Health Canada Santé Canada

December 20, 2013

Notice

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Final Guidance Document: *Schedule A / Section 3 to the Food and Drugs Act*

This guidance is a revision of the previous 2003 *Schedule A and Section 3: Guidance Document* and includes information pertaining to the regulatory amendments which came into force on June 1st, 2008. These amendments exempt natural health products and nonprescription drugs from the prohibition on labelling and advertising of preventative claims to the general public for diseases, disorders, or abnormal physical states listed in Schedule A to the *Food and Drugs Act*. This guidance also includes a description of the data that will be required in support of these Schedule A preventative claims.

Furthermore, on June 19th, 2013, Health Canada published in *Canada Gazette*, Part II amendments to the *Food and Drug Regulations*. The *Regulations Amending Certain Regulations concerning Prescription Drugs* (Repeal of Schedule F to the *Food and Drug Regulations*) provides for the repeal of Schedule F and incorporation by reference of a list of prescription drugs. This regulatory amendment comes into effect on December 19, 2013. As a result of this amendment, a number of existing Guidance Documents have been identified that make reference to Schedule F and the regulatory process for assigning prescription status. Due to the replacement of Schedule F with the Prescription Drug List and the replacement of a regulatory process with an administrative process, the identified Guidance Documents required updating. Accordingly, the Guidance Document, ***Schedule A / Section 3 to the Food and Drugs Act*** has been updated. The Document Change Log has been revised to reflect the changes.

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Health Canada Santé Canada

GUIDANCE DOCUMENT

Schedule A and Section 3 to the *Food and Drugs Act*

Published by authority of the
Minister of Health

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the health-related risks and benefits to health products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : *Ligne directrice : Annexe A et article 3 de la Loi sur les aliments et les drogues*

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Document Change Log			
Version	Schedule A and Section 3 to the *Food and Drugs Act*	**Replaces**	Schedule A and Section 3 to the *Food and Drugs Act*
Date	December 19, 2013	**Date**	October 19, 2010

Change	Nature of and/or Reason for Change
1) July 23, 2008 There were several revisions to content (including addition of an appendix with the data requirements for preventative claims) and an extensive reorganization of the document.	The February 2003 document, *Schedule A and Section 3: Guidance Document,* was revised in order to reflect regulatory amendments that came into force June 1, 2008 and was posted in draft form for public consultation. At the same time the guidance document was re-organized to match the current standardized guidance document format.
2) October 19, 2010 Some revisions throughout the document and appendices.	The guidance document was revised and finalized subsequent to the 2008 consultation.
3) December 19, 2013 Some revisions throughout the document and appendices.	Changes were made to the document to reflect an amendment in the *Food and Drug Regulations* that replaced Schedule F with Prescription Drug List.

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1 INTRODUCTION

This guidance provides information relating to the interpretation and enforcement of section 3 and Schedule A to the *Food and Drugs Act* (FDA), as well as sections A.01.067 and A.01.068 of the *Food and Drug Regulations* (FDR) and sections 103.2 and 103.3 of the *Natural Health Products Regulations* (NHPR) (which exempt natural health products (NHPs) and nonprescription drugs from the FDA's general prohibition on labelling and advertising of preventative claims for the diseases listed in Schedule A). Nonprescription drugs in this guidance document include those drugs that are regulated under the FDA and the FDR as nonprescription drugs and are also regulated as Class A precursors under the *Precursor Control Regulations* of the *Controlled Drugs and Substances Act* (CDSA).

1.1 Policy Objectives

To ensure that products with claims subject to the prohibitions of section 3 and Schedule A are appropriately labelled and/or advertised, thus encouraging individuals to seek the advice of health care professionals and/or practitioners where circumstances so warrant.

1.2 Policy Statements

Health Canada maintains that direct-to-consumer advertising should not be allowed for prescription drugs, nor for products that are subject to the prohibitions contained in section 3 of the *Food and Drugs Act* and its *Regulations*.

1.3 Scope and Application

This guidance describes section 3 and Schedule A as they relate to drugs (pharmaceuticals, biologics and NHPs), food, cosmetics and medical devices. The current list of Schedule A diseases is found in the *Food and Drugs Act* and is appended here for convenience as are some of the other relevant statutory provisions referenced in this document (Appendix A).

Definitions of some of the terms used in this document are provided in Appendix B. When referring to labelling and advertising information, this document uses the term 'claim' which includes the product's therapeutic indication. The term 'disease' is used as a general term to include 'diseases, disorders, or abnormal physical states'. In terms of advertising, information packages, brochures and other material in any medium may be considered to be advertising for a drug product when displayed in close proximity to, or distributed with products containing the same ingredient, in the same retail outlet. (Refer to Health Canada's policy "The Distinction between Advertising and other Activities" at http://www.hc-sc.gc.ca/dhp-mps/advert-publicit/pol/actv_promo_vs_info-eng.php for more details.)

Pursuant to the regulatory amendments that came into force in 2008 that exempted the section 3 prohibitions on labelling NHPs and nonprescription drugs with preventative claims, some sponsors may wish to market their products for such purposes. However, it is to be noted that market authorization for labelling claims is still required pursuant to the relevant regulatory requirements of the NHPR and FDR respectively. As such, guidance on Health Canada's expectations in terms of the type of data necessary to support market approval of claims for the prevention of diseases of a serious nature such as those included on Schedule A are appended for ease of reference (Appendix C).

1.4 Background

1.4.1 Clarification of the General Prohibition for Schedule A and Section 3 to the *Food and Drugs Act*

Section 3 prohibits any label claim or advertisement that has *both of the following characteristics:*

- is aimed at the general public; and
- contains treatment, preventative or cure claims for a Schedule A disease.

Consideration should also be given to sections 5, 9, and 20 of the *Food and Drugs Act* which require that label claims and advertisements be truthful and not misleading or deceptive.

1.4.2 Clarification of the Exemption to the Preventative Claims Prohibition for NHPs and Nonprescription Drugs

Section 3 of the FDA has not changed. However, as of June 1st, 2008, sections A.01.067 and A.01.068 of the FDR and sections 103.2 and 103.3 of the NHPR exempt NHPs and nonprescription drugs from the FDA's section 3 general prohibition on labelling and advertising of **preventative** claims for Schedule A diseases. A simplification of how to identify circumstances where prohibitions apply is provided by the flowchart in Appendix D.

The regulatory amendment to exempt NHPs and nonprescription drugs under the FDA from the section 3 preventative prohibition for Schedule A diseases does not include:

- drugs listed or described in the Prescription Drug List; and
- drugs included in any of Schedules I though V to the *Controlled Drugs and Substances Act* (CDSA) (pursuant to section A01.066 of the FDR).

Food, medical devices, and cosmetics also continue to be prohibited from carrying preventative claims in labelling and advertising to the general public for diseases remaining in Schedule A (unless otherwise permitted in other provisions in the FDA or its regulations).

Food

Food is not included in the preventative exemption in the 2008 regulatory amendment because section B.01.601 of the FDR already provides that a food with a label or advertisement that carries a statement or claim set out in the table following section B.01.603 is exempt from the provisions of the FDA, including section 3, and the FDR with respect to drugs, where applicable.

Medical devices

Medical devices are not included in the preventative exemption since class I and II medical devices do not undergo pre-market review nor are their claims authorized by Health Canada. Class I medical devices do not have a license requirement and are not subject to pre-market review. Class II medical devices do have a license requirement, but are licensed by attestation of safety and effectiveness by the manufacturer. Class III and IV medical devices undergo pre-market review, but generally require the intervention of a practitioner. Some in-vitro diagnostic devices are designated class III for home-use, but since their use is as a diagnostic (not as a preventative, treatment, nor cure), they were never subject to the section 3 prohibition.

Condoms are exempt from section 3 pursuant to section 24(1) of the *Medical Devices Regulations* (MDR) and may be advertised and sold to the general public for the purpose of preventing the transmission of sexually transmitted diseases if the advertisement and the label of the condom claim only that the condom reduces the risk of transmitting sexually transmitted diseases.

Cosmetics

Cosmetics are defined in the FDA as "any substance or mixture of substances manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth, and includes deodorants and perfumes". Cosmetics are not permitted to carry drug claims, therefore cosmetics are not included in the preventative exemption. If they carry drug claims, the product is either regulated as a drug or an NHP as explained in sections 2.1 and 2.2 of the “Guidelines for Cosmetic Advertising and Labelling Claims” posted on the Health Canada website, and as explained in the “Guidelines for Cosmetics Manufacturers, Importers and Distributors” also posted on the Health Canada website.

2 GUIDANCE FOR IMPLEMENTATION

2.1 General Public

The prohibition in section 3 applies to sale or advertising directed to the general public. “General public” does not include health care professionals and/or practitioners. Consequently, advertising to these individuals - as well as to health professional associations such as the Canadian Pharmacists Association and the Canadian Veterinary Medical Association - through a print ad in a professional journal for example, is not prohibited by section 3.

2.2 Treatment, Preventative, or Cure

Section 3 uses the specific words “treatment”, “preventative”, and “cure”. However, it also prohibits certain claims that do not include these exact words. The broad terms "preventative" and "treatment" are terms used in the FDA and are interpreted by Health Canada to encompass "risk reduction" and "symptomatic treatment," respectively. Reference to a Schedule A disease may be permitted in the context of precautions or contraindications as part of directions for use.

2.3 References to Schedule A Diseases

Section 3 prohibits the labelling and advertising to the general public of products that refer to Schedule A diseases. It is to be noted that it is not only explicit references to Schedule A diseases that will be prohibited by section 3. Rather some claims that do not expressly mention a Schedule A disease may also contravene section 3. The following must be considered to determine whether or not a claim is acceptable: (a) diseases considered to be synonymous or subsets of Schedule A diseases; (b) certain symptoms and signs of Schedule A diseases; and (c) risk factors for Schedule A diseases.

2.3.1 Synonyms and subsets

Some diseases are generally considered to be synonyms or subsets of the diseases listed in Schedule A and as such, these synonyms and subsets are subject to the section 3 prohibitions. For example, ‘syphilis’ is a subset of ‘sexually transmitted diseases’, and ‘hardening of the arteries’ is a synonym for ‘arteriosclerosis’. Appendix E provides some synonyms for Schedule A diseases.

2.3.2 Symptoms and signs

Many Schedule A diseases are closely associated with symptoms or signs, such that reference to them implies the disease itself. A claim to treat, prevent, or cure a description of a Schedule A disease (that is [i.e.], signs or symptoms) is considered to be a claim to treat, cure, or prevent the disease itself. For example, a claim to treat the symptoms (or a

specific symptom) of depression would be considered to be a claim to treat depression. Accordingly, such a claim is prohibited by section 3.

In rare cases, a claim that mentions the symptomatic prevention or treatment of a Schedule A disease may not be considered to fall under the prohibitions of section 3 if the claim meets certain criteria including that it: does not lead the consumer to believe the disease itself is prevented, treated or cured; does not relate to a situation where self-treatment is ill-advised; does not relate to a symptom listed on Schedule A (for example [e.g.], convulsions); and relates to a non-specific type of symptom (e.g., pain) common to many diseases.

2.3.3 Risk factors

Section 3 should be interpreted to allow references to risk factors common to a number of diseases including Schedule A diseases, if there is no reference to the Schedule A disease itself. For example, a claim such as “this product helps lower cholesterol levels” which may relate to arteriosclerosis (a Schedule A disease) as well as to other diseases not listed on Schedule A, would not be considered to be a reference to a Schedule A disease and therefore would not be prohibited by section 3.

APPENDIX A - Statutory Provisions

Schedule A, *Food and Drugs Act*

Acute alcoholism
Acute anxiety state
Acute infectious respiratory syndromes
Acute psychotic conditions
Acute, inflammatory and debilitating arthritis
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
Septicaemia
Sexually transmitted diseases
Strangulated hernia
Thrombotic and embolic disorders
Thyroid disease
Ulcer of the gastro-intestinal tract

Section 3, *Food and Drugs Act*

3. (1) No person shall advertise any food, drug, cosmetic or device to the general public as a treatment, preventative or cure for any of the diseases, disorders or abnormal physical states referred to in Schedule A.

(2) No person shall sell any food, drug, cosmetic or device
(a) that is represented by label, or

(b) that the person advertises to the general public

as a treatment, preventative or cure for any of the diseases, disorders or abnormal physical states referred to in Schedule A.

(3) Except as authorized by regulation, no person shall advertise to the general public any contraceptive device or any drug manufactured, sold or represented for use in the prevention of conception.

Section 5*, Food and Drugs Act*

5. (1) No person shall label, package, treat, process, sell or advertise any food in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety.

Section 9*, Food and Drugs Act*

9. (1) No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety.

Section 20*, Food and Drugs Act*

20. (1) No person shall label, package, treat, process, sell or advertise any device in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its design, construction, performance, intended use, quantity, character, value, composition, merit or safety.

Section A.01.066*, Food and Drug Regulations*

Sections A.01.067 and A.01.068 do not apply to

(a) a drug included in Schedule I, II, III, IV or V to the *Controlled Drugs and Substances Act*; or

(b) a prescription drug.

Section A.01.067*, Food and Drug Regulations*

A drug is exempt from subsection 3(1) of the Act with respect to its advertisement to the general public as a preventative, but not as a treatment or cure, for any of the diseases, disorders or abnormal physical states referred to in Schedule A to the Act.

Section A.01.068, *Food and Drug Regulations*

A drug is exempt from subsection 3(2) of the Act with respect to its sale by a person where the drug is represented by label or is advertised by that person to the general public as a preventative, but not as a treatment or cure, for any of the diseases, disorders or abnormal physical states referred to in Schedule A to the Act.

Section C.01.010, *Food and Drug Regulations*

If it is necessary to provide adequate directions for the safe use of a parenteral drug or prescription drug that is used in the treatment or prevention of any disease, disorder or abnormal physical state mentioned in Schedule A to the Act, such diseases, disorders or abnormal physical state may be mentioned on the labels and inserts accompanying the drug and, in that respect, the drug is exempt from subsections 3(1) and (2) of the Act.

Section C.01.044, *Food and Drug Regulations*

If a person advertises a prescription drug to the general public, the person shall not make any representation other than with respect to the brand name, the proper name, the common name and the price and quantity of the drug.

Section C.01.625, *The Food and Drug Regulations*

Contraceptive drugs that are manufactured, sold or represented for use in the prevention of conception and that are not prescription drugs may be advertised to the general public.

Section 103.2, *Natural Health Products Regulations*

A natural health product is exempt from subsection 3(1) of the Act with respect to its advertisement to the general public as a preventative, but not as a treatment or cure, for any of the diseases, disorders or abnormal physical states referred to in Schedule A to the Act.

Section 103.3, *Natural Health Products Regulations*
A natural health product is exempt from subsection 3(2) of the Act with respect to its sale by a person where the natural health product is represented by label or is advertised by that person to the general public as a preventative, but not as a treatment or cure, for any of the diseases, disorders or abnormal physical states referred to in Schedule A to the Act.

APPENDIX B - Definitions

The following are taken from the *Food and Drugs Act* or its *Regulations*, except as otherwise indicated.

Advertisement: includes any representation by any means whatever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device.

Cosmetic: includes any substance or mixture of substances manufactured, sold or represented for use in cleansing, improving, or altering the complexion, skin, hair or teeth, and includes deodorants and perfumes;

Device: means any article, instrument, apparatus or contrivance, including any component, part or accessory thereof, manufactured, sold or represented for use in

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
(b) restoring, correcting or modifying a body function or the body structure of human beings or animals,
(c) the diagnosis of pregnancy in human beings or animals, or
(d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring,

and includes a contraceptive device but does not include a drug;

Drug: includes any substance or mixture of substances manufactured, sold or represented for use in

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
(b) restoring, correcting or modifying organic functions in human beings or animals, or
(c) disinfection in premises in which food is manufactured, prepared or kept;

Food: includes any article manufactured, sold, or represented for use as food or drink for human beings, chewing gum and any ingredient that may be mixed with food for any purpose whatever;

Health Care Professional: means a person who is entitled under the laws of a province to provide health services in the province;

Label: includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package;

Natural Health Product: means 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

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

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.

SCHEDULE 1 - INCLUDED NATURAL HEALTH PRODUCT SUBSTANCES

1. A plant or a plant material, an alga, a bacterium, a fungus or a non-human animal material
2. An extract or isolate of a substance described in item 1, the primary molecular structure of which is identical to that which it had prior to its extraction or isolation
3. Any of the following vitamins:
   biotin
   folate
   niacin
   pantothenic acid
   riboflavin
   thiamine
   vitamin A
   vitamin B6
   vitamin B12
   vitamin C
   vitamin D
   vitamin E
   vitamin K1
   vitamin K2
4. An amino acid
5. An essential fatty acid
6. A synthetic duplicate of a substance described in any of items 2 to 5
7. A mineral
8. A probiotic

SCHEDULE 2 - EXCLUDED NATURAL HEALTH PRODUCT SUBSTANCES

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

Precursor Drug: means a substance included in Schedule VI of the CDSA (defined in the *Controlled Drugs and Substances Act*);

Practitioner: "practitioner" means a person who
(a) is entitled under the laws of a province to treat patients with a prescription drug, and
(b) is practising their profession in that province;

Sell: "sell" includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration.

APPENDIX C - Data Requirements for Market Authorization

Requirements for Schedule A Preventative Claims for Nonprescription Drugs and Natural Health Products

1. Scope

Pursuant to the regulatory amendments that came into force in 2008 that exempted the section 3 prohibitions on labelling natural health products and nonprescription drugs with preventative claims, some sponsors may wish to market their products for such purposes. However, it is to be noted that market authorization for labelling claims is still required pursuant to the relevant regulatory requirements of the NHPR and FDR respectively. As such, this appendix represents the expectations of the Therapeutic Products Directorate (TPD), the Biologics and Genetic Therapies Directorate (BGTD), and the Natural Health Product Directorate (NHPD) regarding the nature of the scientific evidence necessary to support market authorization of a preventative claim for a Schedule A disease, disorder or abnormal physical state that may be proposed for a nonprescription drug that is regulated by TPD or BGTD or a natural health product regulated by NHPD.

2. Submissions to Health Canada for Market Authorization

As is required for any therapeutic claim, an application for market authorization for preventative claims being proposed with respect to a Schedule A disease must be filed with TPD or BGTD for nonprescription drugs, or with NHPD for natural health products. In the case of nonprescription drugs that are regulated by TPD, a preventative claim for an existing product that is currently regulated under Division 1 of the *Food and Drug Regulations* may render that product a New Drug, subject to Division 8 of the aforementioned regulations. In addition, either a nonprescription drug or a natural health product with Schedule A preventative claims may be deemed to require prescription status as outlined in the guidance document entitled "Determining Prescription Status for Human and Veterinary Drugs" (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/pdl-ord/pdl_gd_ord_ld-eng.php).

Prior to filing the drug submission or natural health product application for market authorization, it is recommended that the submission sponsor / applicant meet with the relevant Directorate to ensure that the appropriate data requirements are met.

Those submitting an application for market authorization regarding a nonprescription drug are asked to complete the "Schedule A form for nonprescription products" which is found in Appendix 5 of the 3011 form. For information regarding submission evaluation fees for drugs, please refer to Health Canada's "Guidance Document on Cost Recovery Submission Evaluation Fees" (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/fees-frais/fee_frais_guide-eng.php).

3. General Principles

The following are general principles which should be considered when filing a submission to TPD, BGTD, or NHPD in support of a Schedule A disease preventative claim. These principles are in line with current review practices in the evaluation of claims relating to diseases of a more serious nature.

Evidence submitted by the sponsor in support of a Schedule A disease preventative claim for a nonprescription drug or a natural health product will be evaluated on a case-by-case basis since the context in which these claims are presented will influence the regulatory decision. Granting of market authorization will be based on an evaluation of the totality of the credible scientific evidence. The likelihood of achieving market authorization is commensurate with the strength of the evidence submitted.

Preventative claims for Schedule A diseases will be evaluated in the form of a systematic review assessing the strength of the scientific evidence to support a proposed claim about a product-disease relationship by considering study design types, quality and quantity of evidence (i.e., numbers of studies and study size) for and against the claim, statistically significant outcomes, clinically meaningful differences, relevance to the target population and overall consistency of the results across all studies of acceptable quality. Thus the totality of the evidence with respect to the product will be considered. Data requirements in support of preventative claims for Schedule A diseases embody as much scientific rigour as that applied to treatment claims.

3.1. Characterization of the disease

The disease (or the underlying disease in the case of a condition/abnormal physical state listed on Schedule A) that is the subject of the preventative claim must be defined and evaluated in accordance with generally accepted criteria established by a recognized body of qualified experts. The validity of the definition and evaluation criteria chosen must be demonstrated in the submission. The validity of the findings are limited if the diagnostic procedures used to identify the disease are not well defined or standardized.

The background incidence (in the case of a primary prevention) or baseline incidence (in the case of secondary prevention) of the disease to be prevented must be well characterized in the target population. Primary prevention refers to measures taken in a healthy population free of the disease that is the subject of the claim. Secondary prevention refers to measures taken in a population already suffering from the disease that is the subject of the claim.

4. Data Requirements

4.1. Primary clinical evidence required to support a preventative claim

The strongest evidence in support of cause-and-effect statements are data generated by well-designed, appropriately analysed, prospective Phase III intervention studies conducted in accordance with modern, internationally recognized Good Clinical Practices, scientific principles and procedures utilizing reduction in the incidence of disease as the clinical endpoint to be assessed. Such studies take the form of randomized, controlled, and preferably blinded, clinical trials where the substance/product is administered for the purpose and under the conditions of use specified in the submission. Conditions of use include dosage, dosing frequency, route of administration, formulation, and use of subjects representative of the proposed target population. Justification for sample size and duration of treatment and of follow-up must be provided. It also must be demonstrated that randomization has achieved balanced groups at study commencement (all groups should have comparable baseline values, particularly for those factors that are known to be, or may be, confounders or risk factors).

In most cases, a minimum of two, independently conducted, randomized, controlled clinical trials of good quality (as determined by a validated assessment tool, such as the Jadad scale) are required to substantiate the proposed Schedule A disease preventative claim. However, a single robust multicentre study may be acceptable provided it is well designed, well conducted, appropriately analysed and provides statistically significant and clinically relevant results. Prospective observational studies may also be acceptable under certain circumstances (e.g., diseases with long latency for which there are no validated surrogates). In such cases, more than one prospective observational study, along with other levels of evidence that are strongly supportive, would be required.

Generally such studies are conducted using the product formulation for which market authorization is being sought. In some cases, it is possible to extrapolate the results from formulation-specific, randomized, controlled, clinical trials to support the same claim for the same active ingredient either by:

(1) conducting bioavailability studies to show that the product formulation can provide blood levels of the active ingredient comparable to that of the formulation(s) used in the randomized controlled clinical trials; or,
(2) demonstrating that multiple, good quality, randomized, controlled clinical trials show that the clinical outcome which is the subject of the claim is not affected when the ingredient is incorporated in a variety of formulations.

4.2 Secondary supportive evidence

4.2.1 Observational studies

Randomized, controlled, *intervention* studies provide the most conclusive evidence of a causal relationship between the use of a product and a disease because they control for possible confounders of the results, including the amount and composition of the product. In contrast to intervention studies, *observational* studies cannot determine whether an observed relationship represents a relationship in which the product caused a reduction in disease or is a coincidence, i.e., they cannot provide convincing evidence of cause and effect. Nevertheless, well designed observational studies can provide useful information by measuring the degree of association between the use of a product and the incidence and course of a disease. Since observational studies are conducted in a more realistic setting, they can provide evidence to supplement that generated by randomized controlled clinical trials if they are of acceptable quality (e.g., are of sufficient duration, involve an appropriate number of subjects representative of the target population, and the data have been adjusted for known confounders). Observational studies include, in decreasing order of strength of evidence, cohort (longitudinal) studies, case-control studies, cross-sectional studies, uncontrolled case series, time-series studies, ecological or cross-population studies, descriptive epidemiology, and case reports. Assessment tools are available to evaluate the quality of cohort and case control studies.

The prospective cohort study provides the strongest evidence of an association but it is not a useful design for rare diseases or diseases with a long latent period. A case control design is useful when the disease is rare or has a long latent period. Evidence based solely on observational studies is not sufficient to support a Schedule A preventative claim.

4.2.2 Systematic literature review

Unpublished clinical trial data should be complemented by a systematic search and review of all available scientific literature that pertains to the safety and/or efficacy profile of the product. With respect to both published and unpublished data, it is expected that the sponsor will file, to the best of their knowledge, all available data, be it positive or negative. These studies should be grouped according to study design type and presented in summary table with each study assigned a quality rating.

4.3 Endpoints to substantiate preventative claims

Claims to prevent any disease, other than deficiency conditions, are difficult to support since developing the evidence base for a product-disease relationship entails an understanding of the complex interplay between the genetic makeup of an individual and the many etiologic factors

involved in the development of the disease. Preventions are interventions which reduce the incidence of the disease generally by modifying risk factors (with possible exceptions, such as vaccines).

Risk reduction claims are based on evidence generated by randomized, controlled, clinical trials with clinical outcomes that can be expressed either as a decreased incidence of the disease or a reduction of a factor, or a surrogate thereof, of the many that contribute to the development of a disease. Surrogate endpoints can be used to predict disease risk provided that the relationship between the surrogate endpoint and the disease has been conclusively established.

Substantiation of risk reduction claims involves the same scientific rigour as that applied to preventative claims and is based on the same types of study design and strength of evidence. The acceptability of utilizing a surrogate endpoint in lieu of clinical measurements of the incidence of disease or other clinical endpoints should be discussed with the appropriate Directorate prior to the initiation of studies involving the use of surrogate markers. Data justifying the validity of the surrogate marker must be provided at that time.

4.4 Statistical analysis of data

Standard statistical methods to calculate the sample size, setting the power and the significance level at the conventional 80% and $p < 0.05$ respectively, should be utilized. The statistical approach and the model underlying the analysis (i.e., the assumptions made) should be justified and documented by literature references. Acceptance by the scientific community and regulatory agencies is a good guide as to the suitability of the method.

Meta-analysis is a statistical method that combines the results from different studies to achieve an overall measure of the effect. To be appropriate, the meta-analysis must meet certain rigorous criteria that define study quality. A meta-analysis should combine only studies with similar design, populations, interventions and outcome measure. It is important to compare methods of statistical analysis and study design when evaluating the weight of the evidence. If these parameters differ between studies, the conclusions of the meta-analysis are not valid. If a meta-analysis is submitted, details must be provided to demonstrate that only studies of good quality were included, that combining the studies is justified and appropriate statistical procedures were used.

4.5 Assessment of safety

For products used for prevention of a disease that likely will be ingested on a daily basis for prolonged periods of time, the study must be of sufficient duration to ensure that there are no safety concerns with respect to long-term use and involve sufficiently large numbers of subjects

to estimate incidence and nature of potential adverse reactions. For all products, adverse reactions reported in clinical studies must be specifically identified and evaluated, and a causality assessment conducted according to accepted algorithms.

The risk factors underlying the development of a disease may change over time (e.g., changes in blood pressure). Potential risks associated with use of the drug or natural health product must be described and shown not to pose a health risk that outweighs the benefits under these changing circumstances as well as in the more vulnerable subgroups of the target population, such as the elderly, pregnant or lactating women. It is anticipated that preventative claims will be limited to the adult population unless conclusive evidence, based on data generated by randomized, controlled, clinical trial(s), is provided to justify such use in children.

Potential for interactions amongst natural health products, foods and drugs should also be investigated. If a potential for interaction is suggested by metabolic profile, by the results of non-clinical studies or by information on similar drugs, interaction studies are highly recommended. This is particularly true for drugs and natural health products that are known to alter the absorption or metabolism of other drugs (see International Conference on Harmonisation [ICH E7]), or whose metabolism or excretion can be altered by other drugs or foods.

Post-market data from any other jurisdiction, if available, must be included in the submission together with the label authorized by that jurisdiction.

4.6 Studies that serve only as background information

4.6.1 Traditional use

Evidence based on references to "traditional use" for natural health products, that is, the use of a medicinal ingredient within a cultural belief system or healing paradigm for at least 50 consecutive years, or references to claims from other healing paradigms (such as homeopathy) not based on conventional pharmacology, will not, on their own, provide a sufficient standard of evidence to support preventative claims for any Schedule A or other serious disease.

4.6.2 Animal and in vitro studies

Animal and *in vitro* studies can provide useful background information regarding mechanisms that may underlie the relationship between use of a product and the disease that is the subject of the preventative claim. However, such studies do not provide information from which scientific conclusions can be drawn regarding a causal relationship between a product and prevention of a disease in humans.

4.7 Chemistry and manufacturing

Chemistry and manufacturing requirements for products will be based on the regulatory framework under which they fall.

5. Labelling

Consumer research may be considered in order to demonstrate that the claim is understood and not misleading.

The labelling of products with authorized preventative claims will also be required to provide information regarding, among other things, appropriate cautions, warnings, contraindications, known adverse reactions, and, if applicable, lifestyle changes that would contribute to the benefit accrued from the use of a product used as a preventative measure.

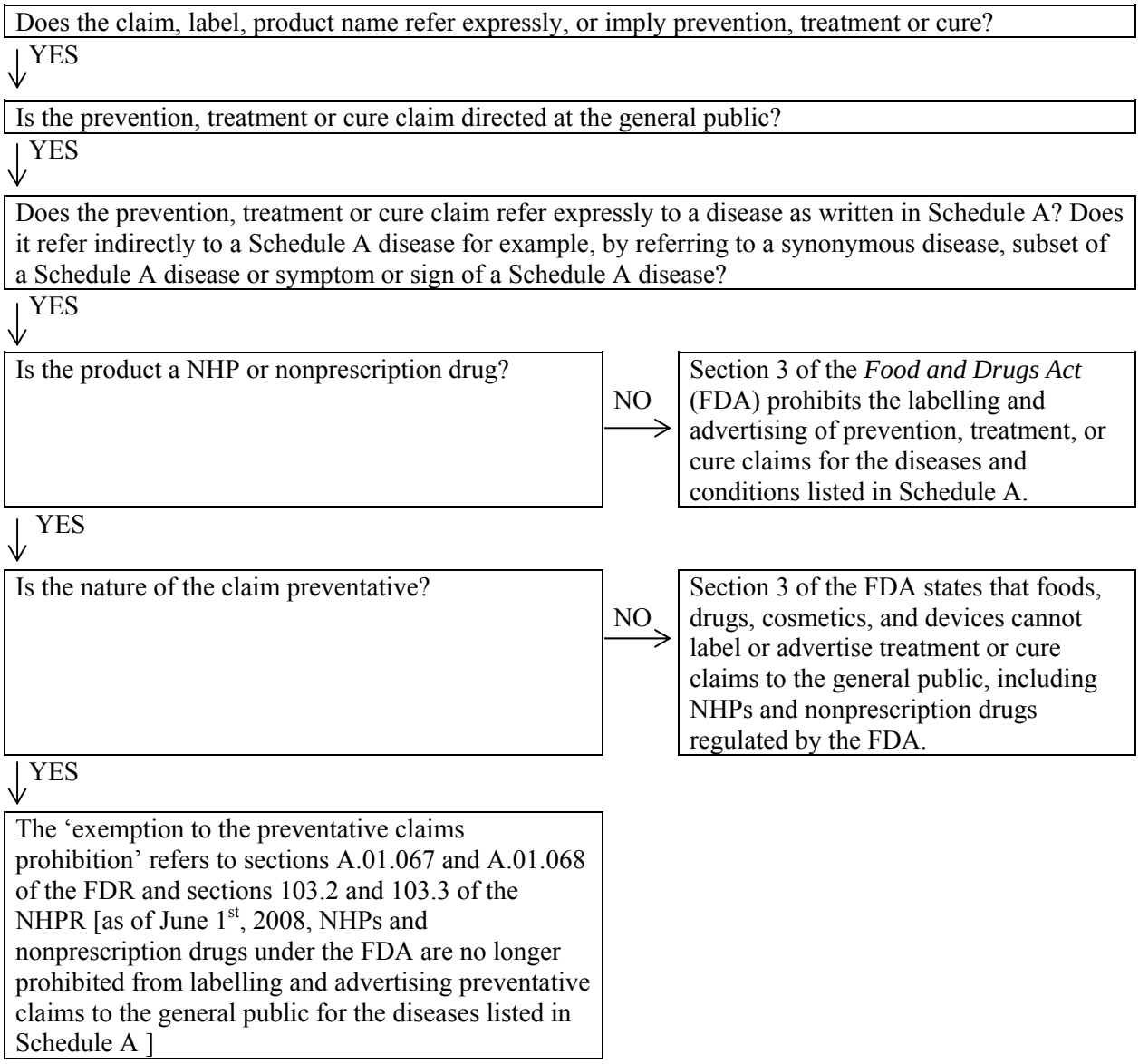
Limitations of the evidence must be reflected in the labelling by the use of appropriate qualifiers. Appropriate use of qualifiers is essential to detail the parameters upon which market authorization is based and to help Canadians make informed decisions. Such limitations could be included in the indications, directions for use, contraindications and/or warning statements. For instance, if the study involved only males of a certain age to reduce the incidence of asthma, the preventative claim can only be made with respect to asthma in men within the age bracket studied.

Labelling utilizing risk reduction claims in which a surrogate endpoint was used must indicate that the surrogate, or factor, which is the subject of the claim is only one of many that may contribute to the development of the disease to which it has been linked.

Claims on product labels should match the authorized wording. (Claims used in advertising may deviate in their wording as long as the claims are consistent with the product's terms of market authorization (TMA) and do not directly or indirectly exceed the scope of the TMA.)

APPENDIX D - Schedule A / Section 3 Flowchart

The following flowchart may assist in the assessment of claims. The flowchart is a **simplification** and must be read in conjunction with the *Food and Drugs Act* and its *Regulations*. The ultimate acceptability of any claim must be evaluated within its overall context.



APPENDIX E - Schedule A Synonyms

This section identifies examples of terms that may be understood as synonyms of the diseases, disorders or abnormal physical states referred to in Schedule A of the *Food and Drugs Act.* It is not an all encompassing list, nor should it be construed as exact medical definitions of the condition; this list merely serves as a guide and will be updated from time to time.

ACUTE ALCOHOLISM
Possible synonyms: alcohol intoxication; Alcohol poisoning.

ACUTE ANXIETY STATE
Possible synonym: panic attack/disorder; periods of intense anxiety or fear.

ACUTE INFECTIOUS RESPIRATORY SYNDROMES:
Possible synonyms: SARS; acute bronchitis; acute pneumonia.

ACUTE PSYCHOTIC CONDITIONS:
Possible synonyms: *schizophrenic episode*.

ACUTE, INFLAMMATORY, AND DEBILITATING ARTHRITIS
Possible synonyms: sudden onset of severe or sharp joint pain that impairs quality of life.

ADDICTION (except nicotine addiction)
Possible synonyms: alcoholism; substance abuse; drug habit; drug fixation; psychological/physiological dependence.

APPENDICITIS
Possible synonyms: none identified at this time.

ARTERIOSCLEROSIS
Possible synonyms: coronary artery disease; cerebrovascular disease; arteriosclerotic ulcer, clogging or hardening of the arteries, atherosclerosis.

ASTHMA
Possible synonyms: none identified at this time.

CANCER
Possible synonym: cancerous tumour; metastasis.

CONGESTIVE HEART FAILURE
Possible synonym: heart failure.

CONVULSIONS
Possible synonyms: twitching and jerking of limbs; seizures; epilepsy.

DEMENTIA
Possible synonyms: Alzheimer's Disease; Pick's Disease; irreversible impairment of cognition.

DEPRESSION
Possible synonyms: *words describing depression such as suicidal ideation, prolonged marked mood changes, prolonged periods of sadness, etc.*

DIABETES
Possible synonyms: none identified at this time.

GANGRENE
Possible synonyms: none identified at this time.

GLAUCOMA
Possible synonyms: none identified at this time.

HEMATOLOGIC BLEEDING DISORDER
Possible synonyms: hemophilia, Von Willebrand disease; abnormal hemostasis; clotting disorder; bleeding disorders; clotting factor VIII or IX deficiency; impairment of platelet adhesion/aggregation.

HEPATITIS
Possible synonyms: none identified at this time.

HYPERTENSION
Possible synonym: high blood pressure.

NAUSEA AND VOMITING DUE TO PREGNANCY
Possible synonym: morning sickness.

OBESITY
Possible synonym: morbidly overweight.

RHEUMATIC FEVER
Possible synonyms: none identified at this time.

SEPTICAEMIA
Possible synonyms: infection of the circulatory system; sepsis; blood poisoning; systemic inflammatory response syndrome.

SEXUALLY TRANSMITTED DISEASES (STDs):
Possible synonyms: sexually transmitted infections (STIs), AIDS (HIV infection); gonorrhea; syphilis; chancroid; genital and anorectal warts; genital herpes; chlamydia infections; trichomoniasis; amebiasis.

STRANGULATED HERNIA
Possible synonyms: none identified at this time.

THROMBOTIC AND EMBOLIC DISORDERS
Possible synonyms: none identified at this time.

THYROID DISEASE
Possible synonyms: hyperthyroidism; hypothyroidism; thyroiditis; goiter; thyrotoxicosis.

ULCER OF THE GASTROINTESTINAL TRACT.
Possible synonyms: peptic ulcer; ulcerative colitis; duodenal ulcer; inflammatory bowel disease; stomach ulcer; esophageal ulcer.