Identifying Natural Health Products Listed in NAPRA's National Drug Schedules

August 2006
[Revised October 2006, based on input from Health Canada's Natural Health Products Directorate]

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EXECUTIVE SUMMARY

The Natural Health Products (NHP) Regulations are a set of relatively new regulations under the Food and Drugs Act that came into force on January 1st, 2004. Currently the National Association of Pharmacy Regulatory Authorities (NAPRA), through the National Drug Schedules (NDS), maintains the model conditions of sale for a number of medicinal ingredients that also fall under the NHP Regulations. The NDS are uniformly accepted throughout most of Canada, and drugs are placed in the respective schedules based on the need for a pharmacist's involvement in their sale. Under NHP Regulations, products that meet the criteria for licensure as NHPs are assigned a Natural Product Number (NPN) or a Drug Identification Number – Homeopathic Medicine (DIN-HM). In the case of currently marketed products, this number will replace the Drug Identification Number (DIN). The transition to regulation under the NHP Regulations is required by the end of 2009. This is causing considerable confusion over the conditions of sale of such products, especially those that currently require some level of pharmacist intervention. The intent of this report is to identify the drugs currently listed in the NDS that will likely transition to NHPs, as well as to provide a basis for discussion with the Natural Health Products Directorate (NHPD) to highlight the need for a complementary framework to the NDS to address safety concerns.

The initial effort to identify NHPs in the NDS was made by a NAPRA Pharmacy Summer Student, in 2005. This list was subsequently reviewed by strictly following the specificities of Schedules 1 and 2 of the NHP Regulations[1], with the help of the various guidance documents produced by Health Canada. The NHPD reviewed the preliminary findings and provided confirmation with little modification, resulting in this validated report. Taking into consideration the source of each of the ingredients listed in the NDS, processes by which it is extracted, and the final form of the molecule when it is sold, 95 medicinal ingredients included in 116 NDS items are expected to be identified as NHPs by Health Canada. The following table summarizes the number of identified NHP items found in each category of the NDS.

National Drug Schedules Category	Number of Identified NHP Items
I	11
II	44
III	27
Unscheduled	34

The detailed and referenced process undertaken to identify these items as NHPs is included in the Appendix.

There are a total of 55 identified NHP items from the National Drug Schedules I or II. Currently, patients can only purchase these medications through a direct interaction with a pharmacist, and require a prescription in the case of drugs in Schedule I, as these items are deemed inappropriate for self-selection. Although they meet the criteria to be sold as NHPs, these items have the highest potential for negatively impacting patient safety if their availability becomes unrestricted. In addition to these safety concerns, this situation causes considerable confusion over the regulation of the sale of these products. This document provides a background on the issue and addresses the implications of the NAPRA Board's decision in April 2006 to exclude all NHPs from the NDS.

[1] Accessed on-line at http://laws.justice.gc.ca/en/f-27/sor-2003-196/219027.html

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Section 1: BACKGROUND

1.1 National Association of Pharmacy Regulatory Authorities

Established in 1995, the National Association of Pharmacy Regulatory Authorities (NAPRA) is the national voluntary association of provincial and territorial pharmacy regulatory authorities (PRAs) as well as the Canadian Forces Pharmacy Services, whose mandates are the protection of the public. NAPRA's members regulate the practice of pharmacy and operation of pharmacies in their respective jurisdictions in Canada.

NAPRA enhances the activities of the pharmacy regulatory authorities by:

- Representing the common interests of the member organizations;
- Serving as a national resource centre; and
- Promoting the national implementation of progressive regulatory programs and standards.

1.2 Purpose of the National Drug Schedules

May 1995

- NAPRA endorsed a proposal for a national drug scheduling model, to align the provincial drug schedules so that the conditions for the sale of drugs would be more consistent across Canada.
- The national model consists of three schedules and four categories: Schedule I, Schedule II, Schedule III and Unscheduled, with specific conditions with regards to prescription status and involvement of the pharmacist in their sale.
- The National Drug Scheduling Advisory Committee (NDSAC) was formed to make scheduling placement recommendations to NAPRA.

February 2004

- By this date, all provinces except for Quebec have accepted the National Drug Schedules (NDS) as a provincial model, with some provinces incorporating slight modifications.

1.3 Drug Scheduling Process

Assigning a drug into one of the four categories (Schedule I, II, III or Unscheduled) is a rigorous and standardized process that consists of uniform inclusion factors for each schedule which allow NDSAC to make scheduling placement recommendations to NAPRA. The process involves careful analysis of the drug's indication, adverse drug reactions, dependency potential, monitoring requirements, therapeutic index, and drug interactions. The criteria that are considered when placing a drug in the NDS are described in detail on the NAPRA website at http://www.napra.ca/docs/0/92/112/154.asp.

1.4 Development of the Natural Health Products Regulations

May 1997

- Canadians began to express concern about the regulation of Natural Health Products (NHPs).
- Health Canada responded by establishing an Advisory Panel on NHPs.

October 1997

- The federal Minister of Health announced a full public review by the House of Commons Standing Committee on Health (SCOH) of the legal regime governing natural health products.
- The focus was on the balance between the freedom of choice and patient safety.

October 1997- April 1998

- The SCOH consulted a wide range of interested parties both at home and abroad. It heard from over 150 individuals, associations and coalitions representing many Canadians, including: health care providers, industry, consumer groups, herbalists, and the Advisory Panel on Natural Health Products.
- The SCOH prepared recommendations on a distinct regulatory framework for natural health products.

May 1998

- The Final Report of Health Canada's Advisory Panel on Natural Health Products entitled *Regulatory Framework for Natural Health Products* was presented to the House of Commons Standing Committee on Health.

November 1998

- The Standing Committee on Health tabled its report *Natural Health Products: a New Vision* in the House of Commons.

March 1999

- The government accepted all 53 of the Standing Committee's recommendations and indicated that these would form the basis of the broad policy framework to be established for natural health products.
- Announcement of the creation of the Natural Health Products Directorate (NHPD).

May 1999

- A 17-member Transition Team was appointed to help establish the NHPD and its regulatory framework.

May 2000

- The Transition Team submitted to the Minister of Health its *Final Report: a Fresh Start*, as a summary of the discussions and recommendations of the Transition Team meetings, outlining broad policy directions toward a regulatory regime for natural health products.

November 2001

- After several revisions to the draft of the regulatory framework, an industry-working group was formed so that the Natural Health Products Directorate could better communicate and consult with Industry as the NHPD moved toward the regulation of natural health products.

December 2001

- The proposed Natural Health Products Regulations, to regulate NHPs as a subset of drugs under the Food and Drug Act, were pre-published in the Canada Gazette, Part I. Over 600 responses were submitted during a 4-month comment period.

July 2002

- The NHPD completed a cross-country consultation on its Good Manufacturing Practices for Natural Health Products Guidance Document.

November 2002

- The NHPD proceeded with cross-country information and town hall consultations on the proposed Standards of Evidence for the evaluation of safety and claims of natural health products.

December 2002

- In the interest of understanding the impact of the proposed Regulations on the natural health product industry, the Natural Health Products Directorate undertook a Business Impact Test from December 6, 2002 until January 22, 2003.

January 2003

- The Natural Health Products Directorate proceeded with the publication of the Regulations in the Canada Gazette Part II, followed by a short period to come into force, namely January 2004 and a transitional period that will span from 2 to 6 years- 2 years for site licensing and 6 years for products with Drug Identification Numbers (DIN).
- All NHPs must comply with the Regulations by January 1st, 2010.

1.5 Role of NAPRA with Respect to Natural Health Products

December 2003

- NDSAC and NAPRA begin discussions about the relationship between NHPs and the National Drug Schedules.

May 2004

- In response to an issue regarding the status of melatonin brought forward by the Council of Pharmacy Registrars of Canada (CPRC), the former Executive Director of NAPRA agreed to consult with the NHPD to relay the concerns of the CPRC and seek clarification regarding the applicability of the NHP Regulations.

November 2004

- The NAPRA Board agreed that NAPRA's experience with NDSAC would potentially be of value to NHPD, and could be shared in consultation, but that NAPRA was not in a position to take a leadership role on this matter nor to get directly involved in any scheduling process that might be established.
- At the CPRC meeting, it was agreed that the Executive Director of NAPRA would compile a list of questions and issues from CPRC members surrounding NHPs and that a meeting with the NHPD Director General would be requested.

December 2004

- At the NDSAC meeting it was noted that the NHPD agreed to provide a list of NHPs that have received Natural Product Numbers and that this would be shared with NDSAC and CPRC.

September 2005

- At the NDSAC meeting, the committee had a lengthy discussion on the overlap of NHPs and the NDS, and the recommendation was made that NAPRA write to Health Canada regarding the applicability of the NDS to NHPs.
- CPRC agreed that the "dilemma of whether there should be different conditions for sale as a regulated OTC vs. NHP" should be brought forward to the Board and NHPD for resolution.

November 2005

- At the NAPRA Board meeting it was agreed that NAPRA should seek clarification from the NHPD on the role of the NDS when Health Canada issues licences for new NHPs or products that switch from DINs to NPNs.
- First bilateral meeting between NAPRA and the NHPD – issues discussed were:
    - How and if to apply, monitor and enforce the NDS in regard to NHPs.
    - Restrictions to drug access as set out by Schedules II and III may have to be modified to include intervention from a naturopathic doctor or alternative health care providers, not solely pharmacists.
    - A review of the NDS may be warranted upon receiving updated information about certain NHPs.
    - The possible regulatory amendment regarding self care is still under discussion within NHPD in regard to its implications.

March 2006

- NHPD participated in the NDSAC meeting and conveyed that collaboration with NAPRA and NDSAC regarding the issue of NHPs is an important matter.

April 2006

- At the NAPRA Board meeting, a motion was carried that all medicinal ingredients that are assigned a NPN or a DIN-HM would not be considered for scheduling within the NDS.
- At the CPRC meeting it was stated that it is important for NAPRA to raise the issue concerning patient safety in using NHPs after they are removed from the NDS.
- NAPRA Bilateral meetings were held with both the NHPD and the Therapeutic Products Directorate (TPD). The NHPD prepared a summary of how the NDS are taken into consideration during the licensing of NHPs.

May 2006

- NAPRA's President sent a letter to NHPD and TPD, initiating communication regarding the implications of the NAPRA Board's decision to remove NHPs from the NDS.

July 2006

- The NHPD and TPD sent a joint response to NAPRA's President stating that they feel it would be beneficial that some NHPs remain on the NDS, and requesting a meeting with NAPRA to discuss this issue.
- A 4th year pharmacy student was employed for the summer term, whose work included the identification of all NHPs that are currently included in the NDS.
- A database was created identifying NHPs, including the rationale behind why each of the items in the NDS does or does not qualify as an NHP.

October 2006

The NHPD reviewed the preliminary findings, and confirmed the results with two exceptions. The analysis and appendix was slightly revised to incorporate the feedback from NHPD.

A joint meeting was held between NAPRA and Health Canada (NHPD and TPD) to review the implications of the NAPRA Board's decision, and discuss the analysis of the NDS with regard to the NHPs. It was agreed that further collaborative work would take place to ensure the full scope of the implications are understood. Health Canada officials recognized and acknowledged the Department's role in ensuring the safe use of these natural health products, cognizant that they would be removed from the NDS.

Section 2: OBJECTIVE

The objective of this project was to provide background on the development of the regulatory framework for NHPs and to describe the implications of the NAPRA Board's decision in April 2006 to exclude all NHPs from the NDS.

Section 3: METHODS

Based on a download of the National Drug Schedules on July 10, 2006, items likely to be regulated as NHPs by Health Canada were identified. The process included:

1. Performing a literature search to identify if the product exists in nature.
2. Ensuring that the product was not modified between the time of extraction to the time of packaging and that it retained the primary molecular structure as found in nature.
3. Verifying that the product is not exempt from qualifying as an NHP according to Schedule 2 of the Natural Health Product Regulations (e.g. the product is not an antibiotic).
4. Confirming that synthetically manufactured products exhibit the same molecular structure and pharmacological properties of the naturally derived entity.
5. Using the Health Canada Drug Product Database to determine if there is a homeopathic formulation of the product concerned, and to identify conflicts with regard to product availability on the Canadian market.
6. Consulting with the NHPD to obtain clarification on matters that could not otherwise be resolved.

This process was applied to all items included in the National Drug Schedules and rationale was also recorded as to why products did not meet the criteria for classification as NHPs. The list of the identified NHPs, the National Drug Schedules in which they currently belong, and the detailed rationale explaining why the product is likely to qualify as an NHP, is included in the Appendix to this report.

All research involved using Medline™ and Embase™ Indexes through the Online Library at the University of British Columbia, and tertiary resources such as the Martindale – The Complete Drug Reference and encyclopaedias.

NHPD staff reviewed the preliminary findings, and confirmed the results with the exception of two NDS listings which were subsequently removed from this report. Thus, the Appendix is accurate to the best of the author's knowledge and has been confirmed by NHPD. NHPD staff will be reviewing the balance of the NDS listings, to ensure that there are no additional items to add to this list that were not identified in the initial review.

Section 4: RESULTS

Summary:

- There were 1640 items listed in the NDS

- 116 items were identified as NHPs
  - 11 in Schedule I (e.g. Papaverine)
  - 44 in Schedule II (e.g. Acetylcysteine)
  - 27 in Schedule III (e.g. Danthron)
  - 34 Unscheduled (e.g. Capsaicin)

- 82 items are in Schedule I, II or III and 34 items are Unscheduled

- Of the 116 identified NHPs, 11 are currently approved as NHPs by Health Canada and have been assigned NPNs[2]:
  - Aloe
  - Arginine
  - Artemisia
  - Cascara
  - Ephedrine
  - Iron
  - Magnesium citrate
  - Niacin
  - Nicotine
  - Pseudoephedrine
  - Ubiquinone

- There are 2 identified NHPs contained in the NDS that are not currently available on the Canadian market, ethylpapaverine and apomorphine.

- 6 items in the NDS only qualify as NHPs under specific conditions:
  - Epinephrine is an NHP only if it is administered without puncturing the dermis.
  - Typhoid vaccine is an NHP only as the oral formulation
  - Under “Vaccines”, the oral Staphylococcus vaccine is the only one that qualifies as an NHP.
  - Silver nitrate is an NHP only in homeopathic preparations
  - Antipyrine is an NHP only in homeopathic preparations
  - Vitamins used in Total Parenteral Nutrition are eligible as NHPs only if they are not administered by puncturing the dermis, in a case of, for example, administration via a gastric feeding tube.

- There are a total of 55 identified NHPs that are currently listed in Schedule I or II of the National Drug Schedules. By provincial regulation (where applicable), interaction with a pharmacist is deemed necessary when purchasing these products. These will likely be the primary concern for NAPRA.

[2] Accessed on-line at www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/lists/listapprnhp-listeapprpsn_e.html, August 2006.

Section 5: IMPLICATIONS

The results of this report have implications for patients, pharmacists, manufacturers, retailers, NAPRA, NHPD, and the provincial pharmacy regulatory authorities (PRAs) that use the NDS as a model for their scheduling.

- Patients – There are significant safety considerations regarding self-selection of a drug that meets the criteria to be sold under Schedule I, II or III of the NDS. Patients may feel that because a product is an NHP, it has few side effects or drug interactions and that the therapy does not need much monitoring. Consumers may also become confused when products that were once sold by prescription or from behind the pharmacy counter are now available for self-selection. Additionally, reimbursement for these medications may be affected (e.g. if the drug required a prescription under the NDS and now is regulated under the NHP Regulations it may not longer be covered by certain insurance plans).

- Pharmacists – If scheduling changes are made to the 82 identified NHPs currently in Schedules I, II, or III of the NDS, there will be considerable confusion regarding the role of the pharmacist regarding their sale. They will also be faced with educating patients if asked for clarification about the new regulations, their safety concerns, and any changes in coverage by insurance plans. Additionally, the pharmacist will likely have to modify the stocking of the drug in the pharmacy to reflect the change in the condition of its sale.

- Manufacturers – There are marketing implications for companies that manufacture NHPs. Since the conditions for the sale of certain drugs will change, the companies may take a different approach in advertising NHPs. Also, manufacturers of NHPs would no longer be required to submit products for scheduling review by NDSAC when they qualify as NHPs.

- Retailers – If the provincial regulatory authorities agree with the NDS changes and implement them, NHP retailers will be able to stock additional products. The retailers will have an expanded role and responsibility of communicating Health Canada safety warnings advisories to consumers.

- NAPRA – The NHPD prepared a document in April 2006 stating that “substances regulated federally as NHPs that are currently on NAPRA schedules have no change in status”. However, the NAPRA Board of Directors has made the decision that all NHPs are to be removed from the NDS. NAPRA now faces the challenge of developing and implementing a process for the removal of NHPs from the NDS once they no longer have assigned DINs, and effectively communicating to Health Canada its safety concerns.

- NHPD – Although set guidelines have been created to identify which products should be sold under the NHP Regulations, the NHPD concurs that these products have to be safe for self-selection. The NHPD recognizes that there are some NHPs that may not require a prescription under Federal law, but the risk that they present to patients requires the imposition of some conditions of sale.

NHPD carries the responsibility of ensuring that products are safe for consumers' use, in light of the NAPRA Board's decision.

- Provincial Pharmacy Regulatory Authorities – Each of the PRAs and their respective governments will have to make decisions about provincial implementation of the changes to the NDS based on the NAPRA Board's decision.

Section 6: NEXT STEPS for NAPRA

These recommended steps are aimed at ensuring patient safety and eliminating ambiguity with regards to the status of drugs contained in the NDS that have been identified as NHPs.

1. As requested by the NHPD, a meeting between NAPRA and the NHPD took place on October 4th, 2006, to discuss the implications of the NAPRA Board's decision to remove NHPs from the NDS in the near future.

2. The enclosed list of identified NHPs in the NDS has been confirmed by the NHPD. The NHPD has agreed to review the full listing of the NDS, to ensure that there were no listings overlooked in the preparation of this report (i.e. to identify any omissions).

3. This project report will be discussed at the November 2006 meetings of the CPRC and the NAPRA Board, to review the findings, address the implications, and determine further action.

4. Communication with external stakeholders should include the results of this analysis, as well as elaboration on NAPRA's next steps to fully implement the Board's decisions.

5. Changes should not to be made to the NDS until all identified products are known to have received a NPN or a DIN-HM, and the complementary framework regarding their conditions of sale has been developed by the NHPD.

6. NAPRA should continue to urge the NHPD to improve their searchable database of products that have been assigned a NPN or DIN-HM, including the addition of an indicator for those products that transition from DINs, so that NAPRA can subsequently cross-reference those drugs with the NDS to determine which drugs are ready to be removed from the listings.

APPENDIX

IDENTIFIED NATURAL HEALTH PRODUCTS in the NATIONAL DRUG SCHEDULES

The following chart summarizes the Natural Health Products (NHP) currently included in the National Drug Schedules (NDS), sorted alphabetically within each NDS category.

Legend:	
Y	The item was identified as a Natural Health Product
Y*	The item qualifies as an NHP on certain conditions which are described in the *Comments* section
DPD	Health Canada Drug Product Database
NOC Database	Health Canada Notice of Compliance Database

NDS Listing	**NDS**	**Y/***	**Comments**
Schedule I			
Ephedrine and its salts *(in preparations containing more than 8 mg per unit dose, or with a label recommending more than 8 mg/dose or 32 mg/day, or labelled or implied for use exceeding 7 days, or if indicated for other than nasal congestion.)*	I	Y	Chemically, ephedrine is an alkaloid derived from various plants in the genus *Ephedra* (family Ephedraceae). It is the principal alkaloid constituent of ephedra. The applicable part of ephedra used in drug preparations are the stem and leaf. Ephedra in dietary supplements is usually either a formulation of powdered stems and aerial portions or a dried extract. [Ref: J Clin Pharmacol 1997;37:116-22.]
Epinephrine and its salts *(other than in pre-filled syringes intended for emergency administration by injection in the event of anaphylactic reactions to allergens)*	I	Y*	Is a hormone and a neurotransmitter. Epinephrine is a catecholamine, a sympathomimetic monoamine derived from the amino acids phenylalanine and tyrosine. May be isolated form the medulla of the suprarenal (adrenal) glands of certain mammals. Products where epinephrine is a single entity product and which are not administered by puncturing the dermis (like ophthalmic solutions), are NHPs [Ref: Martindale 34th Ed. Pg. 852]
Ethylpapaverine and its salts	I	Y	Not in DPD or the NOC Database. Also known as ethaverine. Opioid alkaloid extracted from Papaverine plant. [Ref: Naunyn-Schmiedebergs Archives of Pharmacology. 294(3):271-5, 1976 Sep 24, Determination of ethaverine and papaverine using ion-selective electrodes - The Analyst [0003-2654] Eppelsheim yr:1991 vol:116 iss:10 pg:1001 -3].

Nicotinyl-tartrate	I	Y	Nicotinyl tartrate is the tartaric acid ester of nicotinyl alcohol. Nicotinyl alcohol is the alcoholic version of nicotinic acid, however, unlike nicotinic acid, nicotinyl alcohol is not naturally occurring and it is synthetically prepared by catalytic hydrogenation of 3-pyridinecarboxaldehyde, the aldehyde version of this family of compound. Even though the nicotinyl alcohol and its derivatives are not found in nature, some published articles confirm that nicotinyl alcohol is known to be metabolized rapidly to nicotinic acid in the human body. Since nicotinyl tartrate is acting as a source for nicotinic acid, it will be considered as an NHP, under Schedule 1, item 3 (Priority 5) of the NHP Regulations. [Ref: Dr. Robin Marles, NHPD]
Pancreatic enzymes *(in products for the treatment of established pancreatic insufficiency)*	I	Y	Prepared from the pancreas of mammals such as hog or ox. [Ref: Martindale's 34th Ed. Pg. 1726].
Pancreatin *(in products for the treatment of established pancreatic insufficiency)*	I	Y	Prepared from the pancreas of mammals such as hog or ox. [Ref: Martindale's 34th Ed. Pg. 1726].
Pancrelipase *(in products for the treatment of established pancreatic insufficiency)*	I	Y	Prepared from the pancreas of mammals such as hog or ox. [Ref: Martindale's 34th Ed. Pg. 1726].
Papaverine and its salts	I	Y	Papaverine is a naturally-occurring, crystalline alkaloid found in the papaver somniferum (opium poppy) plant. [Ref: http://www.phytomedical.com/Plant/Papaverine.asp]
Quinidine salts	I	Y	Stereoisomer of quinine, originally derived from the bark of the cinchona tree and their hybrids as well as some other plants such as *Remijia pedunculata*. [Ref: Martindale 34th Ed. Pg. 991]
Typhoid vaccines/Salmonella Typhi vaccines (NHPD: *vaccines are natural products but will be regulated as biologics by BGTD*)	I	Y*	If administered IM, this drug is not eligible for sale under NHP Regulations. The oral vaccine is meets the NHP criteria. It is prepared from bacteria *Salmonella typhi.* The bacterium is inactivated by heat, so no structural modifications are made to the antigen. Although vaccines are Schedule D to the Act, this product in exempt as per Schedule II Item 2. [Ref: Martindale 34th Ed]
Vaccines (except for - those which are part of a routine immunization program in most/all provinces and territories: Diphtheria toxoid, Tetanus toxoid, Pertussis, Poliomyelitis, Haemophilus influenza type B, Measles, Mumps, Rubella, Pneumococcus, Hepatitis (NHPD: *vaccines are natural products but will be regulated as biologics by BGTD*)	I	Y*	The other vaccines that are not mentioned in the exception are: AIDS (IM), Anthrax (IM), BCG (SC), Brucellosis (IM), Hep A (IM), Japanese Encephalitis (SC), Leptospirosis (IM), Lyme Disease (IM), Rabies (IM, SC), Rift Valley Fever (IM), Staphylococcus (Oral, IM and IV), Strep B (IM), Tetanus (IM), Trichomoniasis (IM), Tularaemia (IM), Typhoid (IM, Oral has been discontinued), Typhus (IM), Chicken Pox (IM), Yellow Fever (IM). The only vaccine in this list that qualifies as an NHP is the oral Staphylococcus vaccine, prepared from the bacteria Staphyloccocus ssp. Although this drug is in Schedule D to the Act, it is exempted as per Schedule II to the NHP Regulations.

Schedule II			
Acetylcysteine	II	Y	Listed in Natural Medicines Comprehensive Database, a reference text for NHPs. Found in vegetables such as garlic, onion, peppers, and many other vegetables. [Ref. Nutrition & Metabolism 2005, 2:20 Accessed online at http://www.biomedcentral.com/1743-7075/2/20
Apomorphine and its salts	II	Y	Apomorphine is a naturally occurring aporphine alkaloid of the dibenzoquinoline class. Comes from mainly plant families such as Papaveraceae, Annonaceae, Apocynaceae, Ranunculaceae. [Ref: J. Chem. Inf. Model. 2005, 45, 645-651]. It is synthesized by heating morphine in an acidic environment. [Ref: http://www.uspharmacist.com/index.asp?page=ce/3180/default.htm]. It does not seem to be available in Canada.
Arginine and its salts	II	Y	L-arginine is an amino acid necessary for protein synthesis. It is found naturally in foods such as red meat, poultry, fish, and dairy products. [Ref: Tenebaum A, Fisman EZ, Motro M. L-arginine: Rediscovery in progress. Cardiology 1998;90:153-5]. It meets the requirements for licensing under the NHP regulations. Also termed "NHP" in the Health Canada in the "Summary of NHP/DRUG Classification of TPD Category IV Labelling Standards Ingredients".
Artemisia, its preparations, extracts and compounds (except in trace amounts in homeopathic preparations)	II	Y	Artemisia comes from a plant called mugwort. It belongs to the Asteraceae/Compositae family. The applicable parts of mugwort are the above ground parts and root. [Ref: Natural Medicines Comprehensive Database, keyword: Artemisia]
Belladonna alkaloids, and their salts and derivatives (except in preparations for topical use or in trace amounts in homeopathic preparations)	II	Y	Belladonna is a plant, and the applicable parts used medicinally are the leaf and root. Its anticholinergic activity is due to the 0.3%-0.5% tropane alkaloid constituents; mainly l-hyoscyamine, but it also contains traces of l-scopolamine and atropine (dl-hyoscyamine). On extraction, most of the l-hyoscyamine is racemized to atropine. [Ref: Leung AY, Foster S. Encyclopaedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics. 2nd ed. New York, NY: John Wiley & Sons, 1996.].
Benzocaine and its salts (for parenteral or ophthalmic use)	II	Y	One biological source is as a constituent of the stems of Strychnos cathayensis [Ref: Dictionary of Natural Products on CD-ROM ver. 15:1, Copyright © 1982-2007 Chapman & Hall/CRC, Copyright © 2007 Hampden Data Services Ltd.; Cheng M-J, Tsai I-L, Chen I-S. 2001. Chemical Constituents from Strychnos cathayensis. Journal of the Chinese Chemical Society]
Boric acid and its salts (in preparations for systemic use, or ophthalmic preparations in concentrations over 2%[Note: does not apply to contact lens solutions intended to be rinsed off prior to insertion in the eye]) (NHPD: *the acceptable maximum dose of boron has not yet been set*)	II	Y	Boron is a trace mineral for which a clear biological function in humans has not been established. Boron is well absorbed from dietary beverages including prune and grape juice; wine; coffee; milk; and in some geographical locations, water. Avocados, peanuts, pecans, apples, dried beans, and potatoes also contain boron. [Ref: Food and Nutrition Board, Institute of Medicine.]

Camphor (in oleaginous vehicles and in liquid forms in concentrations greater than 11%)	II	Y	The applicable parts of camphor are the bark and wood. Camphor was formerly obtained by distilling the bark and wood of the camphor tree. Today, camphor is typically obtained by synthetic production from turpentine oil. [Ref: Love JN, Sammon M, Smereck J. Are one or two dangerous? Camphor exposure in toddlers. J Emerg Med 2004;27:49-54.].
Cantharides, their preparations and derivatives	II	Y	Also known as the Blistering Beetle. Prepared form the dried beetle. All 50 products with this ingredient are homeopathic medications. [Ref: Natural Medicines Comprehensive Database]
Chymotrypsin (parenteral and ophthalmic)	II	Y*	A proteolytic enzyme obtained by the activation of chymotripsinogen extracted from the pancreas of beef. Both chymotripsin and chymotripsinogen are unchanged through this process and both are naturally occurring in the beef pancreas. [Ref: Martindale 34th Ed. pg. 1671]. Parenteral formulations are not eligible for NHP status under Item 5 of Schedule II of the NHP Regulations, but ophthalmic products are.
Collagenase (as debriding agent)	II	Y	Proteolytic enzyme derived from the fermentation of *Colostridium histolyticu.* It has the potential to break down collagen. The enzyme is also made by a variety of microorganisms and by many different animal cells. [Ref: Harper, E., Collagenases, Annu. Review of Biochemistry 49, 1063 (1980)].
Dihydroquinidine and its salts (except phenylbarbiturate)	II	Y	Dihydroquinidine is a derivative of quinidine, from which it differs only by saturation of the viny side chain of the quinuclidine ring. [Ref: Cardiovascular Drugs & Therapy. 2(5):679-86, 1988 Dec.] This compound does exist in nature and is extracted from the Chicona Tree Bark. The application of high-performance liquid chromatography to resolve the individual alkaloids present in marketed Cinchona alkaloids was investigated in one study, and an alkylphenyl column resolved quinidine, quinine, dihydroquinidine, dihydroquinine, cinchonine, cinchonidine, dihydrocinchonine and dihydrocinchonidine.[Ref: Journal of Chromatography. 299(1):233-44, 1984 Sep 7].
Histamine and its salts (except for topical use)	II	Y*	Naturally occurring amine. Also produced in spoiled foodstuffs, such as fish, by conversion of histidine to histamine. There are also homeopathic products that contain histamine. Histamine is eligible as an NHP, providing that the product is not administered by injection. [Ref: D MacGlashan - The Journal of Allergy and Clinical Immunology, 2003].
Hyaluronic acid and its salts (preparations in concentrations of 5% or more) (NHPD: *some applications have been classified by Health Canada as medical devices*)	II	Y*	A glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is one of the chief components of the extracellular matrix. It is obtained from cocks' coombs or by fermentation from streptococci. Topical preparations are eligible as NHPs. [Ref: Martindale 34th Ed. Pg. 1697].

Hydroquinone *(topical preparations)*	II	Y	Hydroquinone (HQ) is currently synthesized via hydroperoxidation of p-diisopropylbenzene as well as oxidation of aniline or hydroxylation of phenol with hydrogen peroxide. Some biochemical compounds in nature have this sort of HQ section in their structures, such as Coenzyme Q, and can undergo similar redox interconversions. HQ also occurs naturally in foods and in the leaves and bark of a number of plant species, wheat and some types of fruit,. [Ref: Toxicological Sciences 2004 82(1):9-25;]. Certatin forms of HQ have been isolated from trees, for example, a new prenylated hydroquinone from the roots of *Garcinia atroviridis.* Another study has also isolated HQ from natural sources. Analysis of possible food sources of HQ by GC indicated significant amounts of arbutin in wheat products (1-10 ppm), pears (4-15 ppm), and coffee and tea (0.1 ppm). Free HQ was found in coffee (0.2 ppm), red wine (0.5 ppm), wheat cereals (0.2-0.4 ppm), and broccoli (0.1 ppm). [Ref: Biochemical Toxicology Section, Eastman Kodak Company, Rochester, New York 14652-6272, USA.]
Hyoscine and its salts and derivatives [scopolamine]	II	Y	Hyoscine is a tropane alkaloid drug obtained from plants of the family Solanaceae (nightshades), such as henbane or jimson weed (*Datura* species). It is part of the secondary metabolites of plants. This drug has been frequently used as the "date rape drug", and it is in the best interest of the public that the sale of this drug be monitored. Otherwise, it does meet the criteria for sale under NHP Regulations. [Ref: SP Clissold, RC Heel - Drugs, 1985 - ncbi.nlm.nih.gov].
Hyoscyamine and its salts and derivatives (except for topical use)	II	Y	Hyoscycamine is a tropane alkaloid drug that can be extracted from plants of the Solanaceae family, notably Datura stramonium It is part of the secondary metabolites of plants. SAFETY NOTE: This drug has been frequently used as the "date rape drug", and it is in the best interest of the public that the sale of this drug be monitored. [Ref: J Payne, Hamill, Robins, Rhodes - Planta medica, 1987.]
Iodine and its salts and derivatives (except topical preparations or in oral doses of 1 mg or less per day)	II	Y	Iodine occurs in the environment chiefly as dissolved iodide in seawater. However, it is present in some minerals and soils as well. The element may be prepared in an ultrapure form through the reaction of potassium iodide with copper (II) sulfate. There are also several other methods of isolating this element. Although the element is actually quite rare, kelp and certain other plants have the ability to concentrate iodine, which helps introduce the element into the food chain as well as keeping its cost down. [Ref: J Fabryka-Martin, H Bentley, D Elmore, PL Airey - Geochimica et Cosmochimica Acta, 1985].
Ipecac and its extracts and derivatives *(when used as an emetic)*	II	Y	Consists of the fragmented and dried underground organs (rhizomes) of *Cephaelis ipecacuanha,* a plant native to parts of Central and South America. [Ref: Martindale 34th Ed. Pg. 1122, Natural Medicines Comprehensive Database].

Iron and its salts and derivatives *(in preparations with more than 30 mg elemental iron per solid dosage unit or 5 mL oral liquid)*	II	Y	Most abundant metal on earth, extracted from iron ore. Occurs naturally both within the earth's core and on the surface. [Ref: Natural Medicines Comprehensive Database].
Mannitol and its salts	II	Y	Naturally occurring sugar alcohol. May be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. [Ref: www.medicinescomplete.com/mc/excipients/2006/100030 2864.htm]
Methyl salicylate *(in liquid dosage forms in concentrations greater than 30%)*	II	Y	Also known as salicylic acid methyl ester, oil of wintergreen, betula oil, and methyl ester) is a natural product of many species of plants. Some of the plants producing it are called wintergreens, hence the common name. The following plants produce methyl salicylate in varying amounts: most species of the family Pyrolaceae, particularly those in the genus Pyrola, some species of the genus Gaultheria in the family Ericaceae, some species of the genus Betula in the family Betulaceae, particularly those in the subgenus Betulenta. [Ref: RA Culp, JE Noakes - Journal of Agricultural and Food Chemistry, 1992]
Niacin *(in extended-release formulations nicotinic acid)*	II	Y	Is defined as an NHP as per Schedule I Item 3 to the NHP Regulations.
Phenol (preparations with concentration of more than 20%)	II	Y	This substance occurs in the essential oils of certain mints such as Perovskia angustifoliaand Elscholtzia nipponica, in seeds of Mexican cotton (Gossypium mexicanum), white peony (Paeonia albiflora), and Chinese skunk vine (Paederia chinensis), in the wood of trembling aspen (Populus tremuloides), and in the leaves of mulberry (Morus spp.) [Ref: Harborne JB, Baxter H. 1993. Phytochemical Dictionary: A Handbook of Bioactive Compounds from Plants. Taylor & Francis, London].
Physostigmine salicylate (for oral or topical use)	II	Y	Parasympathomimetic obtained from the Calabar bean, which is the seed of a leguminous plant, Physostigma venenosum, a native of tropical Africa. [Ref: The Review of Natural Products by Facts and Comparisons. St. Louis, MO: Wolters Kluwer Co., 1999., accessed through the Natural Medicines Comprehensive Database].
Potassium salts *(in oral preparations containing more than 5 mmol per single dose)*	II	Y	Potassium makes up about 2.4% of the weight of the Earth's crust and is the seventh most abundant element in it. Potassium salts such as carnallite, langbeinite, polyhalite, and sylvite are found in ancient lake and sea beds. These minerals form extensive deposits in these environments, making extracting potassium and its salts more economical. The principal source of potassium, potash, is mined in California, Germany, New Mexico, Utah, and in other places around the world. [Ref: American Journal of Clinical Nutrition, Vol. 69, No. 4, 727-736, April 1999]

Povidone - iodine (vaginal preparations, except in concentrations of 5% or less)	II	Y	Povidone is short for poly-1vinyl-2pyrrolidinone, which is a synthetic carrier polymer. Povidone iodine is an iodophore, meaning a loose complex of iodine and the polymer which is used to stabilize the iodine. Povidone is an inert excipient, i.e. a non-medicinal ingredient. Iodine is not chemically modified or derivatized in any way by the povidone. [Ref: USP 29, p. 1779.]
Pseudoephedrine and its salts and preparations in single entity products	II	Y	Pseudoephedrine is a phenethylamine, and an isomer of ephedrine. Although pseudoephedrine occurs naturally as an alkaloid in certain plant species (for example, as a constituent of extracts from the ephedra species, also known as Ma Huang, in which it occurs together with other isomers of ephedrine), the majority of pseudoephedrine produced for commercial use is derived from yeast fermentation of dextrose in the presence of benzaldehyde. In this process, specialized strains of yeast (typically a variety of Candida utilis or Saccharomyces cerevisiae) are added to large vats containing water, dextrose and the enzyme pyruvate decarboxylase (such as found in beets and other plants, inter alia). After the yeast has begun fermenting the dextrose, the benzaldehyde is added to the vats, and in this environment the yeast converts the precursor ingredients to l-phenylacetylcarbinol (L-PAC). L-PAC is then chemically converted to pseudoephedrine via reductive amination. [Ref: Gurley, BJ American Journal of Health-System Pharmacy, Vol 57, Issue 10, 963-969]
Pyrethrins	II	Y	The pyrethrins are contained in the seed cases of the perennial plant pyrethrum (Chrysanthemum cinerariaefolium), which is grown commercially to supply the insecticide. [Ref: Natural Medicines Comprehensive Database]
Racemethionine	II	Y	Racemic mixture of D and L methionine, which is an amino acid. The NHP Regulations do not differentiate between L and D amino acids, although only the D amino acids are essential.
Rue and its preparations and extracts	II	Y	Rue (Ruta) is a genus of strongly scented evergreen subshrubs 20-60 cm tall, in the family Rutaceae, native to the Mediterranean region, Macaronesia and southwest Asia. Different authors accept between 8-40 species in the genus. The most well-known species is the Common Rue. The leaves are bipinnate or tripinnate, with a feathery appearance, and green to strongly glaucous blue-green in colour. The flowers are yellow, with 4-5 petals, about 1 cm diameter, and borne in cymes. The fruit is a 4-5 lobed capsule, containing numerous seeds. The applicable parts of rue are the above ground parts. Rue contains the alkaloids arborine, arborinine, and gamma-fagarine; and the furocoumarins rutamarin, bergapten, and xanthotoxin. [Ref: Natural Medicines Comprehensive Database]
Salicylic acid and its salts *(in topical preparations in concentrations greater than 40%)*	II	Y	Salicylic acid was first isolated from the flower buds of the herb called Filipendula ulmaria or Spiraea ulmaria in 1839. [Ref: http://raskin8500-226.rutgers.edu/~alexanderpoulev/NatAspirin.pdf]

Scopolamine and its salts (hyoscine)	II	Y	Also known as hyoscine, which is a tropane alkaloid drug obtained from plants of the family Solanaceae (nightshades), such as henbane or jimson weed (Datura species). It is part of the secondary metabolites of plants. This drug has been frequently used as the "date rape drug", and it is in the best interest of the public that the sale of this drug be monitored. [Ref: SP Clissold, RC Heel - Drugs, 1985 - ncbi.nlm.nih.gov.]
Silver nitrate (NHPD: *in homeopathic preparations only, not found in nature*)	II	Y*	Silver nitrate crystals can be produced by dissolving silver in nitric acid and evaporating the solution. Not a naturally occurring product. However, some silver nitrate preparations have been sold as homeopathic medicine (Argentum Nitricum). Those would qualify to receive NHP status. [Ref: Martindale 34th Ed. Pg. 1746]
Sodium chloride (single ingredient solutions for parenteral or ophthalmic use in concentrations of more than 0.9% [NOTE: Does not apply to contact lens solutions intended to be rinsed off prior to insertion into eye])	II	Y*	Parenteral products administered by injection are not eligible as NHPs. The ophthalmic solution meets the criteria - NaCl is a naturally occurring sodium salt, both within living organisms and as a mineral. [Ref: Wyllie et al. Elastic Wave Velocities in heterogeneous and porous media. Geophysics, Volume 21, Issue 1, pp. 41-70, January 1956].
Sodium iodide (for sclerosing)	II	Y	Sodium iodide exists in seawater at a concentration of 1000 tons per cubic mile of seawater. [Ref: http://www.speclab.com/elements/iodine.htm]. Sodium iodide also often is used a source of obtaining iodine.
Stramonium, its preparations, extracts and compounds	II	Y	Dried leaf and or flowering tops of the Datura stramonium. [Ref: Martindale 34th Ed. Pg. 489]
Streptokinase (as a debriding agent)	II	Y*	A preparation of protein obtained from culture filtrates of certain strains of haemolytic Streptococcus group C. Qualifies as an NHP, providing that it is not administered IV or intraarterially. [Ref: Martindale 34th Ed. Pg. 1005]
Strontium and its salts (for parenteral use)	II	Y*	Strontium salts are used in ophthalmic solutions and in dental preparations. IV salts are radiopharmaceuticals and are not eligible as an NHP. Due to its extreme reactivity to air, this element occurs naturally only in compounds with other elements, as in the minerals strontianite, celestite, etc. In pharmaceuticals, it is sold as the chloride and acetate salts. It is uncertain if this element exists as these salts in nature, but the salt form is necessary to keep the element stable. [Ref: Earth and Planetary Science Letters, vol. 120, no. 1-2, p. 77-84]
Sutilains	II	Y	Contains enzymes derived from the bacteria Subtilis bacillus as the active ingredient. It is used topically for the debridement of wounds. [Ref: Martindale 34th Ed. Pg. 1751]
Thyroglobulin	II	Y	Proteolytic enzyme extracted from mammalian pancreas.
Urea (in topical preparations in concentrations of more than 25%)	II	Y	Excretory form of nitrogen in most mammals. [Ref: Cornell et al. Urea in rainwater and atmospheric aerosol - their chemistry and availability to phytoplankton. Atmospheric Environment, Volume 32, Number 11, 1 June 1998, pp. 1903-1910(8)].

Vitamins (any parenterals not otherwise included in Schedule I)	II	Y*	If administered by puncturing the dermis, vitamins are not eligible for sale under NHP Regulations as outlined by Schedule II Item 5 of the NHP Regulations. However, if the vitamin is applied topically or via other parenteral routes that do not require puncturing the dermis, they would be considered NHPs.
Xylose	II	Y	A monosaccharide containing five carbon atoms and including an aldehyde functional group. Xylose is found in the embryos of most edible plants. [Ref: Cheng-Shung Gong. Quantitative production of xylitol from D-xylose by a high-xylitol producing yeast mutant Candida tropicalis HXP2. Biomedical and Life Sciences and Chemistry and Materials Science. Volume 3, Number 3 / March, 1981]

Schedule III			
Aloe vera latex, its extracts and derivatives[except aloin] (dosage forms for systemic use containing more than 300 mg per dosage unit)	III	Y	Obtained from the thin-walled mucilaginous cells in the centre of the leaf, particularly just beneath the leaf skin. The active constituents include emodin anthrone, dithranol, chrysarobin, and allantoin. [Ref: Hormann HP, Korting HC. Evidence for the efficacy and safety of topical herbal drugs in dermatology: part I: anti-inflammatory agents. Phytomedicine 1994;1:161-71].
Aluminum oxide	III	Y	A mineral, occurring naturally as the cristalline form called corundum, which is also a salt forming mineral. [Ref: http://www.mercksource.com]
Antipyrine (for otic use)	III	Y*	There are 5 antipyrine products that are sold in Canada. 4 of them are Scheduled as OTC and 1 of them is a homeopathic preparation. The homeopathic preparation (Antipyrinium), would be eligible for sale under NHP Regulations with a DIN-HM. If there were any antipyrine products that belong to Schedule F2 to the Act, they would not be eligible for sale under NHP Regulations, but at this time, there are none. Since this product does not exist in nature (it is a synthetic pyrazole), the 4 OTC products do not meet the criteria to be regarded as NHPs. [Ref: http://www.britannica.com/eb/article-79800, H S.K. HERTZ and BIEMANN Department of Chemistry, Massachusetts Institute of Technology, cambridge, Massachusetts 02139].
Belladonna alkaloids and their salts and derivatives (for topical use)	III	Y	Belladonna is a plant, and the applicable parts used medicinally are the leaf and root. Its anticholinergic activity is due to the 0.3%-0.5% tropane alkaloid constituents; mainly l-hyoscyamine, but it also contains traces of l-scopolamine and atropine (dl-hyoscyamine). On extraction, most of the l-hyoscyamine is racemized to atropine. [Ref: Leung AY, Foster S. Encyclopaedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics. 2nd ed. New York, NY: John Wiley & Sons, 1996.].
Benzocaine and its salts *(for topical use on mucous membranes for teething)*	III	Y	One biological source is as a constituent of the stems of Strychnos cathayensis [Ref: Dictionary of Natural Products on CD-ROM ver. 15:1, Copyright © 1982-2007 Chapman & Hall/CRC, Copyright © 2007 Hampden Data Services Ltd.; Cheng M-J, Tsai I-L, Chen I-S. 2001. Chemical Constituents from Strychnos cathayensis. Journal of the Chinese Chemical Society 48: 235-239]
Berberis vulgaris (Barberry)	III	Y	European barberry fruit. Parts used include roots, berries and bark. [Ref: J Ethnopharmacol 1999;64:161-6.]
Casanthranol	III	Y	Anthranquinone stimulant laxative. Obtained as an extract of cascara. The applicable part of cascara is the dried bark, standardized to anthraglycoside constituent called cascaroside A. This is the same constituent that is present in casanthranol. Also listed in the Approved Natural Health Products. [Ref: Martindale 34th Ed. pg 1255].

Danthron	III	Y	Danthron is a 1,8-Dihydroxyanthraquinone, compounds that are present in laxatives, fungi imperfecti, Chinese herbs and possibly vegetables. In one study, danthron was found in a lettuce extract. [Ref: Food & Chemical Toxicology. 37(5):481-91, 1999 May.]. The manufacturers of the two Danthron-containing stimulant laxatives currently on the market have informed the Therapeutic Products Directorate within Health Canada that they have voluntarily ceased sale of their products in 1997, as it is suspected to be a human carcinogen. [Ref: http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/1997/1997_64_e.html].
Deoxycholic acid and its salts	III	Y	Secondary bile acid formed in the colon by bacterial deconjugation and 7 alpha dehydroxylation. It is extracted from the bile of cattle which is a by-product of the meat processing industry. [Ref: Martindale 34th Ed. pg. 1660].
Electrolyte solutions (for oral rehydration)	III	Y	Oral rehydration solutions usually consist of 4 components: Electrolytes (sodium citrate, sodium chloride and potassium chloride), Bicarbonate source, (like sodium citrate or sodium bicarbonate), water and glucose (dextrose). Sodium Citrate is derived from citric acid, which is a natural product manufactured by fermentation, and the salt is manufactured by neutralising the acid with a mineral salt sources of sodium. Citric acid and its salts are natural components of plants and animals. Citric acid and its sodium, potassium and calcium salts are also produced by a fungal fermentation using natural constituents like glucose syrups, sugar or molasses.[Ref: http://www.ams.usda.gov/nop/PublicComments/Sunset/Handling/ECAMA.pdf]. Sodium chloride is the salt most responsible for the salinity of the ocean and of the extracellular fluid of many multicellular organisms and is a nuaturally occuring salt. Potassium chloride occurs naturally as the mineral sylvite and in combination with sodium chloride as sylvinite.
Ephedrine and its salts in combination products (in preparations containing no more than 8 mg per unit dose, with a label recommending no more than 8 mg/dose or 32 mg/day and for use not more than 7 days, and indicated for nasal congestion.	III	Y	Chemically, ephedrine is an alkaloid derived from various plants in the genus *Ephedra* (family Ephedraceae). It is the principal alkaloid constituent of ephedra. The applicable parts of ephedra used in drug preparations are the stem and leaf. Ephedra in dietary supplements is usually either a formulation of powdered stems and aerial portions or a dried extract. [Ref: J Clin Pharmacol 1997;37:116-22.]
Fluoride and its salts (see sodium fluoride). (in oral preparations containing 1mg or less of fluoride ion per dosage unit)	III	Y	Most of the world's supply of fluoride comes form the mineral calcium fluoride. It is a common mineral in deposits of hydrothermal origin and has been noted as a primary mineral in granites and other igneous rocks and as a common minor constituent of dolostone and limestone. Calcium fluoride is a widely occurring mineral which is found in large deposits in many areas. [Ref: Gaciri, SJ; Davies, TC. Occurrence and geochemistry of fluoride in some natural waters of Kenya. Journal of Hydrology (Amsterdam). Vol. 143, no. 3-4, pp. 395-412. 1993]

Heparin and its salts (for topical use)	III	Y	Prepared from the lungs of oxen or the intestine mucosa of pigs. Does occur naturally and qualifies as an NHP, providing that the administration is topical. [Ref: Martindale 34th Ed. Pg. 927]
Hydrocortisone acetate *(as a single ingredient in topical preparations in concentrations of 0.5% or less)*	III	Y	Several mammals (including humans) do synthesize hydrocortisone. In humans, hydrocortisone is synthesized in the adrenal cortex. In mammals, a complex biosynthetic pathway which involves several enzymes converts cholesterol into hydrocortisone. Cholesterol is converted into pregneolone, which is then hydroxylated by 17-alpha hydroxylase into 17-alpha hydroxypregneolone. Then, the latter is converted to 11-deoxycortisol by 21-hydroxylase, which is then further converted to hydrocortisone by the enzyme 11-hydroxylase. [Ref: http://www.biochem.arizona.edu/classes/bioc462/462bh2006/462bhonorsprojects/462bhonors2003/tilleys/mammalian.htm].
Hydrocortisone *(as a single ingredient in topical preparations in concentrations of 0.5% or less)*	III	Y	Several mammals (including humans) do synthesize hydrocortisone. In humans, hydrocortisone is synthesized in the adrenal cortex. In mammals, a complex biosynthetic pathway which involves several enzymes converts cholesterol into hydrocortisone. Cholesterol is converted into pregneolone, which is then hydroxylated by 17-alpha hydroxylase into 17-alpha hydroxypregneolone. Then, the latter is converted to 11-deoxycortisol by 21-hydroxylase, which is then further converted to hydrocortisone by the enzyme 11-hydroxylase. [Ref: http://www.biochem.arizona.edu/classes/bioc462/462bh2006/462bhonorsprojects/462bhonors2003/tilleys/mammalian.htm].
Iodine and its salts and derivatives (for topical use)	III	Y	Iodine occurs in the environment chiefly as dissolved iodide in seawater. However, it is present in some minerals and soils as well. The element may be prepared in an ultrapure form through the reaction of potassium iodide with copper (II) sulfate. There are also several other methods of isolating this element. Although the element is actually quite rare, kelp and certain other plants have the ability to concentrate iodine, which helps introduce the element into the food chain as well as keeping its cost down. [Ref: J Fabryka-Martin, H Bentley, D Elmore, PL Airey - Geochimica et Cosmochimica Acta, 1985].
Lactic acid (in preparations in concentrations of more than 10%)	III	Y	Lactic acid can be fermented from lactose (milk sugar), and most commercially used lactic acid is derived from bacteria such as *Bacillus acidilacti, Lactobacillus delbueckii* or *L. bulgaricuswhey* to ferment carbohydrates from sources such as the cornstarch, potatoes or molasses. [Ref: Natural Medicines Comprehensive Database]
Magnesium citrate (cathartics)	III	Y	Magnesium salt. Magnesium occurs in green vegetables such as spinach provide magnesium because the centre of the chlorophyll molecule contains magnesium. Nuts (especially almonds), seeds, and some whole grains are also good sources of magnesium. [Ref: J. Agric. Food Chem. 2000, 48, 5715-5722].

Magnesium salicylate (except oral dosage forms which also contain choline salicylate)	III	Y	Both magnesium and salicylate exist in nature, and are NHPs on their own. Although it is unlikely that they exist as this exact salt in nature, salts and derivatives of minerals, vitamins and NHPs are also considered NHPs according to the Product Licensing Document (pg. 10-11).
Narcotine and its salts (Noscapine)	III	Y	One of the alkaloids of plant from the Turkish Papaver species. [Ref: Pure Appl.Chem.,Vol.74,No.4,pp.557 – 574,2002.]
Noscapine	III	Y	One of the alkaloids of plant from the Turkish Papaver species. [Ref: Pure Appl.Chem.,Vol.74,No.4,pp.557 – 574,2002.]
Nystatin and its salts and derivatives *(in topical preparations for use on the skin)*	III	Y	Like many other antimycotics and antibiotics, nystatin is of bacterial origin. It was isolated from Streptomyces noursei in 1950 by Elizabeth Lee Hazen and Rachel Fuller Brown, who were doing research for the Division of Laboratories and Research of the New York State Department of Health. The soil sample where they discovered nystatin, was from the garden of Hazen's friends called Nourses, therefore the strain was called noursei. Hazen and Brown named nystatin after the New York State Public Health Department (now known as the Wadsworth Centre) in 1954. It is not an antibacterial, therefore it does not meet the disqualifying criteria as per Schedule II Item 6. [Ref: Vincente, MF. Microbial natural products as a source of antifungals. Clinical Microbiology & Infection Volume 9 Page 15 - January 2003]
Povidone - iodine (topical preparations, except in concentrations of 5% or less)	III	Y	Povidone is short for poly-1vinyl-2pyrrolidinone, which is a synthetic carrier polymer. Povidone iodine is an iodophore, meaning a loose complex of iodine and the polymer which is used to stabilize the iodine. Povidone is an inert excipient, i.e. a non-medicinal ingredient. Iodine is not chemically modified or derivatized in any way by the povidone. [Ref: USP 29, p. 1779.]
Pseudoephedrine and its salts and preparations in combination products (Note: Pharmacists are advised that in areas where there is evidence of abuse or particular concern about abuse, pseudoephedrine products should not be located in a self-selection area	III	Y	Pseudoephedrine is a phenethylamine, and an isomer of ephedrine. Although pseudoephedrine occurs naturally as an alkaloid in certain plant species (for example, as a constituent of extracts from the ephedra species, also known as Ma Huang, in which it occurs together with other isomers of ephedrine), the majority of pseudoephedrine produced for commercial use is derived from yeast fermentation of dextrose in the presence of benzaldehyde. In this process, specialized strains of yeast (typically a variety of Candida utilis or Saccharomyces cerevisiae) are added to large vats containing water, dextrose and the enzyme pyruvate decarboxylase (such as found in beets and other plants, inter alia). After the yeast has begun fermenting the dextrose, the benzaldehyde is added to the vats, and in this environment the yeast converts the precursor ingredients to l-phenylacetylcarbinol (L-PAC). L-PAC is then chemically converted to pseudoephedrine via reductive amination. [Ref: Gurley, BJ American Journal of Health-System Pharmacy, Vol 57, Issue 10, 963-969]

Sodium biphosphate (cathartics)	III	Y	Also known as sodium monophosphate, which is a sodium salt of phosphoric acid. Phosphoric acid can be obtained pure in crystalline state. [http://www.mbm.net.au/health/296-385.htm]. According to the Product Licensing Guidance Document, salts and derivatives of minerals are considered NHPs. Phosphoric acid and its salts are found in different live organisms, especially in the compounds derived from phosphorylated sugars, such as DNA and RNA and adenosine triphosphate (ATP). [Ref: Taylor & Francis. Hydroxyl and superoxide anion radical scavenging activities of natural source antioxidants using the computerized JES-FR30 ESR spectrometer system. Biochemistry and Molecular Biology International. Volume 42, Number 1. June 1997].
Sodium phosphate *(cathartics)*	III	Y	Also known as sodium monophosphate, which is a sodium salt of phosphoric acid. Phosphoric acid can be obtained pure in crystalline state. [http://www.mbm.net.au/health/296-385.htm]. According to the Product Licensing Guidance Document, salts and derivatives of minerals are considered NHPs. Phosphoric acid and its salts are found in different live organisms, especially in the compounds derived from phosphorylated sugars, such as DNA and RNA and adenosine triphosphate (ATP). [Ref: Taylor & Francis. Hydroxyl and superoxide anion radical scavenging activities of natural source antioxidants using the computerized JES-FR30 ESR spectrometer system Biochemistry and Molecular Biology International. Volume 42, Number 1. June 1997].
Tyrothricine	III	Y	Classified as an antibacterial, not an antibiotic. The former is an antiseptic (acts on the surface of the skin) against bacteria, the latter is a orally ingested medication. Cyclic polypeptide produced by the growth of the bacteria *Bacillus brevis.* [Ref: Martindale 34th Ed. Pg. 275]

Unscheduled			
Aloin	U	Y	Constituent in the yellow sap of aloe. [Ref: J Chromatogr A. 1995 Dec 1;718(1):99-106]
Ammonium hydroxide	U	Y	Formed from ammonia dissolved in aqueous solution. Ammonia does occur naturally at low levels in foods, in both aqueous and ammonium hydroxide forms. It is commonly found in manure and decaying organic matter. However, all commercial sources are synthetically manufactured from atmospheric nitrogen, usually using natural gas as a fuel source. [Ref. http://www.ams.usda.gov/NOP/NationalList/TAPReviews/ammoniumhydroxide.pdf].
Attapulgite (active)	U	Y	A purified native hydrated aluminium magnesium silicate which has been carefully heated. It is essentially consisting of the mineral palygorskite. Palygorskite is a hydrated magnesium aluminium silicate, which occurs as a fibrous chain-structure mineral in clay deposits in several areas of the world [Ref: Martindale 34th Ed. Pg. 1251).
Benzocaine and its salts.. (for topical application on the skin)	U	Y	One biological source is as a constituent of the stems of Strychnos cathayensis [Ref: Dictionary of Natural Products on CD-ROM ver. 15:1, Copyright © 1982-2007 Chapman & Hall/CRC, Copyright © 2007 Hampden Data Services Ltd.; Cheng M-J, Tsai I-L, Chen I-S. 2001. Chemical Constituents from Strychnos cathayensis. Journal of the Chinese Chemical Society 48]
Bile salts	U	Y	Bile salts are steroids with detergent properties which are used to emulsify lipids in foodstuff passing through the intestine to enable fat digestion and absorption through the intestinal wall. Commercial preparations are derived from the bile of the ox, and are used medicinally as a hepatic stimulant or laxative. Also classified as an NHP under the Health Canada "Summary of NHP/DRUG Classification of TPD Category IV Labelling Standards Ingredients"
Bioflavanoids	U	Y	The term bioflavonoids refers to many different ingredients and includes hesperin, hesperidin, eriodictyol, quercetin, quercetin, rutin etc. This nutrient can not be manufactured by the body and must be supplied in the diet. They are naturally occurring antioxidants widely distributed in plants. They can also be found in foods such as fruit, veggies, tea, red wine. Bioflavanoids are also part of the Approved Natural Health Products list.
Boric acid and its salts. (in ophthalmic preparations in concentrations up to and including 2%, and in contact lens solutions intended to be rinsed off prior to insertion into the eye)	U	Y	Boron is a trace mineral for which a clear biological function in humans has not been established. Boron is well absorbed from dietary beverages including prune and grape juice; wine; coffee; milk; and in some geographical locations, water. Avocados, peanuts, pecans, apples, dried beans, and potatoes also contain boron. [Ref: Food and Nutrition Board, Institute of Medicine.]

Camphor. (in oleaginous vehicles and in liquid forms in concentrations up to and including 11%)	U	Y	The applicable parts of camphor are the bark and wood. Camphor was formerly obtained by distilling the bark and wood of the camphor tree. Today, camphor is typically obtained by synthetic production from turpentine oil. [Ref: Love JN, Sammon M, Smereck J. Are one or two dangerous? Camphor exposure in toddlers. J Emerg Med 2004;27:49-54.].
Caprylic acid.	U	Y	Caprylic acid is the common name for the eight-carbon straight chain fatty acid known by the systematic name octanoic acid. It is found naturally in coconuts and breast milk. [Ref: Wolfgang F. Sources of Fine Organic Aerosol Particulate Abrasion Products from Leaf Surfaces of Urban Plants. Environ. Sci. Technol. 1993, 27, 2700-271].
Capsaicin	U	Y	The applicable part of capsicum is the fruit. Capsicum contains the constituent capsaicin, which makes it taste hot. Naturally-occurring capsaicin exists only in the trans-stereoisomer form. [Ref: http://www.naturaldatabase.com/].
Cascara sagrada and its extracts and derivatives	U	Y	Dried, whole or fragmented bark of *Rhammus purshianus*. It contains not less than 8% hydroxyanthracene glycosides of which no less than 60% consist of cascarosides, both expressed as cascaroside and calculated with reference to the dried drug. [Ref: Martindale 34th Edition, pg 1255, Natural Medicines Comprehensive Database]
Digestive enzymes (from plant sources)	U	Y	Sources of naturally occurring enzymes include: variety of plants, in milk, milk products, bacteria, moulds, and animal tissues castor beans and hulled oats, and pork or beef pancreas. [Ref: Natural Medicines Comprehensive Database].
Docosanol *(10% for topical use)*	U	Y	A saturated 22-carbon aliphatic fatty alcohol also called behenyl acid. Fatty alcohols, derived from natural fats and oils, are high molecular straight chain primary alcohols. The are synthetic fatty alcohols are physically and chemically equivalent to the natural alcohols obtained from oleochemical sources such as coconut and palm kernel oil. [Ref:http://chemicalland21.com/industrialchem/solalc/BEHENYL%20ALCOHOL.htm]. A series of 22-carbon up to 28-carbon saturated fatty alcohols, with even carbon numbers predominating, has been identified in the cyanobacterium *Anabaena cylindrica* [Ref: Abreu-Grobois FA et al., Phytochemistry 1977, 16, 351]. Several authors have reported high contents of the 22-carbon alcohol in sediments where an algal origin is plausible. For example, the major alcohol in a sample of the lacustrine Green River Shale of Eocene alge is the 22-carbon alcohol in question, and it comprises over 50% of the alcohols present [Ref: Sever JR et al., Science 1969, 164, 1052].
Glutamic acid and its salts (gastric acidifiers)	U	Y	Naturally occurring amino acid found in a variety of foods.

Guaifenesin	U	Y	Guaifenesin is natural substance that was isolated around the early 1500's for purported uses to cure rheumatism. Also know as Guaiacol glyceryl ether, guaifenesin has been used for years to promote expectoration of secretions in patients with pulmonary disease. The drug is derived from the resin of guaiacum trees and was introduced to European medicine in the 16th century as an analgesic. The extraction from the natural source is involves a very simple steam distillation process followed by a series of acid-base extractions to remove the guaifenesin resin from the other substituents in the distillate. [Ref: Journal of Chemical Education. March 2003. Vol. 80 No. 3., Appl Ther 1967;9:55-9.]
Inositol niacinate	U	Y	Cyclic polyalcohol that plays an important role as a second messenger in a cell, in the form of inositol phosphates. It is found in many foods, particularly in cereals with high bran content. Inositol is synthesized from G6P in two steps. First G6P is isomerized by INYNA1 to myo-inositol 1-phosphate, which is then dephosphorylated by IMPA1 to yield inositol. It exists in 9 different isomers. [Ref: Vincente, MF. Microbial natural products as a source of antifungals. Clinical Microbiology & Infection Volume 9 Page 15 - January 2003]
Ipecac and its extracts and derivatives. (for use other than as an emetic)	U	Y	Consists of the fragmented and dried underground organs (rhizomes) of *Cephaelis ipecacuanha,* a plant native to parts of Central and South America. [Ref: Martindale 34th Ed. Pg. 1122, Natural Medicines Comprehensive Database].
Iron and its salts and derivatives. (in preparations containing 30 mg or less elemental iron per dosage unit or 5 ml oral liquid)	U	Y	Most abundant metal on earth, extracted from iron ore. Occurs naturally both within the earth's core and on the surface. [Ref: http://en.wikipedia.org/wiki/Iron, Natural Medicines Comprehensive Database].
Methyl salicylate. (in liquid dosage forms in concentrations up to and including 30%)	U	Y	Also known as salicylic acid methyl ester, oil of wintergreen, betula oil, and methyl ester) is a natural product of many species of plants. Some of the plants producing it are called wintergreens, hence the common name. The following plants produce methyl salicilate in varying amounts: most species of the family *Pyrolaceae*, particularly those in the genus *Pyrola, s*ome species of the genus *Gaultheria* in the family *Ericaceae,* some species of the genus *Betula* in the family *Betulaceae*, particularly those in the subgenus *Betulenta*. [Ref: : RA Culp, JE Noakes - Journal of Agricultural and Food Chemistry, 1992]
Niacin. (in immediate-release formulations)	U	Y	Is defined as an NHP as per Schedule I Item 3 to the NHP Regulations.

Niacinamide (for topical use)	U	Y	Niacinamide, the amide of niacin, was isolated in 1934 by Warburg and Christian when coenzyme II, NADP, was extracted from horse erythrocytes. While niacinamide and niacin have identical vitamin activities (i.e., they both prevent development of the vitamin B3-deficiency condition, pellagra), they have very different pharmacological activities. Natural sources of niacinamide include beef liver, brewer's yeast, halibut, chicken, sunflower seeds, and peanuts. [Ref: http://www.thorne.com/pdf/journal/7-6/niacinamide_mono7-6.pdf]
Niacinamide. (oral)	U	Y	Niacinamide, the amide of niacin, was isolated in 1934 by Warburg and Christian when coenzyme II, NADP, was extracted from horse erythrocytes. While niacinamide and niacin have identical vitamin activities (i.e., they both prevent development of the vitamin B3-deficiency condition, pellagra), they have very different pharmacological activities. Natural sources of niacinamide include beef liver, brewer's yeast, halibut, chicken, sunflower seeds, and peanuts. [Ref: http://www.thorne.com/pdf/journal/7-6/niacinamide_mono7-6.pdf]
Nicotine and its salts *(when sold as a chewing gum containing not more than the equivalent of 4mg of nicotine per dosage unit)*	U	Y	Nicotine is an alkaloid found in the nightshade family of plants (*Solanaceae*), predominantly in tobacco, and in lower quantities in tomato, potato, eggplant (aubergine), and green pepper. Nicotine alkaloids are also found in the leaves of the coca plant. [Ref: Manuel F. Balandrin. Natural Plant Chemicals: Sources of Industrial and Medicinal Materials. Science 228: 1154-60]
Nicotine and its salts *(when sold in a form to be administered orally by means of an inhalation device delivering 4mg or less of nicotine per dosage unit)*	U	Y	Nicotine is an alkaloid found in the nightshade family of plants (*Solanaceae*), predominantly in tobacco, and in lower quantities in tomato, potato, eggplant (aubergine), and green pepper. Nicotine alkaloids are also found in the leaves of the coca plant. [Ref: Manuel F. Balandrin. Natural Plant Chemicals: Sources of Industrial and Medicinal Materials. Science 228: 1154-60]
Nicotine and its salts *(when sold as a transdermal patch with a delivery rate of not more than the equivalent of 22mg)*	U	Y	Nicotine is an alkaloid found in the nightshade family of plants (*Solanaceae*), predominantly in tobacco, and in lower quantities in tomato, potato, eggplant (aubergine), and green pepper. Nicotine alkaloids are also found in the leaves of the coca plant. [Ref: Manuel F. Balandrin. Natural Plant Chemicals: Sources of Industrial and Medicinal Materials. Science 228: 1154-60]
Pancreatic enzymes, pancreatin, pancrelipase (except in products for the treatment of established pancreatic insufficiency)	U	Y	Prepared from the pancreas of mammals such as hog or ox. [Ref: Martindale's 34th Ed. Pg. 1726].
Papain (as a debriding agent)	U	Y	Papain is actually a mixture of the proteolytic enzymes papain, chymopapain A, chymopapain B, and papaya peptidase A isolated from the fruit of Carica papaya. [Ref: Natural Medicines Comprehensive Database].
Pepsin	U	Y	Prepared from the gastric mucosa of pigs, cattle and sheep. [Ref: Martindale 34th Ed. Pg. 1729]

Peptone	U	Y	Peptone is an enzymatic digest of protein. The raw animal products and enzymes, porcine tissue, used in the manufacturing of Peptone is derived from meat materials originating in the USA. During processing of the product, a batch is heated to a minimum of 80°C for at least 1 hour, including a minimum of 5 minutes at a minimum 105°C. The product is dried at a minimum 140°C. [Ref: http://www.usbio.net/Product.aspx?ProdSku=P3300]
Salicylic acid and its salts. (in topical preparations in concentrations up to and including 40%)	U	Y	Salicylic acid was first isolated from the flower buds of the herb called Filipendula ulmaria or Spiraea ulmaria in 1839. [Ref: http://raskin8500-226.rutgers.edu/~alexanderpoulev/NatAspirin.pdf]
Senna and its extracts and derivatives	U	Y	The applicable parts of senna are the leaf and fruit obtained form the plant *Cassia senna.* [Ref: Martindale 34th Ed. Pg. 1288]
Sodium tartrate	U	Y	Salt of tartaric acid, which is found in many foods, such as grapes and tamarinds. Molecules which contain a charge cannot exist on their own in preparations, hence the tartate is coupled with sodium. The tartrate is the active ingredient in medicinal preparations. Most sodium salts are included in the list of acceptable non-medicinal ingredients, so having sodium as the salt does not disqualify this product from being an NHP.
Trypsin	U	Y	Proteolytic enzyme extracted from mammalian pancreas.
Ubiquinone	U	Y	Also known as Coenzyme Q10. Is found in the membranes of endoplasmic reticulum, peroxisomes, lysosomes, vesicles and notably the inner membrane of the mitochondrion where it is an important part of the electron transport chain. It is produced by the human body and therefore not considered a vitamin. [Ref: Natural Medicines Comprehensive Database].