said during the NHPR consultations, why site licences are addressed by NHPD as opposed to HPFBI, etc.). This data is limited by the fact that it represents the views and opinions of experts or senior officials and is dependent on an individual's ability to recall facts and particular moments in time. In a number of areas, there were widely divergent views on the impacts of the NHPP and its strengths and weaknesses. These views have been reflected in the report. When the views were substantiated with documentary evidence or corroborated by a number of other interviews, these findings have been emphasized throughout the report.

As a result of these data limitations, the findings and evaluation results were vetted by Program staff to confirm any errors or omissions.

2. Ability to address NHP regulatory approaches in other countries.

Although the evaluation attempted to describe a range of approaches to regulating NHPs, the information available in the public domain on how other countries are managing NHPs is limited. As such, the evaluation team was not in a position to verify resource allocations (both human and monetary) in other countries to assist with a determination of whether Canada's approach to regulating NHPs is cost effective when compared to other countries.

3. Lack of a Baseline and Long Term Health Studies.

There was little baseline data available to determine the number of NHPs in use and the health impacts on Canadians from using NHPs, prior to the NHPR coming into effect. Also, there were no long term health studies to indicate the health impacts of using NHPs over time. Therefore, it was not possible to accurately assess whether the NHPP is achieving its intended longer-term outcomes. It is recognized that assessing the health impact of a 'preventative' type of program such as NHP is very difficult and costly. Therefore, case study and anecdotal evidence was used to address these evaluation issues.

2 BACKGROUND ON NATURAL HEALTH PRODUCTS IN CANADA

The use of NHPs has a distinct history in Canada compared to other nations and is creating a new way forward in the world with its current NHPR. The NHP legislation and the creation of a new NHPP are as much concerned with recognizing our unique cultural mosaic as they are about science and medicine. These traditions begin with Canadian First Nations who used and continue to use plants, fungi and some animals and minerals as medicines, and regulate their use through oral traditions and their cosmocentric (i.e. humans as part of interconnected nature) view of life. In Eastern Canada alone, over 400 species of plants are known for over 1,700 medical usage mentions, many of them unique to Canada (Arnason et al., 1981). During the French regime, European medical and pharmaceutical science was integrated with native medicine by médecins du roi Michel Sarrazin (1659-1734) and Jean-François Gaultier (1708-1741), which created a distinct herbal tradition that continues today in Quebec (Tesio, 2006). In the 18th and 19th century, NHPs were a mainstay of North American medical science. In the late 19th century, Dr John Uri Lloyd, a trained American medical physician and founder of the Journal of Natural Products, influenced American and Canadian medicine by advocating use of natural medicines, such as Echinacea, in the "eclectic" medicine movement (Hobbs, 1990). The era of dominance of botanical medicines and homeopathy effectively ended in the early 20th century due to unresolved issues of efficacy, quality and safety in botanicals, and advances in allopathic medicine and pharmaceutical science. The term "allopathy" was coined in 1842 by C.F.S. Hahnemann to designate the mainstream practice of medicine as opposed to homeopathy, the system of therapy that he founded based on the concept that disease can be treated with drugs in minute diluted doses. The *Canadian Food and Drugs Act* (*FDA*) regulations were passed by Parliament in 1920 leading to restriction of prescription drugs to well characterized single entity drugs, and prohibiting the use of over-the-counter medicines for "schedule A" diseases (**Figure 1**).

Figure 1 – Schedule A Diseases

- ✓ Acute alcoholism
- ✓ Acute anxiety state
- ✓ Acute infectious respiratory syndromes
- ✓ Acute, inflammatory and debilitating arthritis
- ✓ Acute psychotic conditions
- ✓ Addiction (except nicotine addiction)
- ✓ Appendicitis
- ✓ Arteriosclerosis
- ✓ Asthma
- ✓ Cancer
- ✓ Congestive heart failure
- ✓ Convulsions
- ✓ Dementia
- ✓ Depression
- ✓ Diabetes
- ✓ Gangrene
- ✓ Glaucoma
- ✓ Haematologic bleeding disorders
- ✓ Hepatitis
- ✓ Hypertension
- ✓ Nausea and vomiting of pregnancy
- ✓ Obesity
- ✓ Rheumatic fever
- ✓ Septicemia
- ✓ Sexually transmitted diseases
- ✓ Strangulated hernia
- ✓ Thrombotic and Embolic disorders
- ✓ Thyroid disease
- ✓ Ulcer of the gastro-intestinal tract

As a consequence, unrefined botanicals or extracts were no longer used in conventional allopathic medicine and botanical use was largely confined to herbalists, aboriginal elders, and a few informal traditional medicine practitioners in Canada (and the US), although their use continued in some other developed countries and other parts of the world, especially Germany and Japan. The sale of botanicals as traditional medicines was largely unregulated in Canada in the period 1920 - 1990, but public interest in these products until the 1990s was generally low.

Events leading to the Standing Committee on Health recommendations creating the NHPP:
In the 1990s, after a 70 year hiatus, interest in Complementary and Alternative Medicine (CAM) and natural therapies boomed in North America, in part due to the ageing of the postwar generation, which embraced a popular health and wellness movement of neo-herbalism (an eclectic combination of European herbalism, Asian medicines and native North American herbs). The use of products such as Echinacea, St John's Wort, ginger, ginseng, dong quai, gotu kola, etc., became widespread. A recent IPSOS Reid (2005) poll indicated that 71% of Canadians now use NHPs. In Canada, the large immigration from Asia, Africa, the Caribbean and Latin America in the 1990s and renewal of self confidence in First Nations communities sparked great interest in traditional medicine and CAM. Schools of Naturopathic Medicine and Traditional Chinese Medicine were established. Sales of NHPs increased dramatically (Brevoort, 1998) until potential problems with safety, quality and efficacy were documented, such as the interaction of St. John's wort with anti-retroviral (Piscitelli et al., 2000) or negative effects of some products on fetal health (Awang, 2000 and Rousseaux and Schacter, 2003). To address the quality issues, early work by the Health Protection Branch at HC developed new regulatory procedures for traditional medicines. An example would be setting a standard of 0.2% parthenolide in feverfew products as a minimum for a claim for migraine prophylaxis (Awang, 1998).

Although there was some recognition of traditional medicines at HC in the 1990s, there was no overall regulatory plan for the majority of NHPs that had now become commercially important health care products. In fact, the Natural Products laboratory group at HC, which had most of the expertise in the area, was closed down for financial reasons during budgetary constraints of national debt reduction in the 1990s. Eventually concern building from stakeholders about access to and safety of NHPs led to a full parliamentary review of the issue. This was initiated by the Standing Committee on Health between 1997-98 in which over 150 stakeholders, including pharmacists, patients, practitioners [Traditional Chinese Medicine (TCM) practitioners, herbalists and Naturopathic and Homeopathic doctors interested in complementary and alternative medicine], NHP manufacturers, First Nations groups, etc., were consulted. After an intensive examination of the situation, the report of the Standing Committee on Health (1998) made 53 specific recommendations. This report noted that the safety of natural health products was of primary importance.

Two key recommendations were that NHPs should be regulated in a distinct regulatory framework for safety and efficacy while access should be granted to traditionally used materials to recognize the ethnic diversity of the Canadian population. In 1999, the recommendations were accepted by the Minister of Health Canada and approved by Parliament. The most important result was that the Office of Natural Health Products (ONHP) was created in 2000 and the NHPR were created as an act of Parliament and formally adopted in 2004. The first director was appointed in January 2000 to oversee an Expert Advisory Group and a transition team, which

developed an approach to implement the 53 recommendations. This approach was published in 2000 as "Final report, a fresh start". From June to September 2000, the ONHP conducted open consultation meetings with interested Canadians across the country on the proposed regulatory framework for NHPs. All feedback from the consultation sessions, including consumer, stakeholder and professional association feedback, was analyzed and modifications were made to the proposal based on the feedback. The proposed regulations were revised and published in Canada Gazette, Part I in December 2001.

A second version of the proposed regulatory framework was drafted and then released for public comment at the end of March 2001. ONHP hosted a series of consultations from March to May 2001. Targeted consultation sessions were held from March to October 2001 with stakeholders to discuss a number of topics including: good manufacturing practices (GMPs); Standards of Evidence (SOE); Aboriginal engagement; bulk herbs and homeopathic medicines. The proposed regulations were revised and published in the Canada Gazette, Part II in June 2003. The NHPR became law in 2004 and included some transitional provisions, such as 6 years for products previously licensed as drugs and assigned Drug Identification Numbers, and 2 years for site licensing and GMP requirements.

Change outside of government:
The NHPR created an environment for change outside of government as well. In response to the new regulations, interest in research in the field has increased markedly. The research community and NHP industry formed the Natural Health Products Research Society[6] in 2004, which has brought together 200-300 scientists for five annual meetings held in different cities across Canada. The Canadian Institute of Chinese Medicine Research[7] was formed a year later and brings together 30-100 scientists annually. Stakeholder organizations, such as the Canadian Herb, Spice and Natural Health Products Coalition, complemented the regulations by developing quality assurance programs of their own, such as the guidelines for Good Agricultural Practices for medicinal plant cultivation[8].

2.1 Background on the Natural Health Products Program

HC is responsible for ensuring that all Canadians have ready access to NHPs that are safe, effective and of high quality, while respecting freedom of choice and philosophical and cultural diversity. The NHPP in HC undertakes this responsibility according to its authority under the *Food and Drugs Act* and the NHPR.

The NHPR are the result of a comprehensive and inclusive consultation process with Canadian consumers, academics, health care practitioners and industry stakeholders, and are a part of the Government's response to the House of Commons Standing Committee on Health's report and 53 recommendations on the regulation of NHPs in Canada, March 1999. The NHPR, which came into effect on January 1, 2004, are set out in 6 parts and include provisions for:

6 http://www.nhprs.ca
7 http://www.bepress.com/jcim/cicmr_announcements.html
8 http://www.saskherbspice.org/gacp-overview.html

- Product licensing and adverse reaction reporting (Part 1);
- Site licensing (Part 2);
- Good manufacturing practices (GMPs) (Part 3);
- Clinical trials involving human subjects (Part 4);
- General issues including labelling requirements among others (Part 5); and,
- Amendments and transitional provisions (Part 6).

Figure 2 – Natural Health Products

Section 1 of the NHPR defines a NHP as:

"A substance set out in Schedule 1 or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in:

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

However, a natural health product does not include a substance set out in Schedule 2, any combination of substances that includes a substance set out in Schedule 2 or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2."

Under the NHPR, NHPs must be safe for consideration as over-the-counter products and not require a prescription to be sold. NHPs include: vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines (such as traditional Chinese medicines), probiotics and other products (like amino acids and essential fatty acids) that are manufactured, sold or represented for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans, restoring or correcting organic functions in humans or modifying organic functions in humans (such as modifying those functions in a manner that maintains or promotes health).

With the NHPR, NHPs are regulated in a different way from other pharmaceutical products. NHPD recognizes a variety of SOEs for licensing products, which is particularly innovative. It allows different cultures access to safe medicines that they use traditionally and are part of their ethnic practices. Furthermore, the NHPR introduced NHP specific Good Manufacturing Practice requirements, differing from the drug GMP standards. However, as a result of these unique standards, the terms in the Mutual Recognition Agreements held with other countries, which were largely based on compliance with pharmaceutical Good Manufacturing Practices (GMPs), could not be met. As a result, the NHPP committed to issuing Certificates of Compliance for facilities manufacturing, packaging/labelling, importing, distributing and or testing NHPs in addition to drugs that indicates which NHPs are held to a drug GMP standard.

While the NHPR apply to all NHPs as of January 2004, an estimated 30,000 new, previously unregulated or previously regulated (>10,000 products with DINs) products were brought forward for product licensing. This created an enormous challenge for the NHPD to evaluate/assess all these application files and grant or refuse NHP licences for them in a timely fashion. In addition to the large numbers of applications, the diversity of products and lack of previous regulatory guidance for many varied and highly unusual products has made product assessment a very challenging task. As such, the Compliance Policy for NHPs (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/ legislation/ pol/complian-conform_pol-eng.php) was developed to allow for a transition period for distributors of NHPs to obtain their product licences and to also help prioritize HC resources for enforcement activities. Under this policy, if a product licence application (PLA) was submitted to the NHPD by a specified date, depending on the type of product (its 'priority deadline date'), it would be considered a lower priority for enforcement actions, unless a risk to health was identified. As such, it has been noted that it appears to have been difficult for some companies to adjust to the new regulations and meet the requirements, while other companies which have invested heavily in quality have expressed concerns regarding the policy and unapproved products being available on the market.

2.2 Program Objectives

The NHPP's ultimate outcome is **to assure that the health of Canadians is improved and maintained through access to NHPs that are safe, effective and of high quality, while respecting freedom of choice and philosophical and cultural diversity**. In order to achieve this outcome, Program partners are committed to achieving the following objectives:

- To reduce the product and site licence application backlog by 60% by March 2009 and address the backlog by March 2010; and,
- To develop and incorporate a new risk-based approach with the following four principles:
  - Strengthen the NHP regulatory framework through a risk-based approach for pre-market activities;
  - Maintain a post-market surveillance management framework that is standardized across product lines and strengthen regulation of industry's monitoring responsibilities, such as authority to request post-market studies;
  - Contribute to developing strong, enforceable regulatory frameworks and programs with partners and enhance the confidence of Canadians in an NHP Regulatory System; and,
  - Maintain and strengthen a compliance and enforcement framework that enables HC to act effectively, when necessary, to mitigate risk and protect the health and safety of consumers.

A logic model was developed by the NHPP Evaluation Framework Development Team and presented in the Program's Results-Based Management and Accountability Framework on October 24th, 2008[9]. This logic model outlines the NHPP's activities and their linkages to the outputs, reach as well as immediate, intermediate and long-term outcomes. Each level of outcomes builds on the next to produce the ultimate outcome for Canadians. The logic model is illustrated in **Figure 3.**

In achieving the NHPP's objectives, the Program contributes to the following strategic outcome defined by HC and the HPFB[10] in the Program Activity Architecture (PAA):

- Access to safe and effective health products and food and information for healthy choices.

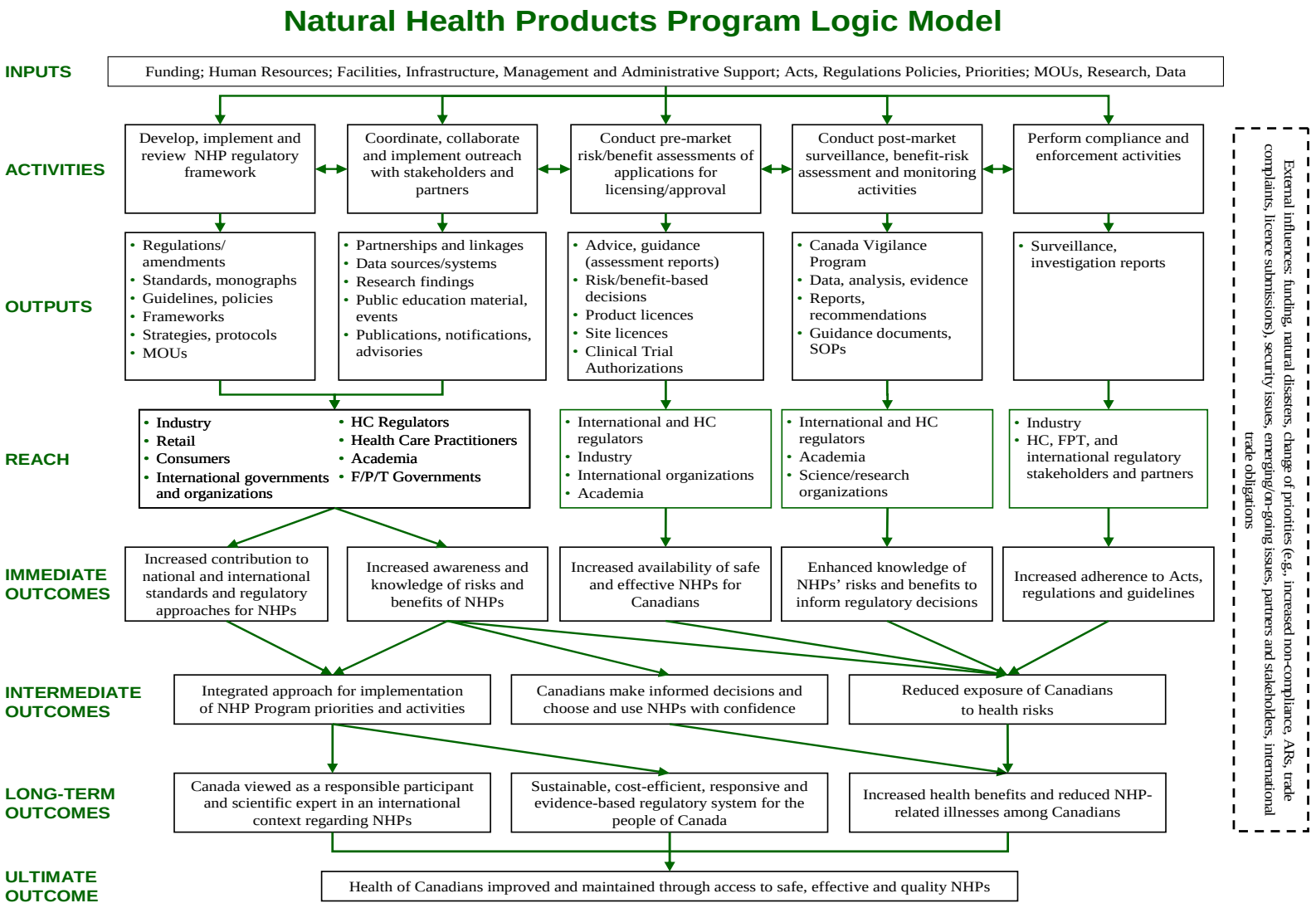
The PAA sub-activity 2.1.5 is more specific to the activities related to implementing the NHPP and includes:

- pre-market regulatory NHP evaluation and process improvement, specifically, processing product licence and site licence applications and clearing the backlog;
- monitoring and surveillance of safety and therapeutic effectiveness information and risk management, specifically, improving safety and efficacy of health products authorized for sale in Canada; and,
- compliance and enforcement of the FDA and the NHPR involving compliance verification and investigative functions, laboratory analysis, and support of prosecutions.

[9] Prior to this report, the NHPP was not a formal program that worked towards the achievement of a common set of objectives and desired outcomes.

[10] HC's Health Products and Food Branch (HPFB) is responsible for a broad range of health protection and promotion activities that affect the daily lives of Canadians. The Branch employs an integrated, science-based approach to managing the risks and benefits relating to health products, food and nutrition. Currently the Natural Health Products Directorate is placed in the HPFB.

Figure 3 - NHPP Logic Model



2.3 Roles and Responsibilities

The activities linked to the work identified in the NHPR are carried out primarily by three groups in HC:

1. The NHPD is the federal organization responsible for the implementation of the NHPR. The employees of NHPD perform a variety of activities aimed at ensuring Canadians have ready access to NHPs that are safe, effective and of high quality (i.e., core regulatory responsibilities, such as processing and screening submissions and clinical trials; evidence assessments; working with partners on enforcement, compliance and surveillance; and, policy/guideline development along with information dissemination, international cooperation, and research).
2. The MHPD is responsible for post approval safety surveillance, risk communications and regulatory oversight of advertising; and,
3. The HPFBI, in partnership with the Regions and Programs Branch (RAPB), is responsible for compliance and enforcement activities, such as compliance verification and investigations, compliance monitoring including recall monitoring, border integrity activities, analysis of NHP samples, and compliance promotions and outreach activities.

The term "NHPP" refers to the totality of the above activities, even though the activities were never designed as a structured and comprehensive set of actions as would normally be expected under a "program". As such, the Program's outcomes presented in the logic model (section 2.2) are reflective of what the Program should be achieving under the existing funding envelope (as described in the Program's Results Based Management Accountability Framework) and are not entirely reflective of how each organization completed NHP activities from 1999 to 2008.

A brief overview of the core activities that constitute the NHPP is provided below.

2.3.1 The Natural Health Products Directorate

The key activities undertaken in NHPD for assuring the safety, efficacy and quality of NHPs include pre-market, risk-benefit assessments of product and site applications for licensing and approval, which includes assessing the substantive scientific and traditional evidence of NHPs with respect to safety, efficacy and quality, including the assessment of clinical trials.

Product Licensing:
NHPs sold in Canada require a product licence before being marketed. Obtaining a licence requires submitting to HC detailed information on the product, including: medicinal ingredients, source, potency, non-medicinal ingredients and recommended conditions of use. Once a PLA has been assessed and granted market authorization by HC, the product label will bear an eight digit product licence number preceded by the distinct letters NPN (Natural Product Number), or, in the case of a homeopathic medicine, by the letters Drug Identification Number- Homeopathic Medicine (DIN-HM). The aim of the product licence number on the label is to assure consumers that the product has been reviewed and approved by HC for safety, quality and efficacy.

Site Licensing and Good Manufacturing Practices (GMP):
The site licensing system requires that all manufacturers, packagers, labellers, and importers be licensed. A site licence demonstrates that HC has assessed an application to determine that the activity being conducted is in accordance with GMPs, as outlined in part 3 of the NHPR. GMPs help ensure the consistent quality of a NHP and include requirements such as having procedures in place for distribution records and product recalls, for ensuring quality assurance is in place such that products meet their specifications, that premises and equipment are clean and prevent contamination, and other requirements critical to ensuring the safety and quality of a NHP. Although a site licence is not required for storage and distribution of NHPs, these activities must also adhere to GMPs as indicated in the NHPR.

Applicants must provide NHPD with a Site Licence Application Form and a Quality Assurance Report Form, which is a report based on the applicant's assessment against the GMP requirements set out in HC's GMPs Guidance Document (HC, 2006). NHPD assesses applications for completeness and for compliance with the NHPR. This assessment is a paper-based exercise as sites are not inspected by the Program. Sites that meet the required criteria are issued a site licence, while those that do not meet the required criteria are issued a refusal notice by the NHPD.

Clinical Trials and Health Hazard Evaluations and Health Risk Assessments:
The Bureau of Clinical Trials and Health Sciences (BCTHS), authorizes clinical trials and conducts Health Hazard Evaluations (HHEs). Clinical trials involving NHPs on human subjects must be authorized by NHPD before commencement of the trial. Clinical trials require the sponsor or a designated representative of the sponsor to submit an application package with detailed information about the proposed trial for review by the NHPD.

An HHE is a formal scientific evaluation of a particular NHP product to classify the level of risk posed, when the level of risk needs to be determined. A HHE is often requested by the HPFBI in response to a product being sold that may be non-compliant (ie. is contaminated with bacteria or heavy metals, contains an adulterant, is mislabelled) and the level of risk needs to be determined. HHEs may also be conducted in response to new and emerging post-market safety information on a product or ingredient via the MHPD signal assessment process (e.g., through adverse reactions reports). Requests for HHEs are received through NHPD's Compliance Coordination Unit, which assigns a file number and then passes the request onto the BCTHS. HHE requests come from a variety of sources, including: MHPD (via the signal assessment process); or HPFBI via consumer complaints; physician or practitioner complaints; trade complaints (i.e., when industry files complaints against competitors); and, warnings from another jurisdictions. The BCTHS' performance standard is 48 hours to complete a HHE after receipt of call; however, if preliminary evaluation determines a risk to life, the Bureau will send a verbal response to the Compliance Coordination Unit within 24 hours.

HHEs examine the composition, pharmacology, toxicology and quality to determine the level of risk posed by the product or ingredient. To conduct evaluations of a NHP the Bureau reviews peer-reviewed journal articles, reports from other health agencies, adverse reaction information from MHPD, and laboratory reports from HPFBI. Once the evaluation is complete, the Bureau assigns a level of risk to the product as noted in Figure 4 (Type 1, 2 or 3).

Figure 4 – HHE Types of Risks

- ✓ **Type 1** life threatening risks
- ✓ **Type 2** broad category between life threatening and no significant risks (HC is currently developing a guidance document to clarify and define the Type 2 level of risk)
- ✓ **Type 3** no significant risks

Health Risk Assessments (HRAs), also conducted by BCTHS, are similar to HHEs but focus on a substance that may be found in one or more products (e.g., diethylene glycol in toothpastes, or melamine in food) and the potential risks to health associated with that substance. Requests for HRAs will often come from similar sources (ie. HPFBI, MHPD) but may also include the NHPD's Product Assessment Unit, as well as ingredients relevant to the Food Directorate (e.g., gluten).

HHE and HRA assessments are used by HPFBI to determine risk management activities required and necessary compliance and enforcement activities, as well as by product, site and clinical trial assessment groups within NHPD to inform future authorizations in order to prevent risks and to review previous authorizations. Risk communications to industry, consumers, and health care practitioners is an important risk mitigation outcome of this approach. Communications are coordinated with the Program partners (led by either HPFBI, MHPD, or NHPD depending on the nature of the situation) and HC's Public Affairs, Consultation and Communications Branch (PACCB).

2.3.2 The Marketed Health Products Directorate

The Marketed Health Products Directorate (MHPD) works to assure that the HPFB's programs take a consistent approach to post-approval safety surveillance, assessment of signals and safety trends and risk communications concerning all regulated marketed health products. These products include:

1. Marketed Pharmaceuticals and Human Drugs,
2. Marketed Medical Devices,
3. Marketed Biologics and Biotechnology, and
4. Marketed Natural Health Products.

MHPD's activities are directed by *Planning Our Future: Federal Regulatory Post-Market Surveillance Strategy* (2007-2012). This strategy provides a framework that guides MHPD's post-market surveillance program which involves the collection, monitoring and assessment of adverse reactions to marketed health products and other data, as well as standard market intervention and communication procedures, along with associated policy development and business transformation activities.

MHPD's primary role related to the NHPP is post-market surveillance, benefit-risk assessments and associated monitoring activities of marketed and un-marketed NHPs, including both domestic and international products. Other key activities include risk communication and advertising oversight. These activities are carried out in collaboration with NHPD and the HPFBI as well as other relevant national (e.g., Advertising Preclearance Agencies) and international organizations (e.g., regulatory departments in other countries, the WHO, etc.).

Post-market surveillance:
MHPD's post-market surveillance continuum comprises three principal phases:

1. Information gathering, monitoring and processing

Activities include:

- Collecting adverse reactions reports and information from Market Authorization, Holders (MAHs), professionals and consumers;
- Assessing adverse reaction reports for completeness, entering data into the Canada Vigilance Database in accordance with international standards, coding assessed information [reaction, indication and patient history) information using an international medical terminology (MedDRA)];
- Making adverse reaction information publically available on the Canada Vigilance On-line Database;
- Detecting, prioritizing and assessing safety signals;
- Gathering additional information from a literature scan, other regulatory agencies, the WHO and industry; and
- Detecting risks associated with use of products in the marketplace.

2. Signal detection and assessment

Activities include:

- Assessing many information sources that combine to create a signal[11], i.e., a suspicion that there is a correlation between a product and reported ARs; and,
- Assessment consists of the scientific/medical review of multiple data sources to analyse risks/benefits, considering risk profiles of therapeutic alternatives.

[11] Standard sources of information include: media and medical literature, information from regulatory agencies, information from companies, and additional sources such as HC's Canada Vigilance Program and WHO-UMC's Vigimed.

3. Risk management and intervention

Activities include:

- Defining a risk management approach with HPFBI and NHPD, after safety risks have been identified, which may include interventions, such as communicating risk information to health care professionals and the public, labelling changes, or recommending that a product be removed altogether from the market; and,
- Broadly communicating interventions in the interests of transparency, increasing awareness and accountability (see Risk Communication section below).

MHPD maintains a consistent approach to identifying, prioritizing, and assessing signals for all product lines, including NHPs. Presently, a mix of general and NHP-specific Standard Operating Procedures (SOPs) provide guidance to MHPD staff conducting signal identification, prioritization and assessment activities (e.g., Prioritization and Management of Potential Signal Files SOP, NHP Draft Environmental Scanning Process SOP, etc.).

Signals can be classified as red, yellow, or green.

- *Red cases*: Signals that have to be evaluated as a priority and for which, at the time of the pre-evaluation, it is estimated that there will likely be an intervention if the evaluation confirms the link between the suspected Adverse Event (AE) and the NHP/drug. The AE/ADR (Adverse Drug Reaction) has to be unknown and/or unlabeled and/or insufficiently labelled (i.e. not included in the risk information section of the NHP monographs), and has to be a serious AE/ADR.
- *Yellow cases*: Signals for which further evaluation is recommended but that do not meet the criteria of the Red category because of lack of seriousness and/or newness and still need a comprehensive assessment. These signals are expected, if confirmed, to lead to a change in the risk/benefit ratio or would require changes in the labelling/packaging information, such as in the case of a NHP/drug, addition of a new ADR to the labelling (i.e., in the warnings or adverse events section, not limited to the post-marketing AE section), a new warning, or a change in indications/contraindications.
- *Green cases*: Signals that are related to AE/ADR that already known and/or labelled, or related to possible confounders, or the AE/ADR itself is not a safety problem. These cases do not meet any criterion and are unlikely to affect the way the substance, product or device is used. It is a possibility that they may never get to be reviewed, if all the red and yellow files have not been assigned and completed.

Risk Communication:

The Directorate maintains a range of communication tools for the HPFB to inform the public, health care practitioners and industry of potential risks posed by products. The type of dissemination tool applied depends on the urgency of the safety issue and the target audience(s). The tools include the following: Public Advisory, Public Warning (generally led by HPFBI), Foreign Product Alert, Information Update, It's Your Health, Canadian Adverse Reaction

Newsletter (CARN), Fact Sheets and Backgrounders, Health Professional Communication (e.g., Dear Health Care Professional Letter, Notice to Hospitals) and Public Communications issued by MAHs.

From the time that a signal is detected to final risk management activities, communication tools are used to inform the public, health care practitioners and industry of potential risks posed by products. MHPD has a Risk Communication Issuance process map that outlines the risk communication tool selection process. The process map outlines a strategic, systematic approach to formulating and implementing effective risk communications based on urgency of the communication including extent of potential impact. MHPD works collaboratively with MAHs, i.e. product or site licence holders to ensure communications reach appropriate parties.

Advertising Oversight:
MHPD is responsible for the regulatory oversight of the advertising of marketed health products in Canada. This involves developing guidelines and implementing regulations that govern advertising of marketed health products, including NHPs, in Canada. MHPD works closely with advertising pre-clearance agencies, such as the Pharmaceutical Advertising Advisory Board (PAAB), Advertising Standards Canada (ASC) and MIJO[12] to clarify standards regarding what information – including health claims and product safety information – may be included in advertising health products. MHPD evaluates advertising complaints for health products, including NHPs, to ensure adherence to the Food and Drugs Act and related regulations (i.e. NHPR) and pursues appropriate compliance actions in collaboration with Advertising Preclearance Agencies and the HPFBI. The MHPD chairs the Branch Advertising Working Group to address advertising issues which may have an impact on the activities of the HPFB.

2.3.3 The Health Products Food Branch Inspectorate

The HPFBI in partnership with RAPB is responsible for branch-wide compliance and enforcement of the FDA and its associated regulations, enabling consistency of approach across the spectrum of regulated products, including human drugs, veterinary drugs, natural health products (NHP), medical devices, blood, semen, and cells, tissues and organs (CTO). The key activities HPFBI conducts related to NHPs fall under the overarching Inspectorate Compliance and Enforcement Policy 0001 (POL-0001) as well as the Compliance Policy for NHPs as previously noted. The HPFBI often works with a regulated party to bring it into compliance through a variety of risk management tools and principles as outlined in POL-0001.

i) Compliance Verifications and Investigations

Compliance Verifications
HC identifies non-compliances of NHPs primarily through consumer or trade complaints, or referrals from internal and external partners. Complaints or referrals are received by HPFBI in the form of a suspected non-compliance with the FDA or NHPR. When received, the HPFBI will prioritize the suspected non-compliance according to the possible level of risk it may pose in order to most effectively apply resources on a risk based approach. HC may request a formal risk assessment from NHPD, if needed, to make this determination. HPFBI will then verify whether there is in fact non-compliance through compliance verification. This includes actions such as

[12] (http://mijo.com/mijonet_web/Public/Broadcast_TV_and_Radio/_Advertising_Clearances/Default.aspx)

information gathering through, discussions with or visits to the regulated party, discussions with Program partners, as well as the use of the inspector powers under the FDA to verify a complaint. The HPFBI works with the regulated party to ensure appropriate risk management actions are taken and uses the appropriate level of intervention based on the level of risk. The approach and tools used by HPFBI are further outlined in POL-0001.

Compliance verifications are opened when there is a reported or suspected non-compliance and closed when the non-compliance has been corrected and risk management actions have been taken. The workload related to issues of non-compliance attributable to natural health products continues to increase, now representing close to half of all compliance verifications within the drug compliance verification and investigations unit of the HPFBI. Although these products are often referred to as low risk, many safety concerns have been identified such as product contamination or adulteration with prescription drugs, safety concerns related to specific ingredients, unsubstantiated health claims, interactions with other products, among others. The outcome of these types of compliance verifications often results in extensive risk management activities such as the regulated party conducting a stop sale and product recall as well as the posting of public communications, including public warnings or advisories to communicate to the general public the health risks associated with these products.

Investigations

A vast majority of the time compliance can be accomplished through a dialogue between Health Canada and the regulated party. On rare occasions a regulated party is unwilling to comply with the law for health products, and often wilfully neglects their regulatory obligations creating a risk to health and safety. Investigations are activities conducted to support a case for potential judicial determination. These activities are carried out in accordance with the Criminal Code and not the FDA. Activities may include search warrants, prosecutions or injunctions. Investigations are only conducted when the powers under the FDA have been unsuccessful in bringing a regulated party into compliance. As indicated in POL-0001, this is a final measure that may be taken.

ii) Compliance Monitoring and Recall Monitoring

A portion of the work conducted within the drug compliance verification and investigations unit of the HPFBI is related to recalls which are voluntarily initiated by industry or at the request of HC. Each recall is a voluntary compliance action to remove a product(s) or specific lot(s) of a product from the market. Industry is responsible for notifying HC when they conduct a recall. It is Health Canada's responsibility to verify the quality and effectiveness of the industry submitted recall plans.

In addition, HPFBI has a compliance monitoring project (CMP) which proactively focuses on an area of concern in order to conduct surveillance and take appropriate risk management steps if needed. This often involves going out to retailers to obtain products that fall within a certain category, conducting laboratory testing and taking risk management steps as required. Although this program is not limited to NHPs, it often involves a significant NHP portion. For example, past projects have included erectile dysfunction products, sleep aid products, toothpaste products, as well as children's cough and cold products. Each of these projects has contributed to the knowledge of these groups of categories and also managed to identify products that pose a risk and trigger appropriate risk management actions.

iii) Border Integrity Activities

The HPFBI in partnership with the Canada Border Services Agency (CBSA), ensures the consistent administration of the FDA at the border and provides information to Canadians so that they can make informed choices related to the importation and exportation of health products. When suspected non-compliant shipments of NHPs are received by the CBSA, they are referred to the HPFBI for admissibility determinations. HPFBI verifies compliance with the FDA and NHPR in making an admissibility recommendation for the shipment. Import Alerts are one compliance and monitoring tool used by the HPFBI. They allow HC to flag to CBSA shipments that are of increased risk of non-compliance and therefore of greater interest to HC due to prior instances of non-compliance on the part of the exporter, importer or product. Import Alerts are activated for a six month period and may be extended if required.

iv) Laboratory Analysis

The activity of conducting laboratory analyses provides scientific evidence necessary for compliance verifications & investigations and compliance monitoring to support the FDA and its related Regulations as they apply to NHPs.

v) Compliance Promotion

In collaboration with MHPD and NHPD, the Inspectorate uses compliance promotions and outreach as proactive compliance and enforcement measures. For example, preparing fact sheets on the requirements of the NHPR and sharing these with retailers and industry. As well, the HPFBI partners with the MHPD and NHPD in the presentation of stakeholder sessions across the country on a variety of issues in the NHP lifecycle (from pre- to post-market).

2.3.4 Governance

Established in September 2007, the NHPP Directors General Coordinating Committee (DGCC) provides the focal point for cross-Directorate issues management. Membership consists of the Directors General from NHPD, MHPD and HPFBI. Other participants, such as representatives from the Food Directorate and or Legal Services, are invited to participate on an ad-hoc basis.

Figure 5 – NHPP - Directors General Coordinating Committee

As stated in the DGCC Terms of Reference (September 2007)

The mandate of the DGCC is to provide the NHPP with strategic oversight and direction by:

- ✓ providing the programmatic leadership needed to attain the mission and vision in an efficient and effective manner, consistent with its guiding principles; and,
- ✓ defining Program objectives, goals, targets, and expected results according to available resources and consistent with the Program's mission statement and guiding principles.

The objectives of the DGCC are to:

- ✓ facilitate the exchange of information between the NHPD, the HPFBI and the MHPD on subjects of mutual interest and responsibility;
- ✓ identify emerging issues;
- ✓ discuss operational and strategic issues as well as operational planning pertaining to the NHPP; and,
- ✓ provide an opportunity for a Branch approach to the management of issues of mutual interest or responsibility.

The Director General of NHPD also chairs the NHPD Risk-Management Committee[13] comprised of representatives from NHPD, MHPD, HPFBI and the PACCB[14].

Figure 6 – Natural Health Products Directorate Risk Management Committee

As stated in the Natural Health Products Directorate Risk Management Committee (NHPD-RMC) Terms of Reference (September 2009)

The purpose of the Natural Health Products Directorate Risk Management Committee (NHPD-RMC) is to provide oversight for identification, analysis and decision-making around health issues within the mandate of the Natural Health Products Directorate (NHPD) and to provide advice to the Director General, NHPD. The NHPD-RMC reports to the DG, NHPD.

The objectives of the NHPD-RMC are to:

- ✓ oversee a coordinated response to risk issues and ensure that necessary input from all appropriate parties is obtained;
- ✓ make informed decisions on the recommended option(s) for action;
- ✓ identify those issues which should be taken to Branch Executive Committee – Risk management (BEC-RM) for further decision input, and to BEC Look-Ahead for information sharing purposes;
- ✓ ensure transparency of process and decision-making through ongoing documentation, status reports and follow-up of risk management issues and initiatives; and
- ✓ evaluate the results of situational reviews of risk issues and determine if further action is required.

More recently (2008-2009), operational level working groups have been established within the Program, including the NHP Program working group (NHPPwg), focussing on training and outreach, as well as the NHPP Compliance Committee (NHPP-CC) focusing on compliance and enforcement challenges.

In addition to these internal committees, the NHPD liaises with the Program Advisory Committee (PAC), a committee with up to 15 members who represent a cross-section of NHP sectors, including industry, consumers, health care professionals, retailers, and researchers, that support and provide advice and recommendations to the DG, NHPD, in managing NHPD activities[15].

[13] Established in April 2007, previously known as the Issues Committee.

[14] PACCB integrates national and regional perspectives into all of its policies and strategies, communications and consultation functions. The Branch plays a key role in delivering HC's commitment to transparency.

[15] A Management Advisory Committee (MAC) was established in 2004 by NHPD and provided a forum to liaise with industry and stakeholders about the administration of the NHPR, including policies, policy research needs, regulatory amendments, guidelines, SOPs, and industry specific implementation issues (e.g., GMPs). MAC was comprised of a maximum of 10 members, representing NHP industry and consumer stakeholders. The MAC was retired in August 2009 whereas the PAC was created shortly thereafter.

Figure 7 – Program Advisory Committee

As stated in the NHPD PAC Terms of Reference (October 2009)

The mandate of the PAC is to provide the Director General, NHPD, with timely, expert advice and recommendations on questions related to the ongoing management of the regulatory framework for natural health products (NHPs). More specifically, the mandate of the NHP-PAC is to provide advice and recommendations on:

- ✓ strategic development, to help address identified and emerging issues and to deliver on the NHPP strategy, including key issues related to safety, efficacy and quality standards and requirements for NHPs; and,
- ✓ stakeholder information needs, including advice and recommendations on content (type of information), type of products and dissemination approaches. To support this advisory role, the PAC members will act, in voluntary capacity, as a route for the dissemination of focused information on NHPs, including: points of sale, such as pharmacies and health food stores, NHP sales representatives, the public, Members of Parliament, health care practitioners, pharmacists and regulators.

In addition to the PAC, from 2000 to 2009, NHPD met regularly with the Expert Advisory Committee (EAC) to seek expert advice on issues related to the safety, quality and efficacy of natural health products. This Committee provided the DG of NHPD with advice and guidance on issues of a scientific nature regarding the safety, use and regulation of NHPs. As the Program has matured and developed more in-house scientific expertise, Program managers are relying less on the EAC to clarify technical issues. As a result, the EAC was retired on December 31, 2009 and expertise will be sought on an ad hoc basis with former EAC members or new experts as required.

2.3.5 Resources

When the NHPR came into force in 2004, dedicated, stable funding was not provided[16]. With only approximately $3.9M identified as annual base funding provided by HC, resources for early implementation of the NHPR were derived from various Departmental initiatives as well as Branch and Departmental reallocations, including interim funding by the Treasury Board Management Reserve.

In 2008, funding provided resources to a level of $82.45M over five years ($16.49M annually) (**See Table 3**). The funding received in 2008 represents a significant improvement in funding available to the NHPP's implementing organizations. The funding provided a means for Program spending to occur across three broad themes:

[16] A comprehensive understanding of the resources allocated to the implementing organizations for implementation of NHP activities from 1999-2008 is not available. However, Table 10 provides financial information on actual total spending by NHPD, MHPD and HBFBI on NHP activities.

1. **Active Prevention** [$55M over five years, 146 full time equivalents (FTEs)]: for NHPD activities aimed at providing Canadians with ready access to NHPs that are safe, effective and of high quality. Core activities include: pre-market review; regulatory cooperation and outreach; regulatory, policy and standards development; and, program management and support;
2. **Targeted Oversight** ($14.95M over five years, 22 FTEs): for MHPD activities associated with post-approval safety surveillance, assessment of signals and safety trends, and risk communications concerning natural health products; and,
3. **Rapid Response** ($12.5M over five years, 19 FTEs): for HPFBI activities for continued responsive compliance verification and enforcement.

Table 3 presents a summary of the allocations to each implementing organization.

Table 3 - 2008 Funding for the NHPP ($Millions)

New Funding Initiatives	2008-2009	2009-2010	2010-2011[17]	2011-2012	2012-2013	Total 5-year
Active Prevention (NHPD)	11.0	11.0	11.0	11.0	11.0	**55.0**
Targeted Oversight (MHPD)	2.99	2.99	2.99	2.99	2.99	**14.95**
Rapid Response (HPFBI)	2.50	2.50	2.50	2.50	2.50	**12.5**
Total	**16.49**	**16.49**	**16.49**	**16.49**	**16.49**	**82.45**
Existing A-Base						
Strengthening HC's Food Safety and Nutrition (Active Prevention)	2.96	2.96	2.96	2.96	2.96	**14.8**
Sustaining the Federal Health (Transition) (Active Prevention)	0.99	0.99	0.99	0.99	0.99	**4.95**
BSEII (Active Prevention)	0.47	-	-	-	-	**0.47**
Therapeutic Products Safety Initiative (for Rapid Response Activities)	0.43	0.43	0.43	0.43	0.43	**2.15**
A-Base Total	**4.85**	**4.38**	**4.38**	**4.38**	**4.38**	**22.37**
Total (Budget + A-Base)	**21.34**	**20.87**	**20.87**	**20.87**	**20.87**	**104.82**

[17] Program staff commented that in 2010-2011 program funds were reallocated from MHPD and HPFBI to NHPD. Reallocations are suspected to continue, however, the evaluation was unable to conclude what the reallocated totals would be for the identified or future periods.

3 THE CANADIAN REGULATORY SYSTEM COMPARED TO OTHER WORLD SYSTEMS

Introduction to Regulatory Systems:
Most national regulatory systems dealing with NHPs attempt to ensure that products sold are safe and effective by a series of regulations that may include pre-market assessments (an application and approval process leading to the issue of licences to sell), GMPs (regulations for manufacturing facilities and procedures), licensing (the issuance of legal licences to market and a product identification number), labelling requirements (regulations for ingredients, health claims and cautionary statements made on labels), and/or post-market surveillance and compliance/enforcement, which include pharmacovigilance, such as warnings/advisories and ADR reporting, product testing, and advising manufacturers of potential problems and halting production. This section compares the NHPP to other key world systems – a description of each system is provided below, followed by a comparative table (**Table 4**).

Canada
The NHPP recognizes a broad range of cultural medicines and conventional products combined with a pre-market review of safety and quality (Nestmann et al., 2006). It provides a unique effort on the efficacy of cultural products. Post-market surveillance is reactive and not as thorough as post-market surveillance systems found in other countries (e.g., ongoing targeted facility inspections in Australia).

The definition of an NHP is unique to Canada and is quite broad. It has two parts: a substance and a function component. The substance includes herbal remedies, traditional and homeopathic remedies, material from plants, algae, bacteria, fungi, animals as well as refined substances, such as vitamins, minerals amino acids, fatty acids, enzymes, etc. The function component can involve non-prescription use for diagnosis, mitigation or treatment of disease, for restoring function, or to maintain health. With a thorough pre-market approval approach (absent in many other national programs) and post-market surveillance (responsive but not proactive as in some other national programs), the NHPP emphasizes an evaluation of safety before products reach the market. Another unique focus is to provide access to cultural medicines, and the Canadian regulations now recognize a variety of SOEs for efficacy of natural health products, which has not been attempted in other jurisdictions in the world. Based on the level of risk, they can range from traditional use of NHPs to meta-analysis of clinical trials with placebo-controlled randomized design. For example, it allows some treatment claims appropriate for self medication (not allowed in some national programs) as well as prevention, health maintenance and structure function claims. One aspect of the Canadian system is that it recognizes that traditional products in use for a long period of time are relatively safe for human use if no adverse events have been reported. The traditional use products must have 50 years of safe use, no safety concerns documented in scientific literature and two pharmacopoeial references for dose. Whereas other systems are focused mainly on one cultural heritage, the Canadian system allows a standard validation procedure for licensing of all types of traditional medicines as well as a wide range of other products.

The standard procedure for reduced registrations requirements is provided under the compendial product licensing system. Regulatory monographs have been developed in house by NHPD staff to allow rapid, 60-day registration of many conventional and traditional use products. Canada has the largest monograph system of the countries surveyed, with easy access through the NHPD website to 122 monographs, including 108 single ingredient monographs and 14 product monographs. The complete listing of monographs is available online at: http://www.hc-sc.gc.ca/dhp-mps/prodnatur /applications/licen-prod/monograph/index-eng.php. Many other guidance documents for registration are provided on the website addressing quality issues and application procedures[18]. Some traditional paradigms are accepted in the Canadian system if they can be translated into equivalent modern scientific terms. Licensing results in the issue of a NPN, or DIN-HM in the case of homeopathic medicines. The regulations provide requirements for site licences for manufacturing as well as GMPs that are specific to the NHP Program and are not drug GMPs. Manufacturing SOPs for NHPs are outcome based and allow manufacturers to meet standards by a variety of procedures of their choice as long as the desired outcome is met. At present, site licensing is a paper based process and does not involve inspection. Regulations for prior approval of clinical trials, labelling, and AR reporting and pharmacovigilance are specified. One of the special features of the system is that vitamins may be considered not only to meet daily minimum requirements but, at larger doses, for therapy. For this reason, the Codex Alimentarius system, in use in other countries, was not adopted for NHPs in Canada[19]. Nutriceuticals may be regulated if a health claim is made, which has expanded the mandate of the NHPP beyond that of other countries and beyond expectations in Canada.

The NHPP has developed world-class expertise in its mandate area. To perform its regulatory duties, the NHPP has recruited, in less than a decade, an exceptional number of scientists and health practitioners from many paradigms with specific expertise in NHPs and CAM. These include staff with Naturopathic Doctor, Medical Doctor, Doctor of Homeopathy or Doctor of TCM, as well as Master and Doctoral-level students with training in pharmacognosy, NHPs, phytochemistry and medicinal plants. In addition, the NHPP has developed many other tools for clients and practitioners, including the Licensed NHP database, MedEffect™ Canada for advisories and warnings, and an internal database for regulatory use.

United States of America

Like Canada, there was limited use and interest in NHPs in the U.S. before 1990. In the current US regulatory system, most NHPs are licensed as dietary supplements (DS) under the dietary supplement *Health Education Act* (1994), which places them with foods rather than drugs. It provides no pre-market assessment and only post-market surveillance (Brownie, 2005). Claims must not be false or misleading and, for this reason, mainly structure function claims are made, such as “Echinacea supports a healthy immune system”. Health claims for treatment of disease used in Canada (e.g., “Echinacea is traditionally used for treatment of colds and flu”) are not allowed for DS. Dietary supplements are not assessed, registered or approved by the USFDA (i.e., they do not undergo pre-market assessment) before they are marketed unless a new ingredient is used, another key difference with the Canadian system. All DS products are

[18] For example, see Evidence for Safety and Efficacy of Finished Natural Health Products. Available at: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/efe-paie_sum-som-eng.php

[19] The rationale for not adopting the Codex Alimentarius for vitamin and mineral supplements is provided in the following fact sheet: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/bulletins/codex_fact-fiche-eng.php

assumed to be safe and their surveillance is mostly post-market leading to cease and desist orders for illegal products, which has raised some serious concerns about this approach to regulation (Lahof et al., 2002) and is a significant difference with the Canadian pre- and post-market system. It does, however, provide manufacturers rapid access to the market. Site licensing is required under the *Bioterrorism Act* (2002) for all foods. The office of dietary supplements has been developing standards and methods for quality control. In 2007, new GMP regulations specified quality parameters for DS. There is no formally adopted monograph system. Some products may now be licensed under the new botanical drug legislations (Wu et al., 2008), which allow for more advanced health treatment claims (not allowed for DS), but require a highly standardized product and full toxicological and clinical evidence before licensing. There is some allowance for waiver of toxicology in the initial clinical trial. Vitamins and minerals are regulated as DS and are not subject to the WHO Codex Alimentarius.

European Union

The European regulatory system has rigorous pre-market assessment before the issuance of licences, strict pharmaceutical level GMP standards, and labelling regulations. Post-market surveillance is mostly responsive, with some proactive and targeted activities occurring. In Europe, with the exception of a few countries, notably the UK, NPH (especially phytomedicines[20], herbal products) have been in continuous active use by a wide segment of the population throughout the 20th century, and the market is dominated by manufacturers in Germany, France and Switzerland. Countries such as Germany and Switzerland have the most mature system for regulation of NHPs. Many but not all products are derived from European herbalism and have been thoroughly studied and evaluated for regulatory purposes. The German Commission E monographs provided detailed research and regulatory information (Blumenthal et al., 2000) until 1995; most modern research on herbal products came from this European research and provided key information for re-starting research in North America beginning in the mid 1990s. Individual country legislation on traditional medicines has existed for many years in the individual member countries, but has recently been harmonized by Directive 2004/24/EC and Regulation (EC) No 726/2004 of the European Parliament (Silano et al., 2004). The key features of the Directive are the creation of the Committee on Herbal Medicinal Products (HMPC), a traditional medicine definition, and a simplified registration procedure (Silano et al., 2004). Like Canada, the HMPC has an established monograph system for reduced registration of some traditional medicines, but only 30 products are monographed versus over 120 in the Canadian system. Most phytomedicines are regulated essentially as drugs, which may require a very thorough, very formal and lengthy review process for manufacture, quality control and toxicology, but a similar level of post-market surveillance to Canada. Vitamins are regulated under the WHO Codex Alimentarius, which is a minimum daily requirement system.

Singapore

Singapore provides an interesting regulatory comparison for Canada, because of a British Colonial legal heritage and a strong Chinese and South East Asian cultural heritage. TCM is by far the oldest and best established traditional medicine system in the world and represents about 88% of medicinal use in Singapore (Koh and Woo, 2000). In the Singaporean regulatory system,

[20] Phytomedicines can be defined as: the use of plants, parts of plants, and isolated phytochemicals for the prevention and treatment of various health concerns. Source: Mosby's Dictionary of Complementary and Alternative Medicine. (c) 2005, Elsevier.

effective September 1st, 1999, licensing and labelling requirements were specified as well as control of microbial contamination. The Health Sciences Authority recognizes for registration a western medicine products stream and a Chinese propriety medicine stream (CPM). These CPM products are recognized through a monograph system based on "A Dictionary of Chinese Pharmacy" or "The Chinese Herbal Medicine Materia Medica" and regulated according to the *Medicines Act* (1975) and amendments thereof. Like the US system, and unlike Canada, the EU and Australia, Singapore has no pre-market assessment. Singapore is following the Canadian experience for possible adoption of elements (such as monographs) in their system.

Australia

Australia, with a similar history and diverse ethnic population comparable to Canada, adopted a system for regulations of Complementary Medicines (the NHP equivalent in Australia) that is most similar to Canada. A review of the system by Briggs (2002) provides an overview of the Australian regulations. Regulation was established through the *Therapeutic Goods Act* (1989). "Complementary medicines" are administrated by the national office on TM/CAM, the Office of Complementary Medicines, established in 1999. Similar to Canada, Australia applies full pre-market assessments for complementary medicines, which have not been "listed" using a risk-based assessment system, GMP regulation, or identified in adverse drug reaction monitoring. Australia has a reduced risk-regulatory system for listed traditionally used products but does not have a compendial system to expedite the process like the one used in Canada. No pre-market assessment is made for these listed complementary medicines; however, a portion of licences (20%) are selected annually for post-market reviews (both targeted and random). This is an important feature of the system which ensures compliance at the level of marketed products and could be considered by Canada. Australia collaborates with Canada on regulation issues, through staff exchange, and sharing of information such as the Canadian monographs. Although Canada has a MRA with Australia, the NHPs were not included.

World Health Organization

The WHO is a UN policy agency but has legislated regulatory powers. It has been instrumental in summarizing world regulatory systems, developing policy on herbal products (WHO, 2005) and developing regulatory guidelines for vitamins regulated as foods. The WHO Traditional Medicine Strategy was adopted in 2003 with four primary objectives: framing policy; enhancing safety, efficacy and quality; ensuring access; and, promoting rational use. The WHO has developed monographs and sponsored collaborating research centres on traditional medicine worldwide. In the area of vitamins, WHO has sponsored Codex Alimentarius, which provides a world standard for vitamins (WHO, 2005). Canada, Australia and the US have maintained their own national standards and guidelines.

Table 4 provides a summary of the regulatory elements described above.

Table 4 - Summary of NHP Regulatory Characteristics for Selected Countries

Regulation Characteristics	Canada	US	Australia	EU	Singapore	WHO
Comprehensive pre-market assessment	Yes	No	No	Yes	No	N/A
Regulatory monograph system	Yes	No	Adopting aspects of Canadian	Yes, 30	No	Yes
GMP guidelines specific to NHPs	Yes	Yes	No	No	Yes	N/A
Post-market surveillance	Reactive	Reactive	Proactive targeted and random	Reactive	Reactive	N/A
Treatment claims allowed	Yes	No	Yes	Yes	No	N/A
Use of Codex Alimentarius for vitamins and minerals	No	No	No	Yes	Information not available	Yes

Comparative Elements between Canada and Australia

Canada and Australia are unique in the developed world in having the vision to create a new regulatory stream separate from food and drug regulation for all types of culturally- based medicines and related products (NHPs in Canada, CAMs in Australia). This vision recognizes that these products are important and require different regulatory treatment. Furthermore, validated treatment, prevention and health maintenance claims ensure efficacy of products. While Australia was the first to develop the legislation in 1989, Canada has developed a more advanced regulatory regime starting with the creation of the Office of Natural Health Products in 2000 and legislation implemented in 2004. In particular, Canada regulates not only safety and quality, but has put more effort into efficacy evaluation. This has been achieved in part through development of the largest regulatory monograph system in the world, which is a substantial institutional investment in completing the risk-based analysis of individual products. This compendial route for low risk products provides guidance for both dose and indications. Also, a risk- based sliding scale of SOE is used for evaluation of non-compendial stream. All products are approved through a pre-market application process that ensures closer oversight than the electronic listing system in Australia. The value of the Australian system is seen in its reactive and pro-active post-market inspection. Up to 20% of marketed products are selected for administrative and laboratory examination, ensuring effective policing of materials on the market. Clearly a combination of the best elements from different systems would be an ideal approach.

Finally, world leadership in the development of a well-managed NHP regulatory system has obvious advantages for Canadian industry, which allows it to take the lead in providing international markets with NHPs deemed truly effective, safe and of high quality.

4 FINDINGS, CONCLUSIONS AND RECOMMENDATIONS BY KEY EVALUATION QUESTION

Below are the findings and conclusions for each evaluation question based on the evidence collected from completing each line of inquiry. Recommendations have been developed for select question areas to address identified issues and challenges.

4.1 Relevance

A1. IS THERE A CONTINUED NEED FOR THE NHPP AS IT IS DEFINED?

FINDINGS

Alignment with government priorities – Assessment of the linkages between program objectives and (i) federal government priorities and (ii) departmental strategic outcomes.

This Program responds directly to the Standing Committee on Health's recommendations to provide Canadian consumers with the assurance of safe products while continuing to ensure access to a range of health products; specifically, the recommendation to establish a new regulatory authority for NHPs.

The Government of Canada accepted all 53 recommendations of the Standing Committee on Health and the NHPP in HC is a direct outcome from implementing those recommendations. Two key recommendations were that NHPs should be regulated in a distinct regulatory framework for safety and efficacy while access should be granted to traditionally-used materials to recognize the ethnic diversity of the Canadian population. Flowing from this acceptance of recommendations was the establishment of the ONHP - now the Natural Health Products Directorate - in 2000 and an agreement to introduce the *Natural Health Products Regulations* in January 2004.

In 2000, the Director of the Office of Natural Health Products oversaw an EAG and a transition team which developed an approach to implement the 53 recommendations, published in 2000 as "Final report, a fresh start". A broad period of public consultation across Canada took place with meetings in major cities, and the proposed regulations were revised and published in the Canada Gazette in 2001. The NHPR became law in 2004 with a transition period of 2-6 years for full enforcement.

Consistency with federal roles and responsibilities- Assessment of the role and responsibilities for the federal government in delivering the program.

HC is the most appropriate government department to implement the NHPR as it is the federal department responsible for helping Canadians maintain and improve their health, while respecting individual choices and circumstances. The NHPP's ultimate outcome is directly aligned with the Department's second strategic objective: "Access to safe and effective health

products and food information for healthy choices". While an explicit linkage to the Government of Canada's overall priorities was not found, the NHPP is informally aligned with the current government's objective of *Keeping Canadians Safe*[21]. The NHPP does not duplicate any other program in Canada.

Continued need for the program - Assessment of the extent to which the program continues to address a demonstrable need and is responsive to the needs of Canadians.

The continued need to assure the safety, efficacy and quality of NHPs in Canada is evident in the following:

- The use and availability of NHPs is significant in Canada, and growing:
  - Over 70% of Canadians have taken an NHP (*Ipsos-Reid, 2005) and the* number of NHP firms in Canada has grown 29% annually from 2002 to 2007 (*Agriculture & Agri-Food Canada/Statistics Canada, 2007*).
  - It is estimated that there are between 40,000 – 50,000 NHPs on the market with new products emerging all the time (*Regulatory Impact Analysis Statement for the Natural Health Products Regulation*)[22]. Also, the life cycle of NHPs is often shorter than pharmaceutical drugs, requiring a responsive regulatory system.
  - A 2007 Statistics Canada (StatCan) survey report profiling Functional Food and NHPs states that there were 290 firms active in the sector with a total revenue from all sources at $2.5 billion of which sales and services accounted for 68%. Canadian ownership in this industry is significantly higher than in other health industries such as pharmaceutical drugs, medical devices and biologics. It supports mid-income level employment and good working conditions in agriculture and manufacturing sectors.
  - The total value of the herbal market alone in North America was $4.8 billion in 2008 and grew at a steady pace of 2.8% per year between 2002 and 2008. Canada represents 10% of that market.
- There are domestic and international examples of species adulteration, substitution and the use of pharmaceutical products in NHPs[23] [e.g., cases of hepatoxicity associated with Kava consumption (Teschke, Gaus & Loew: 2003)].
  - There are ARs, documented deaths and serious illnesses associated with NHP use and consumption in Canada and abroad (e.g., Black Cohosh).
  - A majority (84%) of Canadians agree that the Government of Canada should regulate the claims made by manufacturers of NHPs (*Ipsos-Reid, 2005*).

[21] As per the Speech of Throne delivered November 19, 2008. http://www.sft-ddt.gc.ca/eng/media.asp?id=1380

[22] In terms of the scope of this industry, Canadian sales are estimated at about $4.3 billion and to number around 40,000 to 50,000 products. Vitamins represent over 50% of retail sales and involve over 18% of Canadian companies in the NHP industry. Herbs and botanicals represent another 30% of sales.

[23] For instance, the documented counterfeit (mislabelled) and substandard (poor quality) NHPs distributed from other countries (e.g., June 29, 2009 warning on herbal slimming products from China which contained pharmaceuticals and excessive levels of heavy metals). As well, there are a range of issues and concerns associated with NHP claims (e.g., fairy dusting, exaggerated health claims, treatment conditions for self medication).

- Large and small companies and their associations commented in interviews that the licensing of NHPs can give credibility to Canadian industry, enhancing the overall ability to market and sell NHP products nationally and internationally. Conversely, they commented that instances of unsafe products have a very negative effect on the industry as a whole and more effort to remove unsafe products is welcome and desirable.

While there is evidence to indicate that NHPs should be regulated, the approach taken should also reflect the lower risks associated with NHPs as compared to pharmaceutical drugs. As an example, in Hong Kong where TCM use is high, a hospital case study showed that 0.2% of adverse reactions were associated with TCMs and 4% were associated with pharmaceuticals[24] (similar studies from Canada are not yet available). While some intrinsic NHP risks (predictable toxicity, interactions, idiosyncratic toxicity) are similar to pharmaceuticals, NHP risks are often extrinsic and caused by a failure of good manufacturing processes, such as misidentification, substitution or adulteration, mislabelling, contamination, lack of standardization, etc. (Drew & Myers: 1997). In addition, currently less than 2% of all AR reported to Health Canada are associated with NHPs[25]. However, it is not clear if the low number of NHP-specific ARs relative to other product lines is reflective of a low incidence of NHP adverse reactions or if other factors contribute, such as: under-reporting due to the perception by many that NHPs are natural and therefore safe, failure to write up the cases, reluctance of patients to inform their physicians they take NHPs and lack of recognition by health care professionals and/or the public in associating an adverse reaction with an NHP.

Due to the distinct needs relative to NHPs, there have been a number of different approaches globally to managing NHPs, with an increasing trend towards developing regulations specific to NHPs. Canada has developed a regulatory based approach that includes both pre- and post-market elements to address the Program aim of ensuring 'NHPs that are safe, effective and of high quality, while respecting freedom of choice and philosophical and cultural diversity'.

However, there are dissenting voices and a range of views on how robust this Program should be relative to the risks posed by the use and consumption of NHPs (see some published comments in **Figure 8**). As reported in interviews, NHPP internal partners, particularly those responsible for enforcement and compliance, and some larger companies and their associations, prefer a more stringent approach as in the European Union where NHPs are treated as drugs (requiring higher SOE, cost recovery[26], and tighter quality compliance), while a segment of industry (particularly smaller businesses and their industry associations) prefers a more market-driven approach where NHPs are classified as dietary supplements, as in the US (requiring no pre-market review or proof of safety by the manufacturer before marketing).

---

[24] Chan TYK, Chan AYW, Critchley JAJH. Hospital admissions due to adverse reactions to Chinese herbal medicines. J Trop Med Hyg 1992; 95: 296-298.

[25] It is important to understand that ARs are only one indicator in determining whether NHPs are safe or not. Other forms of communication such as notices provided by domestic regulatory agencies and the WHO and scientific literature sources provide information for determining whether specific NHPs are safe or not.

[26] NHPP was part of the cost recovery review process and there is no certainty that program will implement a cost-recovery mechanism in the future.

Furthermore interviews with industry association representatives and companies indicated that the regulation of functional foods and cosmetics has been problematic, in their view, due to the creation of multiple registration streams with different requirements for similar products. This resulted in slower-than-expected processing times of PLAs and redundant costs to industry.

Figure 8 – Published Comments on Canada's Approach to Regulating NHPs

Below is a summary of selected published comments on the NHPR and the NHPP:

- ✓ In a review of the legislation by toxicologists (Nestmann et al., 2006), the authors concluded that the NHPR seeks to provide effective and safe products based on a sound scientific practice and principles and observation of regulatory systems in other countries. It was argued that the NHPR provides an even playing field for manufacturers and distributors however the overall impact experienced from implementing the regulations will not be known for several years.
- ✓ In an editorial at the announcement of the creation of the NHPP, the Canadian Medical Association Journal expressed some scepticism about "respecting freedom of choice and philosophical and cultural diversity" but applauded the emphasis on safety and efficacy.
- ✓ Walji and Boon (2008) found that small industry is less likely to be knowledgeable of the regulations and may find it more difficult to comply than large industry.
- ✓ Kwan et al., (2008) completed a focus group study of consumers and pharmacists which showed consensus that pharmacists should be knowledgeable about NHPs so that they can more effectively manage drug-NHP interactions and identify and evaluate NHP related information to help consumers make informed decisions.
- ✓ Interviews with TCM practitioners, homeopaths, and western herbalists showed all were concerned about how the new NHPR will affect access to the products they need to practice effectively (Moss et al., 2006).
- ✓ In an analysis of the perception of 38 consumers on new NHP product labels, Boon and Kachan (2007) found that NHP label requirements are viewed positively by consumers and that the additional risk information provided by labels may generate more NHP-specific questions for health care practitioners, especially with respect to possible interactions between NHPs and conventional medicines.
- ✓ In a study by H Laeeque et al. (2006) on the attitude of industry towards compliance of the NHPR, it was found that large firms are motivated to comply with the regulations for: reputation reasons (e.g., fear of negative media coverage); social motivations; and competitive reasons (i.e. a belief that complying with the NHPR can provided a potential competitive advantage for licensed NHPs). Motivations for small firms more likely stem from fears of legal prosecution if they are non-compliant and also a corporate duty to comply with the law.
- ✓ In a survey of Canadian western herbalists to the new regulations, Moss et al. (2007) found that herbalists are concerned that many small companies will find the regulations too costly to implement, causing them to reduce the number and diversity of products they manufacture, or go out of business all together. Similarly the lack of availability of whole plant products could severely restrict the practice of Canadian western herbalists.
- ✓ In an analysis of advertising claims, Brosens (2009) found that the US regulatory system allows for more types of NHP specific claims than the Canadian system. His findings suggest that Canada should reduce its restrictions on advertising of health claims associated with food products. This would benefit consumers by making important information about the potential health benefits associated with these products more readily available and positively impact public health.
- ✓ In a published study of post-market surveillance of NHPs in Canada, Murty 2007, found that the reporting of ADRs with NHPs is low (< 2% of all AR events) for 2004-06, but it is difficult to determine whether this is due to low incidence of problems or poor data due to voluntary reporting. Further research is needed to determine the safety with certainty.
- ✓ A key concern about the Canadian system is that an expedited system for regulating functional foods does not exist. Although there is agreement that functional foods should be regulated by the food approval system, the Food and Consumer Products Association (FCPA) has criticized the lengthy delays in approving new products due to a lack of regulatory guidelines (FCPA, 2009) for their products.

In interviews with the evaluation team, several internal partners and external stakeholders recognized that the early phase of implementation of the NHPR have been appropriately focussed on pre-market assessment, as the first step. Now that licensed products are reaching the market, there is a consensus among internal partners and external stakeholders (including academia, industry, and other regulatory agencies) that the NHPP needs to further strengthen its post-market activities. Post-market activities provide greater assurance that NHPs are in compliance with the FDA and NHPR; for example, that they are manufactured in accordance with GMPs and are not substituted, contaminated, adulterated or mislabelled. HPFBI labs have already been successful in detecting a number of these situations (the notable case of black cohosh substitution is described in Technical Report 2). However, industry and research stakeholders have indicated that these potentially very harmful problems are still widespread in the marketplace.

External stakeholders indicated that effective post-market evaluation of NHPs is best served not just by strengthening compliance promotion activities but also by ensuring the Program includes NHP specific expertise. Stakeholders indicated that NHPs are a unique and complex area and that Program staff need to ensure they have expertise in the complexities of phytochemistry and other natural products to support laboratory and related analytical functions.

CONCLUSIONS

1. There is a continued need to assure the safety, efficacy and quality of NHPs in Canada, and HC is the appropriate organization to regulate NHPs.

The evaluation confirms that there is a continued need to assure the safety, efficacy and quality of NHPs available to Canadians because:

- The number of NHPs available on the market is significant and increasing;
- Canadians are using NHPs on a regular and increasing basis;
- There are health risks and concerns with sub-standard NHPs, which include repeated cases of product contamination, adulteration and substitution, and contamination with pharmaceutical products, as well as other serious health and safety concerns;
- Internationally and within Canada, there are documented deaths and serious illnesses associated with NHPs; and,
- Licensing NHPs provides credibility, an even playing field and international marketing competitiveness to industry which favours economic development of this sector in Canada.

Health Canada is the appropriate organization to regulate NHPs as it is the *federal department responsible for helping Canadians maintain and improve their health, while respecting individual choices and circumstances* (*HC website*) and the NHPP's ultimate outcome is directly aligned with the Department's strategic objectives.

2. The NHPP takes a broad-based approach, which may be over-regulating products and under-emphasizing post-market verification.

Currently Canada maintains the broadest definition of NHPs in the world. As a result of this definition, the number and type of products that require approval from NHPD is higher than what is experienced by regulatory authorities in other countries (as presented in Section 3). For example, some products with multiple ingredients already referenced in the Compendium of Monographs are subject to the same application review and are required to meet the same SOE as non-traditional products composed of ingredients where little information is available and the level of risk is unknown. Furthermore, certain unforeseen products (e.g., cosmetics, functional foods) have entered the NHPP regulatory stream since the NHPR came into effect.

Many countries have developed regulations specific to NHPs; however, a range of implementation approaches exist, with Canada's system somewhat in the middle. Canada has initially focussed on the pre-market screening and assessment of NHP applications for safety, quality and efficacy, with the intention to increase post-market work after the regulations have come into full force (in 2010).

With the broad, inclusive definition of NHPs and the focus on pre-market approval of NHPs (with evidence required to prove safety, quality and efficacy of all products), large companies find it easier (and have the resources) to comply with the requirements, while small companies have reported that they find the regulations costly to implement, causing them to reduce the number and diversity of products they manufacture (see also B3).

RECOMMENDATION

R1. The NHPP should continue to be implemented in HC but detailed plans and timelines should be developed to evolve and improve the Program in line with the evaluation findings. Thus, in consultation with HPFB, the DGCC should determine whether:

- The NHPP pre-market evaluation process should be streamlined by considering whether regulatory borders are still appropriate, especially in the areas of functional foods with health claims and cosmetics, and should clarify the classification of which products should be regulated under the NHPR.
- NHP-specific monitoring and surveillance and compliance activities should be enhanced and change from responsive to proactive, without compromising MHPD and HPFBI's ability to complete these activities for other product lines. Proactive monitoring and surveillance and compliance activities could use a risk analysis to choose targeted products, such as weight loss products, products from countries that have had a history of adulteration, contamination and substitution, or products that have non-compliant labels. In addition, a certain percentage of sites could be randomly inspected (see also Recommendation B3 & B5) since findings show that smaller manufacturers comply mainly out of fear of penalties.
- Additional expertise specific to NHPs, as recommended in interviews by researchers, international partners and larger companies and their associations should be developed as a means to enhancing post-market evaluation (see also Recommendation B5).

4.2 Performance

Achievement of Immediate Outcomes

B1. To what extent has the NHPP contributed to the development of national and international standards and regulatory approaches for NHPs?

FINDINGS

Prior to developing the NHPR, NHPD developed a framework that led to the draft legislation. Evidence shows that NHPD undertook extensive consultation on the regulatory framework throughout development, implementation and review. Early stakeholder meetings regarding this framework engaged the provinces and territories, industry, and the public to solicit opinions and share information and awareness about approaches for NHPs as they pertain to practitioners, manufacturers of NHPs and Canadians.

The EAC has provided feedback to NHPD for assisting with the development of national standards and approaches for regulating NHPs. Interviewees commented that this collaboration has provided NHPD with relevant information to develop national standards for manufacturing (e.g., products manufactured under the compendial application stream, vitamin and mineral products) and marketing (e.g., labelling) of health claims of NHPs sold in Canada. Also, the NHPP has worked with the Canadian Homeopathic Pharmaceutical Association to create labelling standards as sources of pre-cleared information.

MHPD in collaboration with ASC published Consumer Advertising Guidelines for Marketed Health Products in 2006 (for non-prescription drugs including NHPs). The Guidelines form the basis upon which Advertising Preclearance Agencies review and approve advertising for non-prescription drugs, including NHPs, and help ensure consistency in advertising review[27].

However, there is no standard to manage the sale of NHPs at the provincial and territorial levels. Thus NHPs are sold in a variety of places (e.g., grocery stores, pharmacies, health food stores, etc.) without the supervision of a health care provider (e.g., Doctor of Naturopathic Medicine or Pharmacist). However, NHPD has had discussions with the National Association of Pharmacy Regulatory Authorities (NAPRA) to discuss NHP-scheduling issues after the Program has addressed the PLA backlog (i.e., after March 31st, 2010) (**See Figure 9**). These discussions may provide a more proactive approach to managing where and how NHPs are sold throughout Canada.

Similarly, interviews with provincially-licensed practitioner groups highlight that there are gaps in the regulation of TCM. In particular, while all over-the-counter NHPs for self medication are captured under the NHPR, some "prescription-like" TCMs, which are designated formally as "TCMs for professional use", remain unregulated by the NHPR or other legislation. These products are not sold over the counter but are given to patients directly by their TCM practitioners. For example, some practitioners use the herb *Aconitum*, a useful therapeutic agent

[27] Guidelines available at: http://www.hc-sc.gc.ca/dhp-mps/advert-publicit/pol/guide-ldir_consom_consum-eng.php

in small doses, but potentially very toxic in larger doses, which suggests that its use needs to be allowed but strictly regulated.

NHPP staff stated that the Program has not made sufficient use of establishing partnerships with the health departments in the provinces and territories due to limited resources. For example, HC has not made an effort to establish formal working relationships (by means of a working group, liaison committee, etc.) with the provinces and territories to promote the NHPP or address issues and challenges associated with implementation at the provincial and territorial levels (e.g., point of sale requirements).

There is some published evidence that the NHPP has contributed to developing international standards[28] and approaches for application in other countries. However, evidence from interviews indicates that Canada's approach to implementing the NHPR has generated interest from other countries, such as Australia, Thailand, Oman and Saudi Arabia. In these cases, countries have approached the NHPD for advice and guidance on how to implement pre-market systems to support their mandate to regulate NHPs. The NHPD is also recognized as a leader (as noted in interviews with international partners) in terms of developing a comprehensive Compendium of Monographs for NHP ingredients and products. Currently, Australia's Therapeutic Goods Administration is collaborating with the NHPD to learn more about the information contained in monographs, particularly the information associated with risk and efficacy. Furthermore, domestic and international NHP experts emphasize that by creating the NHPR and NHPP, Canada has developed a comprehensive approach that incorporates both pre- and post-market elements when compared to approaches practiced in other countries.

Several international standards were used to support the implementation of the NHPR, including adoption of: the Chinese Pharmacopeia (Canada is the first country outside of Asia to do so); approved terminology for naming medicinal ingredients as per TGA's Electronic Listing Facility system; the M5 Controlled Vocabulary for Dosage forms from the International Conference on Harmonization (ICH); the Medical Dictionary for Regulatory Activities (MedDRA) (i.e., medical terminologies for indications and warnings); accepting GMP certificates through international MRAs and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) partner countries; and, WHO Monographs.

Memoranda of Understanding (MoUs) for cooperation on the regulation of health products exist with: Australia (TGA); Switzerland (Federal Department of Home Affairs), China (Ministry of Health), US (USFDA); and Singapore (Health Science Authority). None of these MOUs are specific to NHPs, however some existing MRAs include NHPs.

[28] For instance, in 2004, HC hosted the WHO Consultation on Safety Monitoring of Herbal Medicines in Vancouver, Canada which led to the development of the "WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems."

Figure 9 – The NHP Regulations and the National Association of Pharmacy Regulatory Authorities

- ✓ The NAPRA was founded in 1995 by Canada's pharmacy regulatory bodies to enable its members (e.g., provincial pharmacy boards, pharmacy schools, etc.) to take a national approach in addressing common issues. At the time of its inception, NAPRA endorsed a proposal for a national drug scheduling model, to align provincial drug schedules so that the conditions for sale of drugs would be consistent across Canada. Currently there are four schedules that dictate the condition of sale for drugs sold in Canada. Drugs are placed in the respective schedules based on the need for a pharmacist's involvement.
- ✓ Since the NHPR took effect in January 2004, the applicability of NAPRA National Drug Schedules (NDS) to NHPs has been a point of concern for NAPRA's Board of Directors (and its partner organizations) and HC. The major issue is that products have been approved for sale as NHPs while concurrently appearing in the NDS. This situation creates confusion for pharmacists and other stakeholders over the condition of sale for NHP products that may also be listed in the NDSs. NAPRA interviewees assume that this confusion will worsen as of January 1, 2010 when all DIN-labelled products that qualify as NHPs fall under the NHPR.
- ✓ In August 2006, NAPRA, with collaboration from NHPD staff, identified 95 medicinal ingredients included in 116 NDS items that were expected to be identified as NHPs by HC. Of this total, 55 NHP items (11 under Schedule I and 44 under Schedule II) were identified to have a high potential for negatively impacting patient safety if their availability becomes unrestricted after January 1, 2010. Currently, patients can only purchase these medications through a direct interaction with a pharmacist and require a prescription in the case of drugs in Schedule I, as the items are deemed inappropriate for self selection.
- ✓ In October 2006, a joint meeting was held between NAPRA, NHPD and Therapeutic Products Directorate. It was agreed that further collaborative work would take place to ensure the full scope of the implications are understood. Health Canada officials recognized and acknowledged the Department's role in ensuring the safe use of these NHPs, cognizant that they would be removed from the NDS. In November 2006, NAPRA's Board of Directors released the Policy for NHPs. This policy clarifies NAPRA's position on the status of NHPs with regard to NAPRA's NDS. As a result of new information provided by HC's NHPD, the Board of Directors decided at its April 2009 meeting to re-examine this policy to confirm the status of the NHP items that were identified in the NDSs. This review should be completed by spring 2010.

CONCLUSIONS

3. The NHPP has developed national standards for NHPs, however some gaps exist within the current regulatory framework.

The evidence confirms that the NHPP has developed new and NHP-specific national standards (e.g., novel standards for products manufactured under the compendial application stream, comprehensive new standards for vitamin and mineral products, and new labelling and marketing standards regarding allowed health claims for NHPs sold in Canada) to improve Program delivery from both efficiency and effectiveness perspectives**.**

However, in discussion with provincially-licensed practitioner groups, it appears that there are some gaps in regulatory coverage. In particular, while all over-the-counter NHPs for self medication are captured in the regulations, some "prescription" TCMs used by practitioners remain unregulated.

4. There is international interest in Canada's regulatory approach

Some domestic and international experts noted in interviews that the creation of the NHPR (and the NHPP) in Canada represents a comprehensive world system for regulating NHPs from a pre- and post-market perspective. Evidence from interviews indicates that Canada's approach to implementing the NHPR has generated interest from other countries that have approached the NHPD for advice and guidance on how to implement pre-market systems.

Although the NHPP has been recognized by several experts as a model world system, which provides a regulatory paradigm for the broadest range of cultural medicines and natural products, the beneficial aspects of this approach have not been broadly disseminated domestically or internationally.

RECOMMENDATION

R2. NHPD should work with relevant Provincial/Territorial bodies (governmental and non-governmental) to ensure coordinated and comprehensive application of NHPR across Canada. This would involve:

- Developing an agreement and/or process designed to allow NHP/TCM or other practitioners to have access to regulated 'professional use only products';
- Leveraging information from the practitioner communities; and,
- Developing an integrated action plan for the sale of safe, effective and quality NHPs (with an emphasis on TCMs) in Canada.

B2. To what extent has the NHPP increased awareness and knowledge of risks and benefits of NHPs?

FINDINGS

The evaluation was unable to determine if Canadians are learning more about NHPs as a result of NHPP activities.

In 2003, Canadian consumers viewed NHPs as less safe than prescription drugs, which are more closely regulated with access controlled by health care professionals; and, Canadians rarely or never seek out new information on NHPs (Public Opinion Survey on Post-Market Surveillance, 2003). Similarly the results of the Baseline Natural Health Products Survey (completed by Ipsos-Reid in 2005[29]) highlighted that the majority of Canadians are uncertain about NHP safety and regulation and that additional information about NHPs in Canada is required. Follow up survey work has yet to be repeated to assess trends in the public's understanding of NHPs or to determine if NHPP activities are increasing the level of understanding of NHP risks and benefits.

[29] The survey can be viewed at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/pubs/engconssurvey-eng.pdf

The Program has made an effort to increase the awareness and knowledge of risk and benefits of NHPs through its communication, information dissemination, regulatory and scientific research activities. However, these activities have focused primarily on industry and the scientific community. For example, the Compendium of Monographs is a web-based source of information that provides access to knowledge about NHP composition, including its suspected risks and benefits. The tool is used primarily by industry in their efforts to complete PLAs. Over the last year, NHPD, for example, has developed and disseminated a series of information sheets and held several webinars with industry and NHP practitioners and other members of the medical community to provide additional information about the NHPP as well as highlight the risks and benefits associated with using NHPs. Additionally, MHPD conducted outreach and educational activities with the Canadian Association of Naturopathic Doctors related to AR reporting and increased the dissemination of the Canadian Adverse Reaction Newsletter (CARN) to over 1,000 Canadian naturopaths in 2006. In 2007, MHPD produced a Consumer Adverse Reaction Reporting Education Module presentation entitled "Reporting Side Effects From Your Medicine: What You Need To Know" in order to inform consumers about ARs and reporting ARs to HC.[30]

For specific cases, where there have been complaints or adverse reactions reported with using an NHP, there is a well-defined system for communicating risks (as evidenced in the black cohosh case study, which stakeholders claim is well known among NHP specialists in Canada and abroad). Health practitioners and consumers receive information about the ARs associated with NHPs through standard risk communication methods on an "as required" basis. A total of 241 NHP Risk Communications have been posted on the MedEffect™ Canada website from 2003 to 2010[31] (**See Table 5**). Public Warnings (63) constitute the highest risk communication category, followed by Public Advisories (53), Information Updates (15) and CARN Topics (18). Foreign Product Alerts (163) are public communications of products that are not in Canada but have been associated with a health risk by a foreign regulatory authority which consumers may have purchased abroad. All Program partners contribute to the development of these communication tools. HPFBI provides additional information to healthcare professionals and consumers by posting on HC's website the names of products that have been recalled from the market.

Table 5 - Natural Health Products (NHP) Risk Communications Posted on the MedEffect™ Canada Web site by MHPD

Type of Communication	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009	2009-2010
Public Warning	3	4	12	10	13	11	10
Public Advisory	7	3	5	17	9	4	8
Foreign Product Alert	0	0	0	16	48	55	44
Information Update	0	0	0	2	3	3	7
CARN Topics	2	4	4	2	1	3	2
Total	**12**	**11**	**21**	**47**	**74**	**76**	**72**

Source: MedEffect slide deck provided by Health Canada (July, 2009) and email correspondence (2010)

[30] The presentation can be viewed at: http://www.hc-sc.gc.ca/dhp-mps/medeff/centre-learn-appren/cons_ar-ei_module-eng.php

[31] As of January 2010, 23,612 Canadians have subscribed to receive MedEffect e-notices.

However, the Program has yet to formally assess the effectiveness of their risk communication mechanisms to generate awareness and knowledge of NHPs at the practitioner and consumer levels.

The Program does provide some general public outreach on NHPs (information sheets at pharmacies, news releases); however, most external communications have focussed on technical workshops, consultations and training sessions with industry (which were generally viewed positively by stakeholders interviewed for this evaluation). There is evidence that NHPD is increasing its efforts to provide more consumer and practitioner information on risks/benefits in the future. In November 2009, representatives from NHPD, MHPD and HPFBI designed and delivered a series of workshops throughout Canada to promote the NHPP and its key pre-market and post-market activities to industry and consumers. Additionally these workshops provided an opportunity to consult on a new compliance and enforcement approach for the NHPP. Similarly in March 2009, MHPD contributed to implementation of a Department-wide Social Media Campaign that focused on providing information to Canadians on what services HC provides in the area of health products. Although not specific to NHPs, this campaign addressed all product lines and highlighted the value of the MedEffect Canada website. Advertisements were also presented in Wellness Options, a journal dedicated to the naturopath community and other NHP practitioners.

CONCLUSION

5. There is insufficient evidence to assess if the NHPP has increased awareness and knowledge of the risks and benefits of NHPs.

The evaluation was unable to determine if Canadians are learning more about NHPs due to the Program. The baseline survey conducted (Ipsos-Reid, 2005) has yet to be repeated to assess trends in the public's understanding of NHPs or to confirm if NHPP activities are increasing the level of understanding associated with NHP risks and benefits. In interviews with consumer groups and researchers, most commented that more education is required in this area. The Program has made efforts to increase the awareness and knowledge of NHPs through its outreach and research activities, however until recently, these activities have primarily focussed on industry and scientific communities.

As part of post-market surveillance, there is a well defined system for communicating NHP-specific risks and issues to Canadians. However, the Program has yet to formally assess the ability of its risk communication mechanisms to generate awareness and knowledge of NHPs at the practitioner and consumer levels. Most consumer groups and the scientific community interviewed stressed the need for more communication and education in this area.

RECOMMENDATION

R3. NHPD, with support from MHPD and HPFBI, should develop a comprehensive education and outreach strategy to enhance and extend activities that target and provide information to consumers (i.e., regarding general awareness of the NHPP, and risks and benefits of using NHPs), manufacturers and the retail sector (i.e., regarding compliance promotion) - see also Recommendation B5.

This strategy should include the development of an online information sharing mechanism that clearly communicates the risks and benefits of certain NHPs to consumers and industry. This mechanism should also provide information on issues of non-compliance. To that effect, reports on compliance investigations and regulatory warning letters should be made available to the public to raise awareness of all the compliance activities of the Branch - for transparency and educational purpose as well as an incentive for industry to comply with regulations. In interviews, partners such as consumer organizations, professional associations and the scientific community have indicated their willingness to assist the NHPP in this process.

B3. To what extent has the assessment of applications for licensing/approval increased the availability of safe and effective NHPs for Canadians?

FINDINGS

The licensing of NHPs in Canada aims to assure that those NHPs available on the market (with NPN or DIN—HM) are safe, of high quality and effective, if taken as directed. As of January 29th, 2010 18,540 product licences (representing 23,891 products and 1,093 companies) had been issued since 2004 (NHPD Quick Facts, 29-Jan-10). However it should be noted that 3,443 licences (approximately 18.5% of all approved licences) are due to grandfathered products from the previous NHP regime managed by the TPD. An overview of all licences issued by application stream (as of January 29th, 2010) is presented below in **Table 6**.

Table 6 - Licences by Application Types (2004-10)

Application Type	Completed Licensed
Homeopathic	556
Labelling Standard	4,227
Non-Traditional	2,031
TPD Category IV Labelling Standard	375
Traditional	929
Transitional DIN	3,443
Compendial	6,979
Total	**18,540**

Before the NHPP, only those NHPs regulated as drugs under the *Food and Drugs Act* had safety, quality and effectiveness assurances. Interviewees indicated that more products are being assessed for approval because of the broad definition of NHPs included in the NHPR compared to the previous regulatory regime. Also, when compared to other countries, Canada has the most NHPs licensed in the world. For example, the United Kingdom has only licensed 45 NHPs.

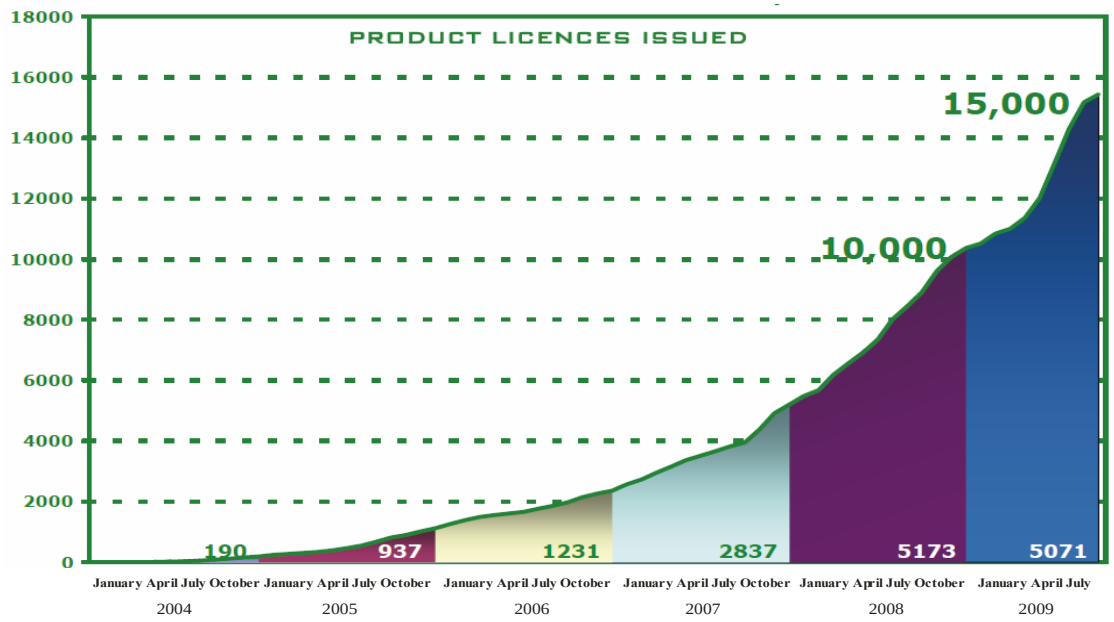
Since the NHPR came into effect in 2004, NHPD has steadily improved its ability to process product licence applications and provide Canadians with NHPs with a registered NPN or DIN-HM[32]. When the NHPR came into force, an industry-led survey estimated that there were approximately 40,000 - 50,000 NHPs already on the market, creating an immediate backlog of NHPs to be processed by NHPD (NHPR RIAS, 2003).

Figure 10 ─ Product Licence Application (PLA) Statistics

- ✓ Of the 45,596 PLAs received by January 29, 2010, 35,278 (77%) were complete (of which 52.5% received a licence, 36% were refused, and 11.4% were withdrawn).

Initially, NHPD had a relatively slow rate of processing applications, due to the need to develop new internal processes and procedures, work with a newly regulated industry, and work within a constrained resource level (e.g., capacity of skilled expertise). However, as of July 2009, NHPD has issued 26 times more licences in a given year than when the Program was first introduced in 2004 (i.e., in 2004, 190 NPNs were issued for that year; in 2009, 5,071 were issued for that year – **Figure 11**).

Figure 11 - Product Licences Issued between 2004-09



[32] As of January 2004, the NHPR allow NHPs that possessed DINs to maintain their DINs, if so desired, and to be sold for six years before obtaining an NHP product licence. Individuals who sell under this transition period must do so in accordance with the requirements of the *Food and Drugs Regulations*, including those relating to labelling and annual notification (Compliance Policy for Natural Health Products, September 2008).

This is due to both increased resources and implementation of S.T.E.P.S. (**S**tandardized **C**laims for NHPs and Pre-Cleared Information; **T**ransparency and **O**penness; **E**lectronic Solutions; **P**rocess Improvements; **S**ervice Delivery) - HC's multi-pronged plan for addressing the current natural health product licence application backlog. STEPS has a number of process improvements to allow quick and easy licensing of NHPs with a documented history of sale and effective use, and also includes an electronic online application process to enhance efficiency.

Similarly, NHPD has made numerous process improvements, including Abbreviated Labelling Standards, the introduction of initial assessment into the PLA review process for Traditional and Non-Traditional applications, a new electronic PLA form for homeopathics, and a Process Improvement Project for quality review. This has reduced processing application times.

In addition to process improvements, there has also been targeted training for assessment officers, additional monographs to facilitate applications under the Compendial Application Stream, additional online/web-based information (e.g., Guidance materials, NHP ingredients database, etc.), and new internal databases to facilitate licence reviews by NHPD staff (e.g., Decision Records database for recording and sharing information on why a particular application was rejected so that future applications on similar products, or from similar companies, can benefit from previous learning).

Yet, despite these achievements, there are notable concerns within HC and among the stakeholder community concerning the Program's ability to provide assurance that NHPs are manufactured safely. For example, the current approach to issuing a site licence is paper based and does not include a physical site inspection. Similarly, since a formal, proactive and continuous onsite compliance program (or inspection of products) is not in place, the NHPP is not well placed to assure that NHPs are manufactured in accordance with the terms and conditions of their respective licences. In comparison, under the current system administered by the TGA in Australia, site licence applicants must have a facility level audit completed before they are granted their site licence. The international benchmarking exercise found that other countries had a more proactive post-market system in place for assuring the safety and quality of NHPs. For example, Australia's post-market system includes a targeted compliance and enforcement system designed to address complaints and/or ARs associated with a particular product type (e.g., NHP weight loss products).

In light of the interim measures (see Section 2.3.1) to meet the terms and conditions of MRAs with other countries, interviewees commented that NHPD needs to find a long term solution to assure that terms and conditions set out in existing Mutual Recognition Agreements are respected.

Although there have been notable improvements to the PLA process, small- to medium-sized industry stakeholders (companies and industry association representatives) have highlighted in interviews that many applications have been refused (10,011 – as of August, 2009) and many more were never submitted for application because it is felt they would not be able to meet NHP regulation requirements for products reviewed outside of the Compendial application stream; thus, these stakeholders believe that the overall number of NHPs available to Canadians has been reduced. These interviewees commented that those applications processed quickly are the

'simple' NHPs that are submitted through the Compendial application stream. Thus, these stakeholders argue that the product licensing process is biased towards approving applications from the Compendial stream as opposed to other application streams (e.g., non-traditional) and that the current system hinders the ability of complex (i.e., multi-ingredient NHPs) and innovative products from obtaining an NPN and going to market.

Products are refused for a number of reasons, ranging from inability to meet basic application requirements (38%), not responding to requests for further information (39%), or insufficient information provided (18%) i.e., not being able to meet SOE[33]. For example, NHPD staff have noted that many of the multi-ingredient products mentioned in interviews do not have enough of any single ingredient to meet efficacy requirements. Many of these products have not been reformulated for the new Canadian regulations and many are imports or older products that were not originally formulated with Canadian regulations in mind.

As of January 29th, 2010, over 35% of product licences have been awarded to applications under the compendial application stream, whereas approximately 11% have been awarded to the non-traditional application stream. Currently, only 40% of all applications have received a NPN (NHPD Quick Facts, 29-Jan-10).

The majority of external stakeholders interviewed (e.g., large industry, academics, industry associations, health practitioners, international agencies) believe that the NHPP has provided access to safe and quality NHPs, but efficacy remains an outstanding issue and that it is difficult for NHP applicants to provide evidence of effectiveness. In interviews, some Program partners, consumer groups and industry representatives believe the interpretation of the existing SOE is too high for low risk products, though it was noted that SOEs do provide a more level playing field in the marketplace. Interviews with the scientific community showed a unanimous view that some level of efficacy is required for NHPs, although flexibility in this regard is warranted. Some small to medium sized industry stakeholders, however, are much harsher in their assessment of the Program and believe that the implementation of the NHPR is impeding access to the marketplace without increasing the safety, efficacy or quality of products (*Ramsay, Sept 2009*). Documentary evidence provides a conflicting picture with some sources showing the number of firms and revenues are increasing post-regulation *(Agriculture & Agri-Food Canada/Statistics Canada, 2007*), while others estimate that 60-75% of all NHPs will disappear from the market and that the cost of licensing NHPs far outweighs the benefits (*Ramsay, Sept 2009*).

Stakeholder consultations on the 2007 NHP Regulatory Review indicated strong support for interpreting the NHPRs differently so that they are proportional to the level of risk. Industry stakeholders argue that there is a lack of evidence to demonstrate that NHPs are harmful to Canadians and that the requirements associated with demonstrating SOE are unreasonable for products that are seemingly low risk.

[33] Over the period 2007-2009 (Source: Internal NHPD database).

A definitive source of information that compares how many NHPs were on the market before the NHPR came into effect with how many NHPs are on the market today (either with a NPN or with an application to be reviewed by NHPD) does not exist. Prior to the NHPR coming into effect in 2004, it was believed that approximately 40,000-50,000 NHPs were available on the Canadian market (NHPR RIAS, 2003).

CONCLUSIONS

6. The licensing of NHPs in Canada assures that those NHPs available on the market (with NPN or DIN—HM) are safe, of high quality and effective, if taken as directed.

In terms of providing access to NHPs that are safe, effective and of good quality, the NHPP has brought stability to a sector that was previously unregulated by approving 18,540 product licences (including 3,443 products previously regulated as drugs) since 2004 (representing 23,891 products and 1,093 companies). Prior to the NHPP, the vast majority of NHPs available on the market did not receive any kind of pre-market assessment, whereas the current product licence application process demands that applicants meet a standard of evidence to demonstrate the safety, quality and efficacy of their product.

However, the evaluation was not able to determine if the total number of NHPs available on the market (whether safe and effective or not) is increasing or decreasing because of the NHP PLA process. In interviews, members from mid and small size industries expressed the view that not being able to meet standards of evidence for efficacy remains the key issue impeding access to the marketplace (particularly for novel/innovative/combination NHPs), as it is difficult for NHP applicants to provide sufficient evidence of NHP effectiveness (the base of scientific evidence and funds available to conduct clinical trials is limited). Consumer groups were equally divided on this issue with half of the interviewees suggesting that consumers could decide for themselves on efficacy and the other half suggesting the consumers should be protected from ineffective products.

7. NHPD efforts have focused on developing process improvements to address the NHP backlog. Greater attention to the existing SOE for efficacy and Program's approach to issuing site licences is required.

NHPD is perceived as a highly knowledgeable and credible organization and is recognized for its innovation in managing NHPs by members of the scientific community. Its efforts to date have focussed on reducing the product licence backlog and the PLA process. NHPD has provided guidance and outreach activities but these have focussed on assisting industry in submitting applications and have not, until very recently, begun to adequately address consumer needs.

Although NHPD has hosted a number of recent workshops on licensing including one in the U.S., NHPD has yet to develop guidance material or resources to assist industry with preparing applications for non-traditional products, especially the consideration of appropriate SOE requirements for the efficacy of combination products (i.e. products containing more than one ingredient that may or may not be referenced in the Compendium).

Furthermore, the Program has yet to modify its approach to issuing site licences to reflect best practices identified in the international community.

RECOMMENDATIONS

R4. NHPD, in consultation with MHPD and HPFBI, should task the PAC to:

- analyze the existing SOE requirements for all product application streams and propose solutions for low-risk and novel products without abandoning the efficacy principle; and
- develop guidance materials and tools that can assist industry (particularly small to medium sized companies) in meeting SOE requirements for non-traditional products (with assistance from the Clinical Trials Division and Monograph Group).

R5. NHPD, in consultation with HPFBI, should develop a strategy and approach for introducing a site inspection element to the NHPP site licensing process to verify that facilities are manufacturing NHPs in accordance with the GMPs referenced in their application packages (see also Recommendation A1 and B4). This exercise should also find a long term solution to addressing the terms and conditions of MRAs.

B4. To what extent have surveillance, assessment and monitoring activities enhanced the knowledge of NHPs' risks and benefits to inform regulatory decisions?

FINDINGS

The evaluation found that the Program has challenges with respect to its ability to obtain accurate and reliable information associated with NHP risks. From 2004 – 2008, approximately 1.5-2% of all adverse reaction reports submitted to HC through the Canada Vigilance System (CVS) were associated with NHPs (**See Table 7**).[34] However, AR reporting is only one source of information that MHPD draws on to identify, prioritize and assess a potential NHP related risk or signal (a 'signal' is considered to be the preliminary indication of a product-related issue). In addition to AR reporting flowing from the Canada Vigilance Program, MHPD reviews multiple sources of information such as:

- Media and medical literature sources;
- International reporting databases (country level and WHO), advisories and risk communications from other jurisdictions (e.g., foreign regulatory agencies); and
- Company information (Phase IV studies, Period Safety Update Reports, Pharmacovigilane Plans (PvPs), registries).

[34] 2009-2010 CVS performance data indicates that ARs for NHPs have doubled in the last year and that the total percentage of ARs attributed to NHPs is now 4%.

Table 7 – NHP AR Reports submitted to Health Canada through the CVS (2004 – 2008)

Product Type	2004	2005	2006	2007	2008	Total
Submissions associated with Natural Health Products	144	181	208	259	310	1102

Despite the seemingly low percentage of NHP specific AR, Program staff and published literature (i.e., Murty, 2007) believe that AR reporting for NHPs is a problem because of the assumption by consumers that NHPs are made from natural ingredients therefore they must be safe for consumption and general use. Thus consumers are less likely to report their symptoms to their health practitioner[35]. Some information as to why NHPs are underreported is found in published literature (Barnes, 2003)). Despite this disadvantage, MHPD has detected and addressed a number of signals. Specific examples include:

- Hydroxycut (liver, cardiac toxicity) - regulatory action in progress;
- Black cohosh and risk of liver toxicity (suspected to relate to non-authentic products) - regulatory action in progress;
- Energy drinks and cardiovascular risk especially in adolescents, labelling revision is in progress;
- Camphor/Eucalyptus oil and neurotoxicity in paediatric population associated with accidental ingestion - regulatory action in progress;
- Caesium chloride and cardiotoxicity in patients using such product for the management of cancer;
- Weight loss products containing ingredients of concern e.g., synephrine (cardiotoxicity) or undeclared pharmaceutical products;
- Oral sodium phosphate for purgative purposes and risk of cardiotoxicity and electrolyte disturbance; and
- Kava-Kava and Comfrey/echimidine-containing products liver toxicity.

To date, MHPD's AR activities have been largely reactive, with only a few recent examples of pilot projects for proactive surveillance with the goal of stimulating reporting of ARs associated with NHPs. For example, an active surveillance program with the University of Alberta is in progress. This program focuses on investigating the feasibility of developing an active surveillance program for collecting NHP adverse event information in community pharmacies.

The evaluation also found evidence to demonstrate that MHPD addresses advertising complaints specific to NHPs. Over the period 2003 – 2010, 88 (30%) of 295 advertising complaints have been associated with NHPs. Advertising complaints have been found to contravene sections of the FDA and have included: unauthorized products/indications; therapeutic claims exceeding the

[35] Barnes, Joanne. Drug Safety 2003 - Volume 26 - Issue 12 - pp 829-851.

Terms of Market Authorization (TMA)[36]; and lack of safety/risk information on the advertisement. Identifying advertising complaints has led to a series of follow up activities including:

- Referring the complaint to the HPFBI for compliance verification.
- Directly contacting the MAH to request immediate corrective actions.
- Contacting Advertising Preclearance Agencies to provide them with guidance.
- Contacting advertising broadcasters to make them aware of HC position on NHP advertising.

HPFBI may also receive complaints related to the advertising of NHPs for which a compliance verification is conducted. They may be independent of those received by MHPD, if they relate to unlicensed products.

Despite these shortfalls, the evaluation did find evidence to confirm that the Program's surveillance, assessment and monitoring activities can and have informed regulatory decision making. For example, the black cohosh case study reviewed in Technical Report #2 highlights how surveillance, assessment and monitoring activities can provide Program staff with the information to determine whether there is a need to exercise a regulatory authority (e.g., Section 16 or 17) or modify the Program's approach to conducting pre- and post-market activities (e.g., revision of the black cohosh monograph's risk statement).

When required, MHPD will complete a risk assessment activity to confirm the potential risk associated with an identified signal (see signal identification, prioritization, and assessment process presented in section 2.3.2). Risk assessment activities include: Information Summary Reports (ISRs), Signal Assessments (SAs), Issue Analysis Summaries (IASs) or Causality Assessments (CAs). The outcomes of these assessments can inform regulatory action and or decisions. Over the period 2004-05 to 2008-09, MHPD had completed 110 CAs, 71 SAs, and 13 IASs (**See Table 8**).

Table 8 - MHPD Risk Assessment Activities

Year	Risk Assessment Activity				
	ISR	SA	IAS	CA (# of files)	CA (# of cases)
2004-05	3	0	4	10	65
2005-06	4	0	3	20	92
2006-07	10	0	3	19	149
2007-08	3	53	0	27	95
2008-09	0	18	3	34	214
TOTAL	**20**	**71**	**13**	**110**	**615**

[36] TMA refers to all labelling information that accompanies a Notice of Compliance (NOC) and/or the document that assigns a Drug Identification Number (DIN), Natural Health Product Number (NPN), or Drug Identification Number for Homeopathic Medicines (DIN-HM) and any related labelling material for health products.

Although the evaluation found that MHPD has continued to improve its processes and procedures for identifying, prioritizing and assessing NHP related signals (see response to question D2), MHPD staff noted that the existing resource levels do not allow them to address all red priority – or urgent - NHP signals sufficiently, thus MHPD staff are identifying red signals at a faster pace than they can assess them. Furthermore, MHPD interviewees commented that the unique lack of substantive information database for NHPs compared to other product lines is well known and is due to a lack of pre-market information on NHPs. Despite these shortcomings, the Directorate is still in a position to reach evidence-based decisions on risk mitigation.

CONCLUSIONS

8. Surveillance, assessment and monitoring activities have informed NHP regulatory decision making, but to a limited extent.

There is limited evidence to confirm that the Program's surveillance, assessment and monitoring activities inform regulatory decision making (i.e. provide the information to determine whether there is a need to exercise a regulatory authority or modify the Program's approach to conducting pre- and post-market activities).

9. MHPD, and more broadly the NHPP, is challenged in its ability to fully understand the risks associated with NHP use in Canada.

While MHPD has provided sophisticated risk assessment services with respect to identifying, prioritizing and assessing NHP specific signals, and reacted to them through risk communications, the organization is not well placed to understand the overall effectiveness of its risk communication activities and it is hard-pressed to address all of its identified red category signals due to its existing resource constraints. Without a substantive base of information to collect, analyze and verify the ill-effects and risks associated with NHP use, the NHPP is challenged in exercising its regulatory authority under the NHPR based on a thorough and comprehensive understanding of risks associated with NHP use.

RECOMMENDATION

R6. MHPD, with HPFBI and NHPD, should improve the Program's surveillance, assessment and monitoring activities by targeting resources to:

- facilitate an active AR reporting program; and
- assess the effectiveness of risk communications in terms of meeting their intended purpose.

B5. To what extent have compliance and enforcement activities increased adherence to Acts, regulations and guidelines?

FINDINGS

The Program is not well placed to provide an estimate of the NHP sector's compliance with the NHPR. The absence of a formal site inspection program, active compliance reporting, and a well developed marketing and oversight function jeopardizes the Program's ability to determine the

level of compliance among product and site licence holders. While survey results show that, overall, NHP companies are starting to comply with the regulations, large manufacturing companies have the view that there are incidents of non-compliance amongst small manufacturers (Laeeque et al, 2006). In interviews, large companies and their associations were concerned that incidents of harm or fraud caused by non-compliant companies will erode consumer confidence in the sector.

Currently, the majority of compliance and enforcement activities are reactive, with a small portion occurring as a result of information collected and analyzed by MHPD as per the signal identification and assessment process. Therefore, the current approach to completing compliance and enforcement activities typically begins with a concern or complaint being submitted to HPFBI. Over the period of 2002-03 to 2008-09, HBFBI opened 1,867 incidents and closed 1,706 of them. Over 400 non-compliant products have been removed from the market via a product recall over the past 7 years; approximately 200 of those posing a Type 1 risk to health, one that could result in death (**See Table 9**). NHPs represent about 40% of all compliance verifications within the Drug Compliance Verification and Investigations Unit within HPFBI.

Table 9 - Number of incidents and recalls actions taken on NHPs 2002-2009[37]

Category Type		FY 2002-03	FY 2003-04	FY 2004-05	FY 2005-06	FY 2006-07	FY 2007-08	FY 2008-09	TOTAL
Incidents	Opened	500	226	204	216	292	174	255	1,867
	Closed	399	131	231	283	238	169	255	1,706
	Administrative closures – low risk incidents - older than 3 years, no compliance action (implemented in FY2006-07)	N/A	N/A	N/A	11	43	32	49	135
Recalls	Class I/Type I	111	8	7	18	5	24	28	201
	Class II/Type II	5	5	3	13	54	13	4	97
	Class III/Type III	4	0	4	1	3	22	10	44
	Unacceptable Risk to Health as per Compliance Policy (new in FY 2005-06)				43	4	17	4	68
Recall Total		**120**	**13**	**14**	**75**	**66**	**76**	**46**	**410**

Source: Data provided from HPFBI databases on NHP's, as well as yearly Project Reports.

Overall, the Program has conducted compliance and enforcement activities primarily on a reactive basis (i.e., compliance verifications and investigations as a result of complaints or referrals) since the regulations came into effect in 2004. Documentary evidence confirming the ill effects associated with noncompliance (e.g., number of illnesses or deaths caused by NHPs) and the NHP sector level of compliance (e.g., with GMPs or advertising requirements) does not exist. As such, an analysis of whether the NHPP's approach to compliance and enforcement is appropriate for the assumed or known level of risk does not exist.

[37] According to HPFBI, enforcement action data are not reliably and accurately tracked.

HPFBI conducts annual compliance monitoring projects (CMP) which proactively focus on an area of concern in order to conduct surveillance and take appropriate risk management steps, if needed. This often involves going out to retailers to obtain products that fall within a certain category, conducting laboratory testing and taking risk management steps, as required. Although this program is not limited to NHPs, it often involves a significant NHP portion. For example, past projects have included erectile dysfunction products, sleep aid products, toothpaste products, as well as children's cough and cold products. Each of these projects has contributed to the knowledge of these groups of categories and also managed to identify products that pose a risk and triggered appropriate risk management actions. These initiatives are limited as they require significant amounts of time, resources and effort.

With respect to inspections associated with the site licence application process, the Regulatory Impact Analysis Statement for the NHPR indicates that NHPD is committed to revisiting the existing approach to issuing site licences and will determine whether it needs to increase its site licence application requirements to reflect the use of third party auditors or HC inspectors to conduct inspections.

Looking forward, NHPP staff and senior management from all three organizations indicated that the existing approach to compliance and enforcement will need to be revised. A firm commitment as to when this revision will occur was not identified. Furthermore, HPFBI program staff and managers argued strongly that HC has yet to provide adequate funding for the NHPP's compliance and enforcement activities.

CONCLUSIONS

10. Compliance and enforcement activities are largely complaint driven and the degree of NHP sector compliance with the NHPR is not known.

In the absence of a formal site or product inspection program or process to actively collect compliance information, the Program's compliance and enforcement activities are largely reactive and complaint driven. However, there are notable successes with this approach, such as the management of product substitution and prevention of further hepatotoxicity in the case of black cohosh and recalls associated with Type I complaints (as presented in **Table 9**). Nonetheless, the Inspectorate is not well placed to provide an analysis of whether the NHPP's approach to compliance and enforcement is appropriate for the assumed or known level of risk. While survey results show that, overall, NHP companies are starting to comply with the regulations; large manufacturing companies have the view that there are incidents of non-compliance amongst small manufacturers.

Overall, the Program has done little to advance its approach to conducting compliance and enforcement activities at the manufacturing and retail levels since the regulations came into power in 2004.

11. HPFBI successfully addresses NHP complaints but has not developed a regular and ongoing compliance promotion element to its NHP-related activities.

HPFBI has demonstrated success in addressing complaints associated with NHPs and has detected adulteration, substitution, and contamination in NHPs. However, HPFBI has yet to work with NHPD and MHPD to develop a proactive inspection program to ascertain the level of compliance of the NHP sector. Overall the Inspectorate is frustrated with its ability to complete compliance and enforcement activities within the NHP sector because of limited resources, conflicting mandate and lack of knowledge about the NHP sector.

RECOMMENDATION

R7. HPFBI, with input from MHPD and NHPD, should improve the Program's compliance and enforcement activities by:

- developing an ongoing monitoring program for sites (see also Recommendation A1 and B3); and
- implementing active compliance promotion (see also Recommendation B2).

Achievement of Intermediate Outcomes

C1. To what extent has the NHPP contributed to the development of an integrated approach (nationally and internationally) for implementation of its priorities and activities?

FINDINGS

Integration across the Program

Interviewees commented that communication and collaboration between the NHPP implementing organizations (i.e., NHPD, MHPD, and HPFBI) has improved since 2006. The Program now maintains several internal committees that include representation from all three organizations.

At a Program-wide senior level, the NHPP DGCC provides the focal point for cross-Directorate issues management. Established in 2007, this committee focuses on sharing information between the implementing organizations, but interviews with senior officials indicated that committee meetings are not providing a place for senior managers to discuss and develop strategic decisions (e.g., decisions about the Program's objectives and priorities, resource allocation, etc.). This affects the overall delivery of the Program and its ability to achieve the expected results articulated in the NHPP Results-based Management and Accountability Framework (RMAF). Instead, DGCC discussions are at the operational and output levels and focus on: revising outreach materials, such as quarterly reports, information sheets, and agendas for technical workshops; responding to stakeholder comments or concerns; and, the need to develop operational working committees (e.g., NHPP-CC).

The NHPPwg was developed in 2009 at an operational level with a mandate of coordinating Program initiatives that deal with internal communications and training. This group implemented two internal Program training sessions that brought together the Program partners to hear about Program initiatives, and express their thoughts on areas of improvement for working together. This NHPPwg reports to the DGCC and includes membership from all three Program partners. The Terms of Reference (ToR) is still being reviewed and it has been discussed that the scope of this group may expand to also include external outreach and education as well.

In addition, the NHPP-CC was developed in 2009 to aid in coordinating compliance and enforcement initiatives including the development of a new compliance and enforcement approach for NHPs, an awareness campaign for AR reporting and enhancing compliance promotions. The first NHPP "road show" in November of 2009 was a key deliverable related to many of these components.

However, there is still a need to strengthen Program coordination and provide an appropriate forum for directing and managing the Program. The absence of any such forum or equivalent mechanism highlights that the Program suffers from a lack of strategic direction and that there is a need to develop an integrated approach to decision-making, planning, and reporting NHPP activities so that Program activities work towards achieving a set of focussed outcomes that are jointly developed, implemented and tracked. The evaluation was unable to determine if HPFB has played an active role in proving guidance to or assisting the implementing organizations with developing program-level planning and reporting instruments.

At the operational risk management level, the Director of the Bureau of Policy and Risk Management (NHPD) chairs an NHPD RMC (previously referred to as the Issues Committee) comprised of representatives from all three organizations and a representative from the PACCB. Established in September 2009, this committee meets weekly and Program staff indicated that it provides a forum for developing a coordinated and integrated approach to prioritizing and mitigating risks associated with ARs or complaints submitted to HPFBI regional inspectors. Records of discussion indicate that this group provides an opportunity for the involved organizations to debate new and emerging issues related to high-risk NHPs, such as Kava and Ephedra, as well as compliance and enforcement, and research opportunities. Similarly, the black cohosh case study illustrated that NHPP organizations have the potential to coordinate their monitoring and surveillance efforts when there is a need to respond to an AR on a priority basis that is determined by risk or ill health effects.

While these internal, integrated committees exist, interviews with senior managers indicate that NHPD, MHPD, and HPFBI have different mandates and maintain different views as to how the NHPP should be implemented. As MHPD and HPFBI work across product lines, they are mandated to provide a generalist approach to completing a common set of activities across all product lines, whereas NHPD has the mandate and experience to design and execute Program activities that are specific to the demands, issues and challenges posed by the NHP sector.

For instance, the Inspectorate's activities are guided by the Compliance and Enforcement Policy. This policy lists several factors beyond health and safety including border security and manufacturing risks; compliance history of the regulated party; intention of the regulated party;

likelihood of reoccurrence; and HPFB and Inspectorate resources and priorities. Collectively these risks direct the Inspectorate's activities. In addition, the Inspectorate has more specific directives to dealing with product lines, e.g., the Compliance Policy for NHPs.

In contrast, NHPD has defined a risk-based approach in the document titled "Charting a Course: Refining Canada's Approach to Regulating Natural Health Products". This document outlines NHPD's process for conducting a risk-based approach by assessing evidence in PLAs. Essentially this process consists of a review of evidence and an interpretation of risk from a safety and efficacy perspective. The document concludes that the overall evidence base for a product must indicate that the overall benefits of allowing an NHP on the market outweigh the potential risks.

As a result of these differences in mandate, these organizations do not maintain a common understanding and approach of how to regulate the NHP sector with the existing Program framework and prescribed resources. Similarly the evaluation found that a comprehensive understanding of the Program's strategic and operational risks has not been developed. As a result, each of the implementing organizations has their own opinion of what the Program's key risks are, and roles and responsibilities among the implementing organizations are interpreted differently.

The evaluation was unable to determine that a corporate risk profile or plan to mitigate Program risks has been developed as per the direction provided in the Treasury Board Secretariat's Integrated Risk Management Framework.

Integration across the Federal Government

Within HC and across the federal government, the Program has established relationships with other federal authorities to implement the NHPR consistently:

- NHPD collaborates with the Department's TPD, not only to classify products at the NHP-drug interface but also to transition products previously regulated under the FDA regulations to the NHPR.
    - TPD interviewees emphasized that stronger collaboration and consultation between NHPD and TPD is needed since there are potentially overlapping regulatory frameworks (i.e., room for interpretation in what is a drug versus an NHP) and potentially the development of a joint classification policy for specific products. Furthermore, TPD believes that the existing ingredients and dosage (quantity) criteria for determining whether a product is an NHP or a drug is not appropriate in all cases - the same product can be categorized as a drug or an NHP depending on a product's ingredients and dosage requirements.

- NHPD has formal relationships (e.g., committees and guideline development) with other sections of HC and other federal departments, particularly around the classification of products at the NHP interface (e.g., food, drugs, cosmetics, etc.). These committees help NHPD and other government departments understand what regulations should be applied to which products.

- External stakeholders noted that immediately after the regulations were introduced, and periodically thereafter, there have been differing perspectives on which organization in HC should have the responsibility for classifying various products (particularly between NHPs and drugs, but also with functional foods and cosmetics). Industry representatives argued that they invest a substantial level of effort to determine what regulations apply to their products and that HC needs to provide additional guidance and support to categorizing products.

- In addition to classification committees, NHPD shares best practices with the Veterinary Drugs Directorate (VDD). This relationship was seen to be beneficial as the Veterinary Drugs Directorate works towards revising its pre-market assessment process for assuring the safety of veterinary drugs that contain NHPs.
- HPFBI also works with the CBSA with respect to border control for NHPs. The CBSA's role is to detain NHPs at the border and refer them to HPFBI for an admissibility determination. HPFBI may also request import alerts/targets with CBSA for products, importers and/or exporters that have been known or are suspected to have imported/exported non-compliant products (based on targets provided by HC). Once detained, CBSA contacts HPFBI regions to get admissibility determination guidance on how to proceed. CBSA has noted that health product targets have increased significantly recently [going from 25 to 250 in 2 years with a significant number (over 50%) of these targets being for NHPs]. CBSA interviewees noted that while there is regular interaction and cooperation with HC to deal with issues, there are no service standards in place for HPFBI to provide timely decisions on how CBSA should proceed with NHPs detained, and decision times can vary regionally. However, with the formation of the border integrity program in 2008, service standards are being established for various modes (e.g., commercial, postal). In addition, CBSA noted that they often are not made aware of what happens to a shipment after they turn it over to HC, and they would welcome greater feedback in this area to better understand how HC corrects non-compliant or illegal products that cross Canadian borders.

Representatives from the cosmetic industry were particularly frustrated about the creation of a third regulatory category, cosmetics registered as NHPs, in addition to cosmetics previously registered as pharmaceuticals or cosmetics. In some cases, products with the same composition can be sent to three different HC organizations depending on whether a health claim is made or not. Furthermore, these interviewees commented that packaging and labelling requirements for NHPs are much stricter compared to pharmaceuticals.

Collaboration with Partners and Stakeholders

Externally, the Program has made an effort to implement an integrated Program across Canada by consulting with partners and stakeholders to develop the NHPR and the necessary guidance materials to ensure that Program processes are streamlined across the country. Through

collaborative forums of experts, research partnerships, stakeholder engagement, and initiatives like the development of GMPs, the Program has worked with partners and stakeholders to develop tools and guidance materials to increase awareness and facilitate Program processes, such as licensing. For example, the vitamin dosing case study illustrated how the Program has drawn on the EAC and NHP experts from the U.S. to establish dosing standards for vitamins and minerals. Specific examples of evidence found during the evaluation are presented below:

- The development of the NHPR included the involvement of over 2,100 participants in 11 cities (Ottawa, Kingston, Halifax, Fredericton, Montreal, Quebec, Vancouver, Calgary, Regina, Winnipeg and Toronto). NHPD reviewed information from many sources to revise the regulatory framework including stakeholder and consumer consultations, consumer research, expert input, and consumer correspondence. There were also ongoing targeted consultations.
- Beginning in 2003, the EAC provided a forum for discussing HC's approach to identifying priorities and addressing issues related to the NHPP. The EAC worked with NHPD staff to review monographs, develop requirements and procedures and provide advice to Program managers and the NHPD Director General. In particular, NHPD staff presented detailed reviews of the peer reviewed scientific literature on such issues as phytoestrogen safety, and how to approach regulation of dietary enzymes, vitamins, etc.
- Beginning in 2004, the Management Advisory Committee provided the Director General and the leadership team of the NHPD with timely advice regarding the regulation of NHPs and the ongoing management of the regulatory framework.
- MHPD chairs an annual bilateral meeting with advertising preclearance agencies where issues pertaining to advertising of NHPs are discussed.
- There are a number of inter-departmental forums on which NHPP representatives participate [(e.g., classification committees with other government departments (e.g., Combination Products Working Group with CFIA), WHO committees, Mutual Recognition Agreements with other regulatory agencies, etc.)] to develop a more informed and consistent approach to managing NHPs in Canada. For example, in 2002, the Office of Regulatory and International Affairs and NHPD conducted the "for youth and by youth" workshop to determine youth priorities on health protection issues. The main objective was to get valuable knowledge on how to meaningfully involve youth in future HPFB public involvement activities while at the same time educating youth on a variety of health protection issues.
- Since 2003, NHPD has worked with the Natural Health Product Research Society of Canada to collect and disseminate information on NHP use and application. Similarly, the Canadian Interdisciplinary Network for Complementary and Alternative Medicine (CAM) is a collaborative research network created to foster excellence in CAM research in Canada. These organizations were partially funded by NHPD between 2002 and 2007.
- In 2004, NHPD provided funding ($390,000) to the Institute of Aboriginal Peoples' Health [through the Canadian Institute of Health Research (CIHR)] to advance research in the areas of traditional anti-diabetic medicines with the Cree in Northern Quebec.

- To better understand the implementation and effects of the NHPR, NHPD has engaged a number of stakeholders such as: the Homeopathic Medical Association of Canada, the Direct Sellers Association, the Western Canadian Functional Food NHP network, the Consumer Health Products Canada, the Canadian Cosmetic Toiletry and Fragrance Association, the Saskatchewan Herb and Spice Association and the NHP Research Society of Canada. Since 2007, MHPD has held 11 events as part of the NHP Seminar Series. Presentations provided by government and non-governmental experts have included various topics, such as homeopathy, soy isoflavones and cancer, in vitro toxicological modelling, NHPs and pregnancy/Motherisk, and drug-NHP interactions.
- The Good Manufacturing Guidance Document (V.I published in 2002, and V.II published in 2006) was developed with input from the NHP industry, academics, researchers, consumers, health practitioners and representatives from other government programs. The experts represented four areas of specialty: herbal medicines and botanicals, homeopathic medicines, traditional herbal medicines, and vitamins and minerals. Shortly afterwards, NHPD held workshops for the public and industry about the GMP requirements of the regulations. These helped provide additional information and guidance for preparing the final Good Manufacturing Practices Guidance Document.
- In November of 2009, the Program partners conducted a cross-country Program road show where over 340 stakeholders attended. The HPFBI led the second day of the two-day series with an intense consultation on the development of a new compliance and enforcement approach. Continued consultation includes the PAC and their formation of an external working group to provide recommendations to the NHPP.

In addition to these engagements, the NHPRP provided a means to conduct projects between scientists, product evaluators and policy makers. This NHPRP provided financial support to a total of 60 projects from 2003 to 2008. The majority (60%) of funding recipients were researchers, scholars, or health professionals affiliated with academic institutions, such as hospitals and research institutes. The NHPRP also supported smaller research projects conducted by not-for-profit educational, health or medical research organizations. The cumulative Program expenditures can be categorized as follows: building research capacity (43.4% of funding); supporting research (28.4%); developing partnerships and community infrastructure (11.5%); enhancing knowledge transfer (16.7%).

Despite notable collaboration with national-level partners and stakeholders, the Program has yet to capitalize on developing a functional working relationship with regulatory authorities in the provinces and territories (e.g., College of Pharmacists, Provincial Health Agencies, etc. as noted in B1) to address the sale and use of NHPs by practitioners at the provincial and territorial levels.

Internationally, Canada participates in the WHO's TM/CAM initiative to develop and adopt international standards for NHPs, and is the Secretary for the International Regulatory Cooperation on Herbal Products (network of national regulatory authorities) to assist in information sharing, regulatory cooperation and harmonization. The evaluation team also found evidence of HC representation at international meetings and conferences.

CONCLUSIONS

12. While there are extensive working relationships and collaborations across the Program, the NHPP has not developed a fully integrated internal approach to Program planning, delivery, and reporting.

Communication and collaboration between the NHPP implementing organizations (i.e., NHPD, MHPD, and HPFBI) has improved over the last few years, with several internal committees operating to better integrate Program activities and address high priority issues associated with risk and risk communications. However, the NHPP suffers from a lack of strategic (e.g., strategic objectives, annual plans, etc.) and operational instruments (e.g., performance indicator tracking, integrated cost and resource expenditure information, etc.) to allow for management as a formal program. Despite the introduction of the ONHP in 2000, the NHPP has yet to develop a strategic plan or comprehensive performance measurement framework that would allow it to make informed organizational and Program-wide decisions. Furthermore, the existing DGCC is operating more at the operational than strategic level to guide Program activities, thus Program managers are not well placed to understand the success of their efforts, relative to the resources allocated to the Program, nor are they in a position to report on Program-wide performance to the Department's senior executives.

13. NHPD has made good use of its resources to work with partners and stakeholders to improve the understanding of pre-market processes and activities.

The Program has made an effort to implement an integrated program across Canada by consulting with partners and stakeholders to develop guidance materials and ensure that the Program's pre-market assessment processes are implemented consistently across Canada. Despite notable collaboration with national-level partners and stakeholders, the Program has yet to capitalize on developing a functional working relationship with regulatory authorities in the provinces and territories.

RECOMMENDATIONS

R8. The NHPD, with the concentration of NHP experts in the Department, should be formally acknowledged as the Program lead (i.e. Champion) and be given the appropriate authority to execute Program leadership, on a consensus basis, with MHPD and HPFBI, through the DGCC (see also Recommendation C1). Specific responsibilities should include designing and developing a series of documents that can shape the Program's direction and guide its activities (see Recommendation 9). Consideration should be given to having ADM participation on the DGCC to build consensus (via active ADM engagement or a separate dispute resolution mechanism) among the implementing organizations and ensure that NHP-specific activities are targeted towards achieving an agreed set of objectives and desired outcomes that are cognizant of each organization's mandate, approaches and resource limitations.

R9. In consultation with HPFB, the DGCC should develop an integrated Program plan (medium- to long-term) and approach to planning activities, monitoring performance and reporting to Health Canada executives. This task should include the development of a set of strategic objectives and priorities to guide all Program activities funded under the latest funding approval.

The DGCC should develop a corporate risk profile that identifies and prioritizes the Program's existing risks and their accompanying risk drivers. Once completed, the corporate risk profile should serve as a starting point for identifying Program priorities, allocating Program resources, and developing mitigation measures to address risks that may impede the NHPP's ability to achieve its anticipated outcomes.

The DGCC should develop TOR to establish an Operational Committee that is responsible for: developing an annual operational plan aligned with an integrated Program plan (for approval by the DGCC); an approach and framework for Program-wide performance reporting; and, financial tracking of Program resources (planned and spent). The Operational Committee should also be responsible for leading initiatives to develop baseline and performance data in order to better understand NHP use and their effects on public health and sector compliance.

Finally, the DGCC should provide the direction to develop a formal plan for introducing an ongoing internal work exchange program (at the technical and management levels) designed to share information and experiences across the Program.

C2. To what extent do Canadians make informed decisions and choose and use NHPs with confidence as a result of Program activities?

FINDINGS

The evaluation was unable to confirm that Canadians are making informed decisions about the safety and efficacy of NHPs as a result of NHPP information or activities. Surveys completed in 2003 and 2005 indicate that the overall level of satisfaction with NHP risk and safety information is low. By 2007, perceptions appeared to have improved: consumers and practitioners reported that HC's risk communications were meeting their expectations.

Studies have shown that NHP use in Canada is high and growing (e.g., AAFC/STATCAN, 2007, HC International Symposium) and suggest that the majority of Canadians see growth in the use of NHPs in Canada and that the use of NHPs in Canada is high. However, while there are elements of the Program that provide communications to support informed decision-making [e.g., activities that support a reasonable NHP label claim; listing of all licensed products on the NHPD website; public AR reporting; mandatory disclosure of risk/safety information in NHP advertising as required by Section 2.21 of the Consumer Advertising Guidelines for Marketed Health Products (for non-prescription drugs including NHPs) etc.], there is little NHP-specific guidance for consumers and little trend evidence to indicate changes in consumer behaviour based on NHPP activities.

The NHPP's pre-market activities aim to ensure that industry is providing Canadians with the information to make informed decisions about whether an NHP is safe for consumption (by determining a dose that will not harm them) and effective (substantiates a health claim reflected in evidence and supported by Health Canada). Increased licensing should translate into increased consumer access to accurate labelling information and safe, effective products of high quality. The intent of these activities is to provide information for Canadians to make informed choices about NHPs they wish to consume/use. However, it is not known whether this is indeed the case because the Program has yet to collect data on consumer behaviour.

CONCLUSION

14. The degree to which Canadians make informed decisions on NHPs is not known, and the NHPP has yet to implement a broad outreach campaign to Canadians.

The evaluation was unable to determine if Canadians are making informed decisions about the safety and efficacy of NHPs as a result of HC information or its activities; and a comprehensive education and awareness campaign has not been implemented. In 2009, the NHPPwg was developed and mandated to develop a coordinated approach for internal Program communications and outreach across each of the implementing organizations. This group is reviewing its TOR for extending its scope to include external outreach to stakeholders.

RECOMMENDATIONS

See Recommendations in B2 and C1.

C3. To what extent has a reduced exposure of Canadians to health risks been achieved as a result of NHPP activities?

FINDINGS

While specific examples exist, and NHPP pre- and post-market processes are in place with the aim of reducing exposure to health risks, there is no tracking or reporting on the overall degree to which the NHPP has reduced the exposure of Canadians to the potential health risks posed by NHPs. There is also no assessment of the degree to which NHPP activities may be reducing or preventing access to NHPs that could be providing health benefits, as claimed by some industry representatives.

Case study evidence highlights that the NHPP has established a monitoring and surveillance system for detecting, assessing and mitigating ARs associated with licensed NHPs (see response to B4). The effectiveness of this surveillance system is difficult to assess because it depends on voluntary reporting of ARs and on MHPD's ability to collect and analyze AR information, conduct causality assessments to determine the severity and risk of an AR, and select and deliver an appropriate risk communication tool and/or risk management action. Depending on the results of MHPD's causality assessment, NHPD, HPFBI or both would be required to intervene, identify and address specific incidents.

The NHPR provides HC with the legislative authority to inquire about the safety of NHPs and their respective manufacturing processes. Section 16 of the NHPR is a mechanism that allows NHPD to ask NHP licensees to provide information and documentation (e.g., corporate standard operating procedures, additional information on GMPs, etc.) to demonstrate that the licensees' products are safe for consumption when administered in conformity with the recommended conditions of use. As illustrated in the black cohosh case study, the activities completed under the authority of Section 16 led to the removal of unauthentic black cohosh products from the Canadian market (as a result of species substitution). These activities minimized the potential risk to Canadians by removing potentially harmful products from the market and forcing manufacturers to improve their laboratory methods to prevent future cases of substitution or adulteration.

Also, the vitamin dosing case study highlighted that the NHPP's approach to establishing a maximum dosage level for vitamins and minerals provides greater assurance that Canadians are safeguarded against the potential negative health effects from consuming vitamins and minerals beyond a recommended daily allowable limit.

While the Program's compliance and enforcement approach is reactive (as previously described in the response to B5); on a case-by-case basis activities have led to the removal of 410 non-compliant products over the last several years. The HPFBI has also provided investigation and laboratory services to verify the health risks associated with NHPs by confirming cases of ingredient substitution or adulteration:

- Over the years, there have been a number of public warnings issued regarding NHPs contaminated with heavy metals. In each case, HPFBI took action to remove these products from the market and to prevent further importation into Canada, if applicable. When required, the Inspectorate has refined their internal methods for the detection and quantification of heavy metals in NHPs.
- The Inspectorate's laboratories have also developed liquid chromatography-phtodiode array (LC-PDA), gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry LC-MS methods to screen products for undeclared pharmaceutical ingredients. A wide variety of pharmaceutical active ingredients have been found in various approved and unapproved NHP. This has led to a number of public advisories or warnings, recalls and other compliance and enforcement activities.
- In 2006-07, the Longueuil laboratory developed a microbiological method especially adapted to sea water products. This method was innovative in that it employs commercially available culture media that are designed to specifically promote the growth of marine organisms. The current pharmacopeial methods do not provide the proper nutrients for microbial contaminants that originate from the sea and, therefore, are not adequate for the control of these potential contaminants. Many products containing sea water have been tested using this method and found to be contaminated with microorganisms. This has led to a number of public advisories or warnings, recalls and other compliance and enforcement activities since 2006.

Inspectorate interviewees emphasized that HPFBI has limited resources and capacity allocated to conduct compliance verification and investigation activities related to NHPs. Compliance verifications and investigations of companies that do not adhere to GMPs are resource intensive because of the necessity to provide evidence of risk to health. Thus Enforcement Officers are required to gather an exceptional amount of evidence and several samples must be analyzed by the Inspectorates scientists. However, the evaluation found that HPFBI does not have the appropriate instruments to track its resource expenditures for NHP-related activities thus an estimate of what resources are required to fully execute HPFBI activities cannot be quantified at this time.

CONCLUSION

15. The NHPP has demonstrated that its activities can reduce Canadians' exposure to health risks, but there is no objective evidence to assess the extent of health benefits derived from the Program.

The NHPR provide HC with the legislative authority to inquire about the safety of NHPs and their respective manufacturing processes. While case studies demonstrate that activities completed under this authority have led to the removal of non compliant NHPs that may pose a risk to health, the extent of the reduction of exposure to unacceptable NHPs in Canada is unknown. Similarly there is no assessment of the degree to which the NHPP may be reducing or preventing access to NHPs that could be providing health benefits.

Despite the lack of a sound base of objective evidence to demonstrate that use of approved NHPs in Canada enhances or maintains the health of Canadians[38], the NHPP does contribute to improving and/or maintaining the health of Canadians by screening and approving product and site licences, as well as compliance and enforcement actions for non-compliances, thereby helping to remove unsafe, poor-quality and ineffective NHPs from the marketplace.

RECOMMENDATIONS

See Recommendations in C1.

Achievement of Long-term Outcomes

D1. To what extent is Canada viewed as a responsible participant and scientific expert in an international context regarding NHPs as a result of Program activities?

FINDINGS

Academics, consumer groups and major industry stakeholders interviewed indicated that the Canadian system is receiving favourable recognition internationally for providing access to safe and effective NHPs, and there is ongoing collaboration with other countries, such as the US and

[38] A statement as to whether the use of NHPs (with an NPN or DIN) can prevent illness or disease cannot be made at this time. Long-term cohort studies on how NHP use can prevent illness or disease have yet to be completed.

Australia. A key innovation of the Canadian system, cited in interviews, was the monograph system providing a good balance between access and safety/efficacy. The clinical trial evaluation was also cited as a tool that allows NHP- specific trials to be conducted in a timely and cost effective manner. However, other small to medium-scale industry stakeholders believe the Canadian system is creating unnecessary barriers to commercialization and access for low risk NHPs, with little thought to international harmonization, creating import-export issues[39].

Canada does actively participate in and contribute to the key international forums to coordinate and develop approaches to regulating NHPs worldwide (e.g., under WHO). The international regulators indicated that Canada was a cooperative international partner by sharing data, such as AR and regulatory information. The US regulators were very positive about Canadian partnerships, however, EU interviewees felt that Canada was barely visible on the international regulatory front at meetings and could make more of an effort to participate.

Many Program staff and external interviewees emphasized that Canada has the largest monograph compendium in the world, and that the existing online application system is leading edge when compared to other countries application management systems. Currently, Australia is collaborating with the NHPD to develop a monograph tool that can be used to facilitate the manufacturing of safe and effective NHPs.

Canada has also shared its vitamin and mineral monograph with Australia for knowledge sharing and capacity development purposes. Similarly, several countries from the Middle East (e.g., Saudi Arabia, Oman) and Asia have approached Canada to learn more about designing and implementing regulation and the policies, tools and procedures required to implement them.

At the laboratory service level, HPFBI has also made several contributions including over 20 collaborative studies with the U.S. Pharmacopeia to establish reference materials for the analysis of NHPs and the ongoing sharing of laboratory results with international partners in Europe, the US, Singapore and Australia either at international meetings or through e-mail communication.

CONCLUSION

16. Canada is generally viewed as a responsible participant internationally, with the majority of domestic and international stakeholders providing favourable reviews of the Canadian system.

Program staff, academics, consumer groups and large industry stakeholders view the Canadian system favourably for providing a regulatory approach that is based on pre- and post-market principles. Several national and international experts viewed the Canadian system as the first well thought-out NHP-specific regulatory system in the world. However, there are also some views (e.g., from smaller industry associations) that the Canadian system is creating unnecessary barriers to access for low risk NHPs, with little thought to international harmonization.

[39] The Program has yet to formally define “low” and “high” risk NHPs and no internationally recognized definition is available.

Canada does actively participate in and contribute to the key international forums to coordinate and develop approaches to regulating NHPs worldwide and Canada is viewed as a cooperative international partner.

D2. To what extent has a sustainable, cost-effective, responsive and evidence-based regulatory system for the people of Canada been achieved as a result of NHPP activities?

FINDINGS

Evidence indicates that the NHPP is addressing Canada's emerging needs and priorities for regulating NHPs (pre- and post-market). For example, in 2005, NHPD conducted an in-depth analysis of available safety and toxicity data, AR reports, and approaches used in other regulatory jurisdictions so that amendments could be made to the NHPR and the Food and Drug Regulations[40]. These revisions allowed for vitamin K to be available to Canadians without a prescription, increasing the availability of vitamin K products domestically and internationally.

> The NHP Signal Identification Working Group was created to act as a filter for incoming potential signals from environmental scanning. This group provides a consensus regarding potential signals that should be screened out and those that require further evaluation.

The case studies illustrated that, at least in some instances, the NHPP is evidence-based and responsive, although most modifications and improvements have focussed on the Program's pre-market activities. Evidence has shown that the Program has implemented several process improvements to deal with the backlog, increase efficiency and consistency, and provide information to industry to assist in complying with the NHPR (as evidence in the response to B3). Collaborative relationships with partners and workshops/training sessions with industry have taken place to improve the implementation of the Program; however, challenges still exist that impact efficiency (e.g., classification issues around the NHP-Food-Drug-Cosmetic interface).

NHPD, MHPD and HPFBI have enhanced their processes and procedures so that they are more effective in their ability to identify and address the issues, challenges and risks associated with NHP consumption in Canada. For example, MHPD developed SOPs for NHP Signal Identification[41] and Signal Prioritization[42]. MHPD also developed the NHP Signal Identification and Coordination Working Group in November 2008. Similarly, as previously noted in the response to C3, HPFBI has developed laboratory methods for testing emerging concerns related to NHPs. HPFBI has also worked to establish joint processes between the Program partners in relation to compliance concerns. In addition, the recent formation of the NHPP-CC has provided a Program forum to further establish procedures across the implementing organizations related to compliance and enforcement.

---

40 Published in the Canada Gazette, Part I, April 9th, 2005.

41 Drafted in 2008. Pending approval.

42 Drafted and approved in 2007.

Despite these advancements, the evaluation was unable to determine if the approach to managing and implementing the NHPP is cost effective[43]. When compared with the management of other product lines within HC, interviews noted that NHPP activities take more time and effort because:

- The industry is very heterogeneous and many companies are not used to complying with regulatory requirements, with prevailing views that the products are inherently 'safe', therefore requiring more upfront work in pre-market stages;
- The products are novel and complex, with limited data available on quality, efficacy and safety, therefore requiring more pre-market assessment and laboratory analysis; and
- The products are widely accessible with no controls in the marketplace and without the advice of a health practitioner (as opposed to drugs and medical devices); thus MHPD staff is pressed to look to non-conventional information sources to detect NHP signals.

Moving forward, many interviewees noted that the key risk to implementing an effective and efficient system was political. Program staff emphasized that the NHPP is under a lot of industry pressure to reduce their requirements for what industry considers 'low risk products', along with the competing public expectation for HC to protect consumers regardless of risk. This pretext underlines the need for the Program to complete a comprehensive analysis to determine whether the current approach to implementing the NHPP is proportional to the level of risk associated with NHPs and whether there is a more effective way to completing Program activities.

CONCLUSION

17. The NHPP has demonstrated that it can be a responsive and evidence-based system, but the evaluation was unable to determine if it is cost effective and/or sustainable.

There is evidence to indicate that the NHPP is evidence-based and responsive, although most modifications and improvements have focussed on the Program's pre-market activities. The Program has evolved over time and has implemented a number of process improvements to increase efficiency and consistency; however, challenges remain that impact efficiency. Under the resource allocations provided to the NHPP, the Program has been slow to develop a more efficient and effective post-market system that is capable of addressing the issues, challenges and risks associated with NHP manufacturing and use.

Although each of the implementing organizations maintains their own approach to recording financial information, the existing framework [i.e. the Systems Applications and Products Database (SAP)] does not provide the organizations with an appropriate format for determining

[43] The response to question E2 speaks directly to cost-efficiency.

the cost effectiveness of their activities across multiple product lines[44]. This is a particular problem for MHPD and HPFBI as they provide a common set of services to multiple product lines in HC. As a result, these organizations are challenged to determine which of their activities are more resource-demanding, by product line.

The evaluation also found that the existing framework is not sufficient for aligning the costs and expenditures of NHP activities with the current activities and outcomes presented in the Department's PAA.

RECOMMENDATIONS

See Recommendations in C1.

D3. To what extent have health benefits increased and NHP-related illnesses decreased among Canadians as a result of Program activities?

FINDINGS

Although there is evidence that approximately 70% of the Canadian population uses NHPs on an ongoing basis, the absence of any baseline data to explain the health of Canadians, either before or at the time the NHPR came into effect, provides a weak foundation for quantitatively evaluating how health benefits have increased or illnesses have decreased as a result of NHPP activities or the use of NHPs.

While Canada's approach to NHPs is designed to provide health benefits, the absence of an ongoing, robust inspection program may mean higher levels of non-compliance than other product lines, thus posing greater health risks. As well, since the Program has not invested significant effort towards understanding the effectiveness of risk communications or public outreach, as evidenced by public surveys and the low levels of adverse reaction reporting, the view that NHPs are 'safe' persists and may also pose health risks associated with NHP misuse. Interviews with Program staff and stakeholders provided two different views, with a minority of vocal industry stakeholders noting that there has been no apparent increase in the safety, efficacy or quality of NHPs, and others recognizing that the NHPP provides greater assurance of health benefits than the previous regime or other countries' regimes.

Interviews indicated that it is very difficult to measure the impact of the NHPP (e.g., there is no recognized method to assess the health risks/illnesses avoided due to Program activities). However, there is a desire by the Program to put more effort into assessing the effectiveness of their various activities, e.g., risk communications, to improve Program performance.

[44] Each implementing organization provided cost expenditure information to the evaluation. The evaluation team noted that the approach to tracking NHP expenditure information is "organization specific" and is not reflective of a standard program-wide approach developed by HPFB or under the direction of the DGCC.

CONCLUSION

18. At this early stage, it is difficult to determine if the NHPP has increased health benefits and/or decreased NHP-related illnesses among Canadians.

Outside of specific examples/cases, there is no comprehensive evidence to confirm that Program activities have led to increased health benefits or decreased illnesses among Canadians. The ability to measure such an outcome in a comprehensive manner is recognized as very challenging.

RECOMMENDATIONS

See Recommendations in C1.

Economy and Efficiency

E1. To what extent has the NHPP designed and implemented a Performance Measurement Strategy?

FINDINGS

As of 2007[45], all three organizations (i.e., NHPD, MHPD, and HPFBI) prepare quarterly performance reports that speak separately to their NHP activities and outputs. NHPD also provides an online progress report for stakeholders and a weekly update to the ADM's Office on the status of the NHP backlog. In addition to these reports, elements of the Program's performance are reflected in the Health Products and Food Branch's Annual Performance Reports and Public Involvement Annual Performance Reports.

Collectively these reports speak to many of the indicators presented in the RMAF's Performance Measurement Strategy[46]. However, an integrated NHPP report highlighting progress towards measuring these indicators was not found and it is unclear as to whether the Program is in a position to report on the indicators presented in the RMAF.

CONCLUSION

19. While a RMAF has been developed and organizations routinely report on Program outputs at the organizational level, there is no integrated Program-wide performance measurement and reporting.

A performance framework has been developed, and progress reports are provided by organizations (at the activity/output level), however, an integrated Program-wide performance measurement strategy has yet to be implemented.

---

[45] As a result of direction provided by an ADM approved performance measurement framework for all organizations operating within HPFB.

[46] The RMAF was approved by the Department's Head of Evaluation on October 24th, 2008.

RECOMMENDATION

See Recommendations in C1.

E2. Was the amount allotted/spent appropriate for the scope of the NHPP?

FINDINGS

The Program was established without the provision of new funding; rather funds were redirected from other areas in HC to support the Program and, over time, small portions of various Treasury Board submissions have provided some funding to the Program. Not until 2007-2008 did the Program receive a dedicated source of funds to complete Program activities.

Program staff emphasized that the previous and existing resource levels were and still are inadequate to meet the work load and to fully implement the Program as intended (e.g., evidenced by the backlog, low level of enforcement activities, accumulation of red signals, etc.). As a result, a number of anticipated activities are not being completed fully including, for example proactive AR reporting and compliance promotion.

In light of the current situation surrounding the resources allocated to the Program versus the expenditures for completing activities in accordance with the NHPR, the evaluation team found that a key finding from the Report of the Auditor General on HC's approach to Allocating Funds to Regulatory Programs[47] (2006) continues to be relevant and is applicable to the NHPP:

> *"For Health Canada, to make responsible spending decisions related to the delivery of programs and services, the Department needs an effective resource allocation process. As part of this process, the Department needs to decide what it is trying to achieve, what its priorities are, and direct resources toward programs and services that help Canadians. It then needs to monitor its programs and services to ensure that they are achieving the intended results. Therefore, to make these important decisions, Health Canada requires sound financial and performance information that must include the cost to achieve the stated objectives. It also needs to be able to link financial and performance information to determine results achieved with the funding received".*

From 2000 to 2008, NHP costs and expenditures have totalled approximately $94,184,377 (**See Table 10**). However, the evaluation team noted a void in the Program's ability to articulate Program allocations versus Program expenditures (at the activity level) from 1999 to 2008. An articulation of what each organization was allocated from 1999 to 2007 was not found. With respect to tracking NHP specific expenditures, implementing agencies with a horizontal mandate are forced to develop proxies to estimate their expenditures for their NHP activities. Staff from these respective organizations emphasized that the current SAP system used to track resources and expenditures is not appropriate for tracking costs and expenditures by product line activities nor is it appropriately aligned with the activities presented in the Department's PAA.

[47] Report of the Auditor General of Canada to the House of Commons, Chapter 8: http://www.oag-bvg.gc.ca/internet/docs/20061108ce.pdf

Furthermore, Program resources are not tracked against a standardized set of performance indicators or comparable metrics to fully understand the cost-efficiency of NHPP activities. **Table 10** presents a summary of the Program's estimated direct costs and expenditures from 2000 to 2008.

Table 10: NHP Direct Costs and Expenditures from 2000 to 2008

	Data	FY									Grand Total
		2000	2001	2002	2003	2004	2005	2006	2007	2008	
NHPD	Amount	$1,445,957	$2,174,957	$3,153.210	$4,731,117	$7,189,727	$9,309,652	$12,551,077	$15,003,793	$16,694,611	$72,253,831
	EBP	$86,133	$224,210	$268,442	$486,356	$678,472	$969,753	$1,461,698	$1,591,902	$1,840,388	$7,607,355
MHPD	Amount				$111,582	$444,337	$916,568	$1,193,144	$974,972	$1,209,820	$4,850,424
	EBP				$16,353	$72,983	$135,090	$190,932	$154,057	$162,359	$731,774
HPFBI	Amount	$49,806	$195,001	$344,726	$401,546	$317,837	$495,254	$1,845,418	$1,809,348	$2,423,302	$7,882,237
	EBP	$0	$14,464	$790	$0	$0	$36,579	$270,036	$242,305	$294,582	$858,756
Total	Amount	$1,495,763	$2,369,687	$3,497,936	$5,244,246	$7,951,901	$10,721,473	$15,589,638	$17,788,114	$20,327,733	$84,986,492
	EBP	$86,133	$238,674	$269,232	$502,709	$751,455	$1,141,423	$1,922,666	$1,988,264	$2,297,328	$9,197,885
TOTAL		**$1,581,896**	**$2,608,362**	**$3,767,168**	**$5,746,168**	**$8,703,356**	**$11,862,896**	**$17,512,305**	**$19,776,378**	**$22,625,061**	**$94,184,377**

Source: Systems Applications and Products (SAP).

CONCLUSION

20. The evaluation was unable to assess the appropriateness of NHP allocations vs. spending.

The NHPP had to build gradually, using existing resources, and when the NHPR came into force in 2004, dedicated, stable funding was not provided[48]. The funding allocated to the Program in 2008 provided resources for a five-year period, however, senior officials from each implementing organization emphasized that the current resource levels are inadequate for delivering all Program activities identified in the Program RMAF. However, the evaluation found that, while detailed financial accounting is conducted at the organizational level, a comprehensive and accurate picture of the entire Program's costs and expenditures versus what is was allocated over the period 1999 – 2008 does not exist and the implementing agencies do not have the appropriate departmental tracking system for determining the effectiveness of their NHP specific activities vs. other product lines.

This finding underlines that the Office of the Auditor General's (OAG) observations from the 2006 Audit Report of HC's approach to allocating funds to Regulatory Programs continue to be relevant and that both the NHPP and HPFB need to establish the appropriate tracking structures and mechanisms to monitor Program performance so that the Department can provide greater assurance that it is achieving demonstrable results for Canadians.

[48] The evaluation found that from 2000-2004, no effort was made to track financial information, which may have allowed the Program or the individual organizations to request TB for funding.

RECOMMENDATIONS

See Recommendations in C1.

E3. In view of the current delivery structures, are there any alternate delivery structures that could be considered and in which areas?

FINDINGS

As a direct response to the Standing Committee on Health's recommendations and as a means to implementing the NHPR, HC designed the NHPP. However, this design focused heavily on introducing a pre-market assessment process (as common with other product lines) and did not focus on comprehensive post-market activities. The current approach to issuing a site licence is paper based and does not include a physical site inspection. Similarly, since a formal, proactive and continuous onsite compliance program (or inspection of products) is not in place, the NHPP is not well placed to assure that NHPs are manufactured in accordance with the terms and conditions of their respective licences. In comparison, under the current system administered by the TGA in Australia, site licence applicants must have a facility level audit completed before they are granted their site licence. The international benchmarking exercise found that other countries had a more proactive post-market system in place for assuring the safety and quality of NHPs. For example, Australia's post-market system includes a targeted compliance and enforcement system designed to address complaints and/or ARs associated with a particular product type (e.g., NHP weight loss products).

The current delivery approach includes international partnerships through MRAs and MOUs to share information and examine alternative approaches taken in other countries that could be used in Canada. As well, academics have been contracted to assess alternatives to implementing some Program components (e.g., examination of enhancing adverse reaction reporting study by University of Alberta).

Internally, there have been some staff exchanges to address work load issues and learn about the alternate ways of implementing the various Program components (e.g., MHPD staff 'on loan' to NHPD). It was noted in the interviews that there are two different delivery structures for NHPP since NHPD is focused solely on delivering NHP-specific activities, while MHPD and HPFBI work in delivering their activities across product lines. This creates challenges in considering and implementing NHP-specific delivery approaches.

There is currently no cost recovery in the Program, as there is with other product lines in HC, and this may be considered in the future. In the short term, interviewees commented that a fee for service arrangement may be put in place for International Trade Certificates that facilitate NHP export for industry.

CONCLUSION

21. The NHPP was designed with an early and appropriate emphasis on pre-market activities and alternate delivery modes or shifts are only now being considered.

The Program has implemented alternative delivery approaches for some activities, but has not yet determined how to strategically focus its current and future pre- and post-market efforts to ensure that it can successfully achieve the outcomes presented in the Program logic model.

RECOMMENDATIONS

See Recommendations in A1.

5 REFERENCES CITED

Arnason T., Hebda, R.J., and John, T. 1981. Use of Plants for Food and Medicine by Native Peoples of Eastern Canada. Can J Bot. 59(11): 2189-2325.

Awang, DVC. 1998. Prescribing therapeutic feverfew. Integrative medicine 1: 11-23.

Awang, DVC. 2000. Recalling the case of the hairy baby. Journal of Herbs, Spices & Medicinal Plants, www.informaworld.com .

Barnes, J. 2003. Pharmacovigilance of Herbal Medicines: A UK Perspective. *Drug Safety. 26*(12), 829-851.

Blumenthal, M., Goldberg, A., and J. Brinkmann (ed.)(2000). Expanded Commission E Monographs, *Integrative Medicine Communications*, 33-35.

Brevoort, P. 1998. The booming botanical market. Herbal Gram 44: 40.

Briggs, D.R. 2002. The regulation of herbal drugs in Australia. Toxicology 181-2:565570.

Brownie S. 2005. The development of US and Australian dietary supplement regulations. Complementary Therapies in Medicine 13: 191-198.

Cynthia, R. (September 2009). *Unnatural Regulation: Complementary and Alternative Medicine Policy in Canada.* Retrieved from http://www.fraserinstitute.org/commerce.web/product_ files/UnnaturalRegulation.pdf .

Drew, A.K. & SP. Myers 1997. Safety issues in herbal medicine: Implications for health professions. *MJA* 166: 538-541.

Health Canada. *NHPD Progress on the 53 Recommendations of the Standing Committee on Health, (1998).*Ottawa, ON: Health Canada.

Health Canada. *Good Manufacturing Practices – Guidance Document Version 2.0, (2006).*Ottawa, ON: Health Canada.

Health Canada.(2007) *Planning for Our Future: Federal Regulatory Post-Market Surveillance Strategy 2007-2012.* Retrieved from: www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/index_e.html .

Hobbs, C. 1990. Echinacea: the immune herb. Botanica Press.

Ipsos Reid. Baseline Natural health Products Survey Among Consumers Final Report, March, 2005. Retrieved from http://www.hc-sc.gc.ca/dhp-mps/pubs/natur/eng_cons_survey-eng.php .

Koh, H.L. and Woo, S.O. 2000. Chinese proprietary medicine in Singapore Drug Safety 23: 351-62.

Laeeque, H., Boon, H., Kachan, N., Cohen, J. and D'Cruz, J. 2006. The Canadian Natural Health Products (NHP) Regulations: Industry Compliance Motivations eCAM 2006; 4(2)257–262.

Lashof JC, Margen, S and Swarzberg, JE. 2002. Regulating Natural Health Products. Science 296: 46:47.

Murty, M. 2007. Postmarket surveillance of natural health products in Canada: clinical and federal regulatory perspectives in Can. *The Journal of Physiol Pharmacol*, 85: 952-955.

Piscitelli, S.C.. 2000. Indinivir concentrations and St John's Wort. Lancet, 355:547.

Rousseaux, C. and Schacter, H. 2003. Regulatory issues concerning the safety efficacy and quality of herbal remedies. Birth Defects Research 68:505-510.

Silano M. et al. 2004. The new European legislation on traditional herbal medicines. Fitotherapia 75: 107-116.

Teschke, R., Gaus, W., Loew, D., 2003. Kava extracts: safety risks and rare hepatotoxicity. Phytomedicine 10:440-446.

Tesio, S. 2006. Pharmacie et univers thérapeutique en Basse-Normandie et dans la vallée du Saint-Laurent au XVIIIème siècle. Praticiens, organisation, pratique. Etude comparative, Caen, Université de Caen, Québec, Université Laval.

Wu K.M., Ghantous, H. and Birnkrant, D.B. 2008. Current regulatory toxicology perspectives on the development of herbal medicines in prescription drug products. Food and Chemical Toxicology 46: 2606-10.