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Health Canada Santé Canada

A New Risk-Based Approach to Site Licensing for Natural Health Products
Concept Paper

Document Objective

This document describes changes proposed to:

- The current site licensing model for manufacturers, packagers, labellers and importers of natural health products (NHPs);
- The Good Manufacturing Practices (GMP) standards for NHPs; and
- The information required to be provided at the time a product licence application is submitted.

This document is intended to provide the reader with sufficient information to allow for an understanding of the proposed changes and associated rationale. Comments received from stakeholders will be considered before any decisions are made by Health Canada.

TABLE OF CONTENTS

INTRODUCTION

The primary objective of the new Risk-Based Approach to Site Licensing (RBASL) initiative is to develop a strengthened site licensing system that will provide a greater level of assurance that Natural Health Products (NHPs) sold in Canada meet appropriate standards of quality, safety and efficacy.

The need to ensure that NHPs are regulated proportionally to their level of risk was highlighted following a Regulatory Review in 2007 of the *Natural Health Products Regulations* (NHPR) and the existing regulatory framework for NHPs. The review made a number of recommendations, including a re-examination of the standards of Good Manufacturing Practices (GMPs) and the way in which GMPs are assessed by Health Canada during the site licensing process *(see Appendix B 3.1 of Charting a Course consultation document http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/chart-course_tracer-voie-eng.php).*

Following the Regulatory Review, the Natural Health Products Directorate (NHPD) held a workshop with over 40 participants representing a broad range of NHP stakeholder groups. This workshop explored the need for a new enhanced site licensing model as well as changes to the current GMP standards in order to provide a greater level of assurance of the safety and quality of NHPs reaching the Canadian market. Based on the information received at the workshop, the NHPD released a Fact Sheet outlining the development of a new risk-based approach for NHPs, including modifications to the licensing of NHPs and the sites undertaking their manufacturing, packaging, labelling and importing. The Fact Sheet is available at http://www.hc-sc.gc.ca/dhp-mps/pubs/natur/nhprr-rba_erpsn-gbr-eng.php

The NHPD has continued to hear from stakeholders that changes are needed to the way in which site licenses are issued to manufacturers, packagers, labellers and importers of NHPs. In particular, there is a desire to see a move away from the existing self-assessment licensing model to one that includes an on-site verification of compliance with the standards of GMPs prior to a site licence being issued.

With the proposed changes, manufacturers, packagers and labellers would be required to have an on-site audit demonstrating compliance with the GMP standards prior to the issuance, renewal or amendment of a site licence. Depending on the product type, the audit would be required to be conducted by either a Health Canada recognised 3rd party auditing body or a Health Canada inspector. Alternatively, evidence demonstrating

compliance with the GMP standards following an on-site audit conducted by a recognised competent authority may also be accepted.

Changes are also being proposed to the GMP standards currently outlined in the NHPR. The proposed changes are designed to provide a greater level of assurance as to a product's quality, clarify who is responsible for ensuring certain product quality information is available and more closely align the standards with key international partners' GMP standards.

Changes are proposed to the information required to be provided at the time a product licence application is submitted. It is proposed that product licence applicants be required to provide details of the product manufacturer(s), packager(s) labeller(s) and if applicable, importer(s), before a product licence is issued. Should this information not be provided, it is proposed that a conditional licence be issued. The issuance of a conditional licence would not provide the authority for a product to be sold. Should the product's safety and efficacy information be acceptable, the product licence would be issued only after acceptable manufacturer, package, labeller and/or importer information is provided.

Finally, it is also proposed that the NHPD publish and maintain a publicly available list of licensed manufacturers, packagers, labellers and importers. The list will also include foreign sites who specifically indicate they would like to be included on the list. Importantly, there will be no publicly available information linking manufacturers, packagers, labellers and importers to specific NHPs.

A Technical Working Group (TWG), comprised of six NHP industry representatives along with Health Canada staff from the NHPD and Health Inspectorate Program, was formed to help in the development of this concept paper. The TWG provided valuable advice and feedback on the proposals developed by the NHPD and played an important role in challenging and validating the proposed changes.

The TWG industry members (listed on page 6) were selected for their individual scientific and technical knowledge, experience and expertise relevant to GMPs and the principles of manufacturing quality. The group was broadly representative of the Canadian NHP industry in terms of company size, activities conducted, product types and geographical locations. The information and proposed changes presented in this concept paper are based on the comments and feedback provided by the TWG.

Consultation with stakeholders on the changes proposed in this concept paper is the first step in the process of building a strengthened site licensing system. This consultation provides stakeholders with an opportunity to comment on the proposed direction before any decisions are made by Health Canada.

Comments received from stakeholders will be reviewed and summarized by Health Canada in a final consultation report. The report will also describe the next steps for each of the changes being proposed.

ACKNOWLEDGEMENTS

The NHPD would like to acknowledge and thank all members of the TWG for their active participation, assistance and advice given to the RBASL project team in developing this concept paper.

Industry members of the TWG included Ms Wendy Clouthier (Ascenta Health Ltd, Nova Scotia), Ms Svetlana Aleksic (Santé Naturelle, Quebec), Mr Gary Leong (Jamieson Laboratories, Ontario), Ms Doreen Steen (i3CanReg, Ontario), Ms Sarah Docker (GSK, Ontario) and Dr Shane Lu (Canadian Phytopharmaceuticals Corporation, British Columbia).

CHAPTER 1: RBASL PROJECT – CONTEXT

The Need for Quality

A product's safety and effectiveness is directly linked to its quality. Without adequate control over the way a product is manufactured, packaged, labelled, imported, distributed and stored, there can be little assurance as to its quality and therefore safety and effectiveness.

The NHPR came into force on January 1, 2004, following extensive regulatory and consultative processes. The NHPR were a direct response to an expressed need for specific regulatory oversight for NHPs in Canada. The NHPR includes the requirement for manufacturers, packagers, labellers and importers of NHPs to be licensed and for these activities to be undertaken in accordance with GMP standards.

There is an expectation from NHP stakeholders, including consumers, healthcare providers, the industry and regulator that the NHPs sold in Canada will contain only the ingredients stated on the label at the levels indicated; that the product will do what it claims it will; and that it will not cause any unintended health problems. In order to deliver on these expectations, those responsible for selling NHPs in Canada must be able to demonstrate they have appropriate quality control over the manufacturing, packaging, labelling, storage and distribution of their products.

A system for ensuring product quality, based on appropriate GMP standards, creates confidence in the capability and capacity of an organization's processes and the quality of their products. Quality assurance and quality control, however, is not simply something done by industry to satisfy regulatory requirements. There are benefits of having and maintaining a system for ensuring quality for all parties involved. Not only do regulators require appropriate standards of quality to be met, but when engaging in business arrangements, customers are looking for the confidence that can be provided by organizations that adopt an effective system for ensuring product quality.

International Alignment

An objective when developing or modifying a regulatory framework, in whole or in part is to consider and encourage international convergence of requirements. This helps facilitate trade while preserving sovereign authority to address the protection of public health by regulatory means considered the most suitable.

In a time of resource constraint, regulatory authorities are compelled to establish innovative and more effective approaches to regulation in closer collaboration with like-minded regulatory partners, while maintaining appropriate standards of quality and safety.

The primary way in which international alignment can be achieved is through the consideration of regulatory frameworks and guidance documents that together capture a global regulatory model. The purpose of such an approach is to avoid unique to Canada requirements and to seek harmonized conformity assessment principles, procedures and documentation that apply to NHPs (or their equivalent in other jurisdictions). Eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows earlier access to products.

In developing an approach to independent on-site verification of GMPs, it is Health Canada's objective to encourage and support international convergence of the GMP standards and the model for verification/licensing sites. Should the objective be realized, it will provide benefits to Regulatory Authorities and industry in establishing, in a consistent way, an effective and economically beneficial approach to the control of NHPs in the interest of public health. It will also strike a balance between the responsibilities of Regulatory Authorities to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

Members of the Technical Working Group agreed that:

- The global environment, within which the NHP industry operates, requires Canada's regulatory framework to align with key international partners (i.e., USFDA and PIC/s member countries) where appropriate.
- International alignment of regulatory requirements has the potential to deliver direct and indirect benefits to both consumers and the regulated industry.
- The current GMP standards for NHPs includes many elements which directly align with key international partners, however there are some areas which fail to align sufficiently.
- Any proposed changes, to either the GMP standards or licensing model, should support future international convergence.
- Including an on-site audit of GMPs by a 3rd party for manufacturers, packagers and labellers of NHPs would be consistent with approaches taken by key international partners.

CHAPTER 2: THE SITE LICENSING MODEL

Current Site Licensing Model

Initial Licensing

Before a company is able to legally manufacture, package, label or import an NHP for sale in Canada, they are required to obtain a site licence from Health Canada.

In order to obtain a site licence, a report is required from a quality assurance person demonstrating that the buildings, equipment, practices and procedures used for each activity conducted by the licensee will comply with the GMPs as outlined in the NHPR. The quality assurance person is required to have the training, experience and technical knowledge relevant to the activity conducted and the requirements of the GMPs outlined in the NHPR. The report generated by the quality assurance person for the purposes of site licensing is termed a 'Quality Assurance Report' (QAR) and is considered a self-assessment document. That is, the QAR is a compilation of documents and information prepared by the applicant to show how they comply with the GMPs. The applicant chooses the documents and information they wish to provide as evidence of compliance.

Following a review of the information submitted in the QAR, the NHPD makes a decision to either issue, or refuse to issue, a site licence.

Should a licensed Canadian importer wish to bring an NHP into Canada that is manufactured, packaged or labelled in a foreign country, the importer must provide evidence that the foreign manufacturer, packager and/or labeller complies with equivalent GMP standards as outlined in the NHPR. The importer either completes a QAR for each foreign site, following the same self-assessment process as described above, or provides evidence that the foreign site has been assessed against, and meets the GMP standards from a recognised international regulatory authority.

Site Licence Renewal

In order to maintain the status of a site licence, the site licence holder must renew it as follows:

- every year, when the licensee has held the licence less than three years from the date of issuance;
- every two years, when the licensee has held the licence for a period of at least three years from the date of issuance but less than nine years; and
- every three years, when the licensee has held the licence for nine or more years from the date of issuance.

Site Licence Amendments

A site licence amendment is required when one or more of the following changes are made to the site licence:

- adding a new activity (i.e. manufacturing, packaging, labelling, storing or importing);
- adding a new building for operations or storage;
- adding manufacturing, packaging, labelling or importing of a sterile dosage form;
- change of address; and/or
- relinquishment of any activity, building or foreign site.

When amending a site licence, the site licence holder is required to meet the same requirements as at initial licensing (i.e., through a self-assessable QAR).

Number of Sites Licenced by the NHPD Since 2004

Domestic Sites
Since 2004, the NHPD has issued site licences to more than 300 Canadian sites for the activities of manufacturing, packaging and labelling. In addition, there have been more than 400 Canadian sites licensed to import NHPs into Canada.

Foreign Sites
There are currently more than 1000 foreign sites annexed against licensed Canadian importers with approximately 65% of these sites located in the United States of America.

Compliance and Enforcement Issues Related to NHPs

Between 2009 and 2011 there were more than 800 complaints received by Health Canada relating to NHPs. Complaints are received from a number of sources including

consumers, health care practitioners, industry, retailers etc. NHPs represent more than 40% of all compliance verification complaints received by Health Canada.

Between January 2009 and March 2011, Health Canada received more than 1000 adverse reaction reports, of which more than 60% were classed as serious. During the 2010/11 fiscal year, Health Canada issued 81 risk communications relating to NHPs of which 52 were Foreign Product Alerts.

Challenges with the Current Site Licensing Model

The absence of an independent on-site audit component is considered the largest single issue impacting the current site licensing model. The current self-assessment approach:

- Does not provide appropriate verification of a manufacturer's, packager's and labeller's compliance with the GMP standards;
- Does not provide sufficient confidence in the quality of the NHPs sold in Canada; and
- Often impacts the ability of Canadian industry to export products as it is incompatible with approaches taken with other international regulatory jurisdictions.

Lack of Confidence in Accuracy of Information Supplied with QAR

Health Canada has occasionally conducted compliance verification visits of licensed NHP sites and found that the information submitted with the site licence application and QAR was inaccurate and did not reflect the activities conducted. This has lead to a lack of confidence in the accuracy of information contained in site licence applications and the QAR.

Limitations of the Paper-Based System

The information that can be provided and assessed through the current paper-based system is limited to outcome-based information. That is, information that shows a 'result' of some kind. Unfortunately, there are many aspects of the GMP standards that cannot be measured or shown through information such as this. The example below further demonstrates this point. In addition, the accuracy of information provided often proves difficult to assess as to how a company complies with the GMP standards.

To illustrate, the NHPR require premises to:

- Be kept clean and orderly;
- Permit the effective cleaning of all surfaces;
- Prevent contamination of the NHP; and
- Prevent the addition of an extraneous substance to the NHP.

While a company may provide a written description of its premises, including a layout or building plans, such documentation does not allow for an accurate and informed assessment to be made as to whether the layout is appropriate for; preventing mix-ups and cross-contamination of raw, packaging and product materials; or if doors, windows, walls, ceilings and floors are structurally sound and prevent contamination from extraneous materials; and whether effective cleaning is possible. Such elements can only be assessed through a physical examination of the actual premises.

Lack of Credibility with International Partners and Export Challenges

The current licensing system has been criticised by Canadian companies wishing to export product due to the site licence issued by Health Canada being considered insufficient/unacceptable for demonstrating the product was produced in accordance with GMP standards.

International Trade Certificates issued by the NHPD attest that the site at which the products are manufactured, packaged and labelled are compliant with Canadian requirements, but this attestation is only provided based on the paper-based review of the self-assessment conducted by the licensee.

The lack of an on-site audit verifying a company's compliance with GMP standards has often been given as the primary reason why key international Regulatory Authorities are unable to accept the current Health Canada site licence as evidence of a company's ability to comply with GMP standards. This situation has lead to export challenges being experienced by Canadian manufacturers, packagers and labellers and brings into question the value of the current Health Canada NHP site licence in terms of facilitating international trade.

Proposed Site Licensing Model

Manufacturers, Packagers and Labellers

- It is proposed that the existing site licensing model be changed to require

domestic and foreign manufacturers, packagers and labellers of NHPs to provide a report or certificate as evidence that the activities undertaken are in accordance with the standards of Good Manufacturing Practices. The report and/or certificate would be issued following an on-site audit of the facility.

  - For manufacturers, packagers and labellers of non-sterile products, the on-site audit would be conducted by: 1) a Health Canada recognised 3rd party auditing body or 2) other recognised competent authority.

  - For manufacturers, packagers and labellers of sterile products, the on-site audit would be conducted by: 1) Health Canada inspector or 2) other recognised competent authority.

- It is proposed that the NHPR be amended to allow for the new licensing model to utilise the results from on-site audits conducted by other recognised competent authorities, such as key international regulatory authorities. Such an approach would require an appropriate recognition process and confidence building phase to be undertaken and would ideally result in reciprocal recognition by the foreign regulator of the site licence issued by Health Canada (e.g. through the establishment of a Mutual Recognition Agreement).

A 3rd party audit model for manufacturers, packagers and labellers of non-sterile NHPs is considered to offer a greater level of flexibility for industry. The model is expected to create a competitive environment in the marketplace in order to keep costs as low as possible and, importantly, allows a distinct separation between the activities associated with issuing a site licence, versus activities undertaken by Health Canada to verify on-going compliance after a site licence has been issued.

Having Health Canada conduct on-site audits of manufacturers, packagers and labellers of sterile NHPs is proposed given:

- The high risks posed by inappropriately manufactured sterile products;
- Health Canada has specialist inspectors trained in the audit of sterile manufacturing facilities;
- The auditor training requirements required for sterile sites are significant and go beyond those required to audit a non-sterile site; and
- There is currently only a very small number (< 1%) of licensed sites manufacturing, packaging or labelling sterile NHPs.

Importers

- It is proposed that an application for a licence to import NHPs continue to be undertaken via a Quality Assurance Report (i.e., self-assessment licensing system). Importantly however, foreign manufacturers, packagers and labellers will be required to demonstrate the same level of compliance with the GMP standards as Canadian manufacturers, packagers and labellers. That is, foreign sites will be required to have undergone an on-site audit by either a Health Canada recognised 3rd party auditing body or other recognized competent authority before they can supply NHPs to Canada.

- It is proposed that a random post-licence on-site GMP compliance verification program be developed by Health Canada to proactively verify the information that was supplied by importers at the time of their licensing.

The same level of scrutiny and regulatory rigour will apply to all manufacturers, packagers and labellers irrespective of where they are located in the world. As such, a report and/or certificate following an on-site audit by a Health Canada recognised 3rd party (or Health Canada inspector for sterile products), or acceptable alternative evidence will be required to be provided for each foreign site.

As importers have an imperative role in ensuring the quality of the products imported into Canada for sale, it is proposed that a random post-licence on-site compliance program be developed by Health Canada to proactively verify the information that was supplied by importers to Health Canada at the time of their licensing. Such a system would aim to select a statistically valid number of licensed importers for a post-licence on-site compliance verification visit in order to provide an appropriate level of confidence in the licensing process.

Proposed Licence Renewal Frequency

- It is proposed that a site licence be valid for a period of:
  - Three years for manufacturers, packagers and labellers of non-sterile NHPs;
  - Two years for manufacturers, packagers and labellers of sterile NHPs; and
  - Three years for importers of non-sterile or sterile NHPs.

The proposed renewal timeframes are considered an appropriate balance between the benefits and credibility that an enhanced licensing program would offer the NHP industry (due primarily to incorporating an on-site audit component) against resources (including cost of audits) required to prepare and successfully apply for a site licence.

The risks posed by inappropriately manufactured sterile products are significantly greater than those for non-sterile products. Therefore, for manufacturers, packagers and labellers of sterile NHPs, a 2-year renewal cycle is being proposed.

Proposed Site Licensing Model Summary Table

<table>
<tr><th colspan="4">Proposed Site Licensing Model</th></tr>
<tr><td rowspan="2"></td><td colspan="2">Manufacturers, Packagers, Labellers</td><td>Importers</td></tr>
<tr><td>Non-sterile</td><td>Sterile</td><td rowspan="2">Quality Assurance Report
May be subject to post-licensing on-site compliance verification inspection by a Health Canada Inspector</td></tr>
<tr><td>Initial Licensing Requirements</td><td>Report following an on-site audit from a recognised 3rd party auditing body or competent authority</td><td>Report following on-site audit conducted by Health Canada or competent authority</td></tr>
<tr><td>Renewal Frequency</td><td>3 years</td><td>2 years</td><td>3 years</td></tr>
<tr><td>Licence Renewal and/or Amendment Requirements</td><td>Report following an on-site audit from a recognised 3rd party auditing body or competent authority</td><td>Report following on-site audit conducted by Health Canada or competent authority</td><td>Quality Assurance Report
May be subject to post-licensing on-site compliance verification inspection by a Health Canada Inspector</td></tr>
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Elements of a Proposed 3rd Party Recognition Process

- It is proposed that Health Canada develop, administer and maintain responsibility for the process of recognizing 3rd party auditing bodies.

Health Canada would be required to establish appropriate procedures and mechanisms to assess, recognize, train, monitor, and remove recognition from 3rd party auditing bodies if required.

The formal recognition process has yet to be fully developed, however 3rd party recognition models are widely available in many industries and Health Canada would assess these models when designing the 3rd party recognition process. For example, Medical Devices, Aviation, Telecommunications and Gas Pump industries all currently utilise 3rd party systems to some degree within their regulatory frameworks.

No matter the industry, the models have common elements. These include:

- A comprehensive application, screening and assessment process to help ensure consistency of audits across the 3rd party auditing bodies.
- Ongoing training of 3rd party auditing bodies and on-going monitoring by the regulator. Monitoring can include on-site assessments of 3rd party head offices and/or witness audits of 3rd party auditing bodies when they conduct an on-site audit.
- The ability to remove recognition by the regulator should the 3rd party auditing body no longer meet the necessary competency standards ; and
- Processes to mitigate confidentiality and conflict of interest concerns.

CHAPTER 3: GMP STANDARDS

The Current Good Manufacturing Practices Standards

Part 3 of the NHPR outlines the regulatory requirements for NHP standards of Good Manufacturing Practices (GMPs). The provisions include specific requirements related to manufacturing, packaging, labelling, importation, distribution, storage, and to other quality control requirements to ensure an effective overall approach to product quality and risk management.

The GMPs outlined in the NHPR are largely principle-based and do not prescribe how the GMP requirements must be met nor outline minimum expectations in order for compliance to be achieved. The NHPD developed, in consultation with industry stakeholders, the *Good Manufacturing Practices Guidance Document (Aug 2006)* as a means for outlining the expectations and ways in which the GMP requirements can be met. However, reliance on non-regulatory means such as guidance documents, fact sheets and communication messages has presented significant regulatory issues when trying to ensure minimum GMP expectations are being met.

Challenges with the Current GMP Standards

While members of the TWG generally agreed that the current GMP standards are to a large extent appropriate and adequate, the following issues were specifically identified as areas that cause difficulties to both the industry and regulator:

- Inadequate clarity of responsibilities due to structure of NHPR, especially when undertaking contract manufacturing and analysis;
- Lack of accountability of Product Licence Holders for assuring product quality, especially in relation to product stability requirements;
- Unclear what evidence and/or minimum requirements are needed to demonstrate compliance against the GMP standards; and
- Lack of enforcement of the GMP standards.

In addition to the above, internationally, different jurisdictions have developed different GMP standards for the manufacturing, packaging, labelling and importing of NHP-type products. The United States Food and Drug Administration (USFDA) cGMP for Dietary Supplements (21 CFR 111) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide for Good Manufacturing Practices for Medicinal Products

(1 September 2009) represent standards that apply to similar products regulated by key international partners.

The following have been identified as important areas in which the NHPR differ from the above international standards and also where industry and the regulator continue to face challenges.

- Lack of raw material control requirements;
- Insufficient manufacturing, packaging and labelling control requirements;
- Lack of requirement for in-process sampling;
- Insufficient requirements to make and keep records; and
- Lack of requirement for control over laboratory operations.

While the above points are not a comprehensive list of differences between the US FDA cGMPs, PIC/S and NHPR, they are areas that the TWG felt could be addressed in order to strengthen the NHP GMP standards and provide greater alignment with key international standards.

Proposed Changes to the Standards

Clarification of Responsibilities when Undertaking or Engaging in Contract Manufacturing and Analysis

- It is proposed that the NHPR be amended to place greater responsibility on the product licence holder for any activities that they contract to other parties for the manufacturing, packaging, labelling and importation of the NHP.

- It is proposed that product licence holders, manufacturers, packagers, labellers, and importers correctly define, agree, and control contracted activities through established written agreements that clarify the roles and responsibilities between parties.

Issues and confusion regarding GMP responsibilities often arise when an activity is conducted under contract. Currently, there is a lack of clarity of GMP responsibilities when site licence applicants undertake contract manufacturing, packaging and labelling activities for product licence holders. Often, site licence applicants are unable to demonstrate they meet all areas of the GMPs due to a lack of appropriate arrangements clarifying responsibilities for ensuring compliance with product specifications, QA release and stability.

While the USFDA cGMPs for Dietary Supplements do not specifically require that contracts be in place, they do assign the responsibility regarding meeting specifications with the person releasing the product to the market. For example, "Before you package or label a product that you receive for packaging or labelling as a dietary supplement (and for distribution rather than for return to the supplier); you must visually examine the product and have documentation to determine whether the specifications that you established under Sec. 111.70 (f) are met."

The PIC/S Guide for Good Manufacturing Practices for Medicinal Products outlines requirements for contract manufacturing and analysis to establish clear responsibilities through the establishment and use of written contracts.

Lack of Accountability of Product Licence Holders for Assuring Product Quality, Especially in Relation to Product Stability Requirements

- It is proposed that Part 1, Product Licence, of the NHPR be revised to assign product licence applicants the responsibility for ensuring information or data is available to support the expiry date on the label of the NHP.

- It is proposed that, if requested by Health Canada as part of a post-license compliance verification process, the product licence holder would be required to submit information supporting the expiry date assigned to an NHP. Health Canada would not request or review this information during either the site licence or product licence application process.

Currently, Part 3 of the NHPR puts the onus on manufacturers, packagers, labellers, importers and distributors to provide a level of assurance as to the quality of the finished product. However, Part 3 is silent with regards to the role of the Product Licence Holder.

The current GMP standards for stability (sections 52, 53(g) & 56(e) of the NHPR) requires manufacturers and importers to provide evidence to demonstrate that the product will continue to comply with its specifications after being packaged for sale and stored at its recommended storage conditions. As a result, in order to attain a site licence, manufacturers and importers must currently provide data or a scientific rational from at least one product demonstrating it meets its specifications at the end of its assigned shelf life.

Through experience, the NHPD has found that importers and contract manufacturers often struggle to provide evidence to demonstrate compliance with the stability requirements. In many cases, the issue stems from undefined responsibilities between the importers and their foreign suppliers or contract manufacturers and their clients as to who is responsible for generating the necessary data. This calls into question the objective of having the stability section included in the part of the NHPR that requires it be evaluated by the NHPD as part of the site licensing process. Requiring a contract manufacturer to demonstrate a product meets its specification at the end of its shelf life is not of itself a true indicator that GMPs may or may not be being followed.

Lack of Raw Material Control Requirements

- It is proposed that the NHPR be revised to require that manufacturers, packagers and labellers achieve greater control over raw materials by establishing standards of quality or specifications and establishing material supplier reliability by means of appropriate supplier qualification.

The current standards do not specifically require the control of raw, packaging or labelling materials. Unlike the approaches taken by Health Canada's international partners, the NHPR do not require site licence holders to establish a specification or standard for the materials used in the manufacturing, packaging and labelling of their NHP. Although there are sections in the NHPR that require materials to be approved by a Quality Assurance Person before being used in the activity, and that records of any material testing should be kept by the manufacturer, package and labeller, they do not require that specifications outlining the quality standards be established and met for materials used in the activity. Due to the way in which the GMP standard is written, it could be interpreted that a manufacturer, for example, could rely on certificates of analysis from their supplier without having established material specifications or without having any assurances regarding the reliability of the supplier's tests or examinations through a qualification program.

Insufficient Manufacturing, Packaging and Labelling Control Requirements

- It is proposed that Part 3 of the NHPR be amended to include a principle-based standard that requires manufacturers, packagers and labellers to maintain control over their operations and processes in accordance with the Master Production Document for the NHP.

- It is proposed that the current definition of the Master Production Document be revised and included in either the NHPR or the GMP guidance document.

The Master Production Document is a critical document designed to ensure that products are consistently produced and controlled to meet their specifications. Currently, the NHPR require only manufacturers to maintain the Master Production Document at their site. These requirements do not currently extend to packagers and labellers. The standard also does not make it clear that manufacturing, packaging and labelling activities should be performed in accordance with this critical document.

Lack of Requirement for Sampling during the Production Process

- It is proposed that the NHPR be amended to require manufacturers, packagers and labellers to establish predetermined sampling procedures that are representative of the batches of material from which they are taken.

- It is proposed that the sampling requirements be included or referenced in the Master Production Document definition.

Currently, the NHPR do not specify whether procedures for sampling during the production process are required in order to ensure that representative samples are taken whenever samples are required for testing. Sampling is an important operation in which only a small fraction of a batch is taken so that conclusions can be drawn on the quality of the entire batch of material or finished product. Sampling procedures that identify, at a minimum, the quantity of sample to be taken, where the sample should be taken from, and that are designed to prevent contamination of materials, ensures samples are representative of the batches they are taken from.

Insufficient Requirements to Make and Keep Records

- It is proposed that Sections 53 (c), (d), 54 (a) and 56 (c) of the NHPR be amended in

order to clarify that records are required to demonstrate that specifications are met.

- It is proposed that the NHPR be amended to require that records of finished product testing be maintained at either the manufacturer's, packager's or labeller's site, depending on who releases the product to market.

- It is proposed that the NHPR be amended to require that records such as material specifications, sanitation records, complaint handling records, written agreements, when applicable, standard operating procedures, and evidence that personnel are appropriately qualified be made and kept by manufacturers, packager, labellers and importers, as appropriate .

- It is proposed that the NHPR be amended to include provisions for manufacturers, packagers and labellers to maintain copies of batch records or evidence demonstrating that each lot or batch of NHP was manufactured, packaged, labelled and stored in accordance with the Master Production Document, with importers being required to have access to this documentation.

The current standards outlined in the NHPR regarding records that are required to be produced and kept do not adequately capture the necessary documentation that is required in order to demonstrate that a product has been produced in accordance with GMPs.

In order to help clarify the requirements, it is proposed that the NHPR be amended to include more prescriptive language in the records section.

Lack of Requirement for Specific Control over Laboratory Operations

- It is proposed that the NHPR be amended to outline the minimum requirements a testing facility would need to demonstrate in order to show a level of control over their operations.

While the results of testing of raw material and finished product are often used as evidence to demonstrate a product meets its specifications, there is currently no requirement for testing to be performed in a facility that is able to demonstrate they have sufficient controls in place to validate the results.

In order to provide a mechanism for ensuring a greater level of control, and confidence that a product meets its specifications when test results are used, it is proposed that the NHPR be amended to outline those characteristics a testing laboratory would need to demonstrate, including:

- Standard Operating Procedures (for training, calibration, out of specification, etc.);
- Appropriate personnel;
- Appropriate equipment;
- Accreditation from an independent organisation (e.g., Health Canada drug Establishment Licence, International Organization for Standardization (ISO), Standards Council of Canada, etc.); and
- A calibration program.

It would be the responsibility of the manufacturer, packager, labeller, importer, as the case may be, who contracts out the testing activity to assess the testing facilities compliance to these characteristics, as part of their supplier qualification program.

The above approach is similar to that taken in the US with the cGMPs.

CHAPTER 4: INFORMATION LINKAGES

The Current Process - Product Licensing

In order to obtain a Product Licence, an application must be submitted via the electronic On-Line Solution or through completion of a paper application form. Applicants are required to provide specific information about a product's formulation, specifications, recommended use or purpose as well as information to support its safety and efficacy; however, it isn't mandatory for an applicant to declare a manufacturer, packager and labeller at the time of application. Rather, the NHPR require product licensees to provide this information prior to commencing sale of the product.

The current system evolved following stakeholder feedback received during the original drafting of the NHPR. It was intended that a product licence applicant would provide manufacturer, packager, labeller and importer information at the time of application; however, this was changed on the basis that this information was not always available at the product licence application stage.

Experience has shown, however, that product licence holders quite often fail to provide Health Canada with manufacturer, packager, labeller and importer information. Given there are challenges in enforcing this requirement, and as there is no easy way for the NHPD to know when a product is actually made available for sale in Canada, an important piece of regulatory information is often missing.

There has always been, and there still remains, an intention for there to be a direct link between products and the site(s) producing the products. Such a link helps ensure products are produced in accordance with GMPs - i.e., in licensed facilities, and meet appropriate standards of quality. Given the length of time that has passed since the NHPR first came into effect, and the number of sites that have been licensed, including foreign sites annexed to importer licences, the concerns raised by stakeholders during original drafting of the NHPR should no longer be as important or valid.

The Current Process - Site Licensing

Health Canada issues a site licence to Canadian manufacturers, packagers, labellers and importers if they fulfill the requirements set out in Parts 2 and 3 of the NHPR. Products manufactured, packaged and/or labelled outside of Canada at a foreign site and

imported into Canada are required to be undertaken in facilities that have demonstrated to Health Canada that they meet the same standards of GMPs as Canadian manufactures, packagers and labellers. If a foreign site is able to demonstrate it meets the NHPR GMP quality requirements it is then annexed to the Importer's Site Licence.

Every time more than one importer wishes to import a product that is manufactured, packaged or labelled at the same foreign site, each importer is required to provide documentation to Health Canada demonstrating the facility's ability to meet the GMP standards – duplication that has resource implications for Health Canada, importers and the foreign site. While the NHPD has implemented, the Foreign Site Reference Number process to help reduce duplication when assessing foreign sites, to date only a very small number of foreign sites have chosen to utilize this process.

In addition to duplication related to importer site licensing and annexing of foreign sites, duplication also exists when product licence applicants are required to supply a product specification at the time of product licensing as well as manufacturers being required to provide product specifications as part of the site licence process. Through developing a stronger link between products and sites, this duplication of activity should no longer be necessary.

Challenges with the Current System

Currently, information collected during the product licence application process does not allow for the accurate identification of those sites associated with the manufacturing, packaging and labelling of an NHP. This has lead to gaps in the regulatory information relating to products and their associated sites, which limits Health Canada's ability to respond appropriately when issues arise.

In addition to the above, while the application processes for product and site licensing are intentionally separate, the current system has lead to:

- Duplication of activities, particularly in relation to the annexing of foreign sites to importers' licences, and assessment of product specifications, which impacts both product licence applicants and site licence applicants; and

- An overly complicated regulatory system that was intended to be balanced in order to manage the different risks presented by the wide range of NHPs.

Proposed Changes - Creating Better Information Linkages

- It is proposed that the NHPD publishes and maintains on its website a list of licensed manufacturers, packagers, labellers and importers. The list will also include those foreign sites that have been assessed by Health Canada as meeting the standards of GMPs who specifically indicate they would like to be included on the list. *Importantly, there will be no publicly available information linking manufacturers, packagers and labellers to specific NHPs.*
- It is proposed that the list be incorporated into the Product Licence Online Application system - the NHP Online Solution.
- It is proposed that the NHPR be amended to make it mandatory that a Product Licence Application contain manufacturer(s), packager(s) and labeller(s) (and importer(s) if applicable) information before a product licence is issued.
- It is proposed that the NHPR be amended to permit a 'conditional licence' to be issued when no manufacturer(s), labeller(s) and packager(s) (and importer(s) if applicable) information is provided at the time of product licence application. Authority to sell would only be given after the information is provided to Health Canada.
- It is proposed that only licensed Canadian manufacturers, packagers, labellers and importers site licences be available for selection and inclusion in a Product Licence Application.
- It is proposed that Health Canada develop an electronic system to allow unique clearance numbers to be assigned to foreign sites that have been assessed as meeting the necessary GMP requirements. The unique number would be provided to the Product Licence Applicant by the foreign site, and entered into the product licence application system by the Product Licence Applicant and validated electronically.

It is important to emphasize that there would be no publicly available information linking manufacturers, packagers and labellers to individual products. The proposed list is intended to indicate the name and address of the manufacturer, packager, labeller and importer, the activities they are licensed to undertake and the types of products they are licensed to produce (e.g., sterile, non-sterile).

In order to ensure appropriate linkage of foreign sites to specific products, Health Canada proposes to develop an IT mechanism that allows foreign sites that have been assessed as meeting the GMP standards, to be issued a unique clearance number. The clearance number would be required to be entered in the electronic On-Line Solution when a product licence application is being completed. The On-Line solution would electronically validate the unique clearance number against the applicant's identity and the foreign site's identity.

While it is recognized that a product licence applicant may not know who will ultimately manufacture, package, label and/or import their product at the product licence application stage, they are required to have their products manufactured, packaged, labelled and/or imported by licensed sites. Therefore, in order to strengthen the information linkages between individual products and the sites undertaking their manufacturing, packaging, labelling and importing, a system that allows for rapid amendment to product records in the event a different licensed site is used at any time in the future, should address stakeholder concerns while closing the information gap and ensuring up-to-date information is available.

In the event that site information is not available at the time a product licence application is submitted, and the applicant decides to not include any information relating to the product's manufacturing, packaging and labelling, (and importation if applicable) it is proposed that a 'conditional licence' be issued. A conditional licence would be granted following a positive outcome of the review of a products safety and efficacy information but requires the products manufacturer(s), packager(s), labeller(s) and/or importer(s) information to be provided before a full product licence can be issued.

Products receiving a conditional licence would not be authorized to sell until Health Canada was informed of the site information and a full product licence has been issued.

CHAPTER 5: CONCLUSION

Canadians expect that NHPs available on the Canadian market will only contain the ingredients stated on the label at the levels indicated; that the products will do what they claim they will; and not cause any unintended health problems. The proposals outlined in this document are meant to stimulate feedback from stakeholders regarding ways in which Health Canada can enhance the current site licensing framework to ensure that those responsible for selling NHPs in Canada are able to demonstrate they have appropriate quality controls over the production and supply of their products. With these proposals, Health Canada would also have strengthened information linkages between products and the sites undertaking their manufacturing, packaging, labelling, or importing.

Since the Regulatory Review in 2007, Health Canada has continued to hear from stakeholders that changes are needed to the way in which site licences are issued to manufacturers, packagers, labellers and importers of NHPs. In particular, there is a desire to see a move away from the existing self-assessment licensing model to one that includes an on-site audit conducted by an independent entity in order to verify and confirm the ability of manufacturers, packagers, and labellers to comply with standards of GMPs.

This new RBASL initiative aims to develop a strengthened site licensing system that will provide a greater level of assurance that NHPs sold in Canada meet appropriate standards of quality, safety and efficacy.

The establishment of the Technical Working Group was the first step in the continuous consultation between Health Canada and its stakeholders on this initiative. Comments received from stakeholders regarding this concept paper will be considered before any decisions are made by Health Canada.

Health Canada intends to continue its collaboration with Canadians, and other partners, in developing an appropriate framework for site licensing of NHPs.

Annex 1: OUTLINE OF PROPOSED CHANGES

Proposed Changes - Site Licensing Model

Below is an outline of the changes proposed to the current site licensing process for manufacturers, packagers, labellers and importers. The proposed changes should be read in conjunction with the information contained in Chapter 2, which provides the context and rationales for each of the proposed changes.

The proposals have been numbered to facilitate discussion.

1. It is proposed that the existing site licensing model be changed to require domestic and foreign manufacturers, packagers and labellers of NHPs to provide a report or certificate as evidence that the activities undertaken are in accordance with the standards of Good Manufacturing Practices. The report and/or certificate would be issued following an on-site audit of the facility.

2. For manufacturers, packagers and labellers of non-sterile products, the on-site audit would be conducted by a Health Canada recognised 3rd party auditing body or other competent authority.

3. For manufacturers, packagers and labellers of sterile products, the on-site audit would be conducted by Health Canada inspector or other recognised competent authority.

4. It is proposed that the NHPR be amended to allow for the new licensing model to utilise the results from on-site audits conducted by other recognised competent authorities, such as key international regulatory authorities. Such an approach would require an appropriate recognition process and confidence building phase to be undertaken and would ideally result in reciprocal recognition by the foreign regulator of the site licence issued by Health Canada (e.g. through the establishment of a Mutual Recognition Agreement)

5. It is proposed that an application for a licence to import NHPs continue to be undertaken via a Quality Assurance Report (i.e., self-assessment licensing system). Importantly, however, foreign manufacturers, packagers and labellers will be required to demonstrate the same level of compliance as Canadian manufacturers,

packagers and labellers. That is, foreign sites will be required to have undergone an on-site audit by either a Health Canada recognised 3rd party auditing body or other recognised competent authority before they can supply NHPs to Canada.

6. It is proposed that a random post-licence on-site GMP compliance verification program be developed by Health Canada to proactively check the information supplied by importers at the time of licensing.

7. It is proposed that a site licence be valid for a period of:
   7.1. Three years for manufacturers, packagers and labellers of non-sterile NHPs;
   7.2. Two years for manufacturers, packagers and labellers of sterile NHPs; and
   7.3. Three years for importers of non-sterile or sterile NHPs.

8. It is proposed that Health Canada develop, administer and maintain responsibility for the process of recognising 3rd party auditing bodies.

Proposed Changes - GMP Standards

Below is an outline of the changes proposed to the standards of Good Manufacturing Practices (GMPs) to apply to manufacturers, packagers, labellers and importers of NHPs. The proposed changes should be read in conjunction with the information contained in Chapter 3, which provides the context and rationales for each of the proposed changes.

9. It is proposed that the NHPR be amended to place greater responsibility on the product licence holder for any activities that they contract to other parties for the manufacturing, labelling, packaging and importation of the NHP.

10. It is proposed that product licence holders, manufacturers, packagers, labellers, and importers correctly define, agree, and control contracted activities through established written agreements that clarify the roles and responsibilities between parties.

11. It is proposed that Part 1, Product Licence, of the NHPR be revised to assign product licence applicants the responsibility for ensuring information or data is available to support the expiry date on the label of the NHP.

12. It is proposed that, if requested by Health Canada as part of a post-license

compliance verification process, the product licence holder would be required to submit information supporting the expiry date assigned to an NHP. Health Canada would not request or review this information during either the site licence or product licence application process.

13. It is proposed that the NHPR be revised to require that manufacturers, packagers and labellers achieve greater control over raw materials by establishing standards of quality or specifications and establishing material supplier reliability by means of appropriate supplier qualification.

14. It is proposed that Part 3 of the NHPR be amended to include a principle-based standard that requires manufacturers, packagers and labellers to maintain control over their operations and processes in accordance with the Master Production Document for the NHP.

15. It is proposed that the current definition of the Master Production Document be revised and included in either the NHPR or the GMP guidance document.

16. It is proposed that the NHPR be amended to require manufacturers, packagers and labellers to establish predetermined sampling procedures that are representative of the batches of material from which they are taken.

17. It is proposed that the sampling requirements be included or referenced in the Master Production Document definition.

18. It is proposed that Sections 53 (c), (d), 54 (a) and 56 (c) of the NHPR be amended in order to clarify that records are required to demonstrate that specifications are met.

19. It is proposed that the NHPR be amended to require that records of finished product testing be maintained at either the manufacturer, packager or labeller's site, depending on who releases the product to market.

20. It is proposed that the NHPR be amended to require that records such as material specifications, sanitation records, complaint handling records, written agreements, when applicable, standard operating procedures, and evidence that personnel are appropriately qualified be made and kept by manufacturers, packager, labellers and importers, as appropriate

21. It is proposed that the NHPR be amended to include provisions for manufacturers, packagers and labellers to maintain copies of batch records or evidence demonstrating that each lot or batch of NHP was manufactured, packaged, labelled and stored in accordance with the Master Production Document, with importers being required to have access to this documentation.

22. It is proposed that the NHPR be amended to outline the minimum requirements a testing facility would need to demonstrate in order to show a level of control over their operations.

Proposed Changes - Information Linkages

Below is a summary of the changes proposed to strengthen the information held by Health Canada concerning the manufacturers, packagers, labellers and importers of NHPs. The proposals are designed to reduce administrative duplication and regulatory information gaps and should be read in conjunction with information contained in Chapter 4, which provides the context and rationales for each of the proposed changes.

23. It is proposed that the NHPD publish and maintain on its website a list of licensed manufacturers, packagers, labellers and importers. The list will also include those foreign sites that have been assessed by Health Canada as meeting the standards of GMPs who specifically indicate they would like to be included on the list. *Importantly, there will be no publicly available information linking manufacturers, packagers and labellers to specific NHPs.*

24. It is proposed that the list be incorporated into the Product Licence Online Application system – the NHP Online Solution.

25. It is proposed that the NHPR be amended to make it mandatory that a Product Licence Application contain manufacturer(s), packager(s), and labeller(s) (and importer(s) if applicable) information before a product licence is issued.

26. It is proposed that the NHPR be amended to permit a 'conditional licence' to be issued when no manufacturer(s), labeller(s) and packager(s) (and importer(s) if applicable) information is provided at the time of product licence application. Authority to sell would only be given after the information is provided to Health Canada.

27. It is proposed that only licensed manufacturers, packagers, labellers site licences be available for selection in a Product Licence Application.

28. It is proposed that Health Canada develop an electronic system to allow unique clearance numbers to be assigned to foreign sites that have been assessed as meeting the necessary GMP requirements. The unique number would be provided to the Product Licence Applicant by the foreign site, and entered into the product licence application system by the Product Licence Applicant and validated electronically.