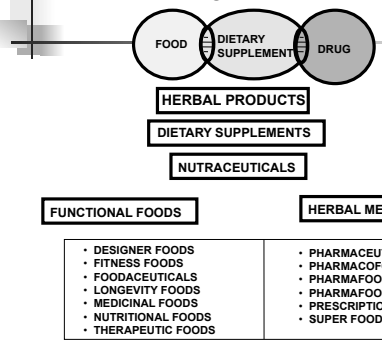
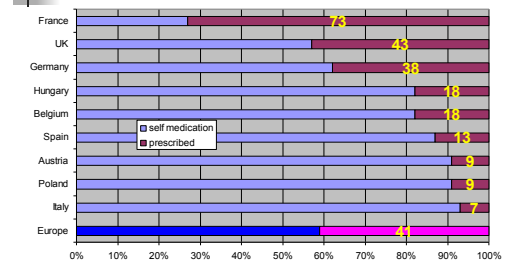
Regulatory Aspects of Herbal Medicines in Europe and North America

- Overview
- Canada
- USA
- Europe
- Conclusions

LEGAL STATUS OF HERBAL PRODUCTS WORLDWIDE

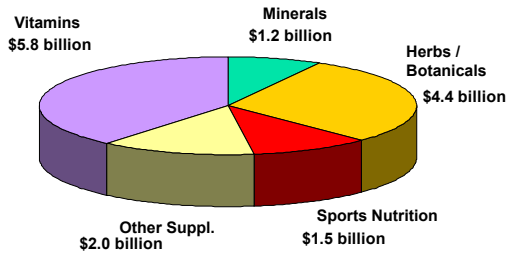


HERBAL MEDICINAL PRODUCTS PRESCRIBED BY MEDICAL DOCTORS PRESCRIPTION SHARES BY COUNTRY IN %



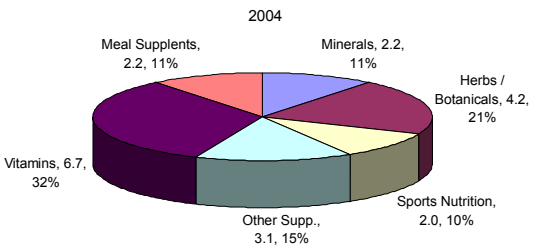
IMS 2002

Dietary Supplements in 1999: $14.9 Billion **in the USA**



Source: NBJ, derived from a variety of sources

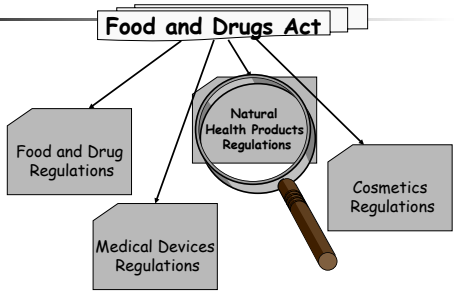
Dietary Supplements in 2004: $20.3 Billion **in the USA**



Canadian Usage of Natural Health Products

- A survey estimated that Canadians spent $3.8 billion on natural health products and non-allopathic medicine between 1996 and 1997

Canada's Regulatory Framework since 2004



Canadian Regulatory Framework for Natural Health Products

- *Food and Drug Act*
  - applies to health products in Canada with one set of regulations for foods and drugs and one for natural health products
- *Food and Drug Regulations*
  - Applies to foods – products that provide nourishment, nutrition, hydration, or to satisfy hunger, thirst or a desire for taste, texture or flavour, and
- Drugs – use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms

Canadian Regulatory Framework for Natural Health Products

- *Natural Health Products Regulations*
  - Product use same as drugs plus restoring or correcting organic functions in humans *and* maintaining or promoting health or otherwise modifying organic functions in humans
  - Suitable for self-medication only
  - Does not apply to raw materials (unless packaged and/ or labeled as a finished product)
  - Provide for products and site licensing, GMPs, adverse reaction reporting, clinical trials, labeling
  - Allow for a full range of health claims (supported by evidence)

Definitions: What are Natural Health Products?

Schedule 1 - Included Substances:

- Plant, alga, bacterium, fungus, non-human animal material
- Extract or isolate of the above
- Vitamins
- Amino acids
- Essential fatty acids
- Synthetic duplicates of the above
- Minerals
- Probiotics

Definitions: What are not Natural Health Product?

Schedule 2: Excluded Substances

- Schedule C, D of the *Food & Drugs Act*
  - Schedule C- Radiopharmaceuticals
  - Schedule D- Biologics (i.e. allergenic substances, aprotinin, insulin, snake venom)
- Substances under the *Tobacco Act*
- Schedules I-V of *Controlled Drugs & Substance Act*
- Substances administered by puncturing the skin
- Antibiotics

Application of the Regulations

- The *Regulations* apply to the sale, manufacture, packaging, labelling, importation, distribution and storage of natural health products
- Do not apply to health care practitioners who compound individual NHPs for the needs of an individual client/patient
- Retail sale of natural health products does not require a site licence

Product Licenses

- Applications must include sufficient data to allow NHPD to evaluate the safety, quality and efficacy of the natural health product
- Product license (with a Natural Product Number or Drug Identification Number-Homeopathic) issued once a product is approved for sale in Canada

Product License Applications

- Product license applications require information on:
  - Health Claim (use or purpose)
  - Ingredients (medicinal & non-medicinal)
  - Safety and efficacy information (Standards of Evidence)
  - Recommended conditions of use (dosage form, route of admin, dose, duration of use, risk info)
  - Attestation of compliance to Good Manufacturing Practices

Levels of Evidence Allowed by Health Canada for Natural Health Products

Level	Type of Evidence
I	Well-designed systematic reviews and meta-analyses of randomized controlled clinical trials (RCTs), or at least one well-designed RCT (preferably multi-centred)
II	Well-designed clinical trials studies without randomization or without control groups
III	Well-designed descriptive and observational studies, such as correlational studies, cohort studies, and case-control studies
IV	Expert opinion reports, peer-reviewed published articles, or conclusions of other reputable regulatory agencies
V	References to traditional uses

Labelling

- Evidence driven label claim
  - Traditional - Literature review:
    - "traditionally used when having a cold"
  - Scientific Data (Structure Function Claim)
    - "improved cold symptoms"
  - Clinical Trial
    - Full Health Claim:
      - "treats cold symptoms"

Clinical Trials

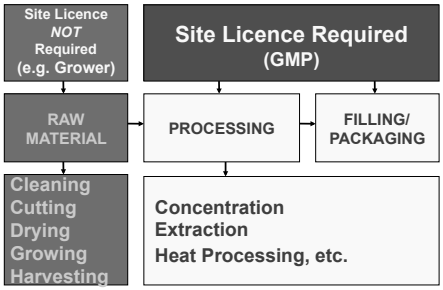
The Natural Health Product Regulations sets out requirements for conducting human clinical trials if needed. A clinical trial may be needed:

- If an NHP previously approved by Health Canada is being tested for a condition of use not captured on the product label.
- For NHPs that are not yet approved by Health Canada and for which additional efficacy and safety evidence is required before marketing can be authorized
- For NHPs with no prior history of use in humans (e.g., new isolates or new extracts on their own or in combination with other medicinal ingredients proven to be safe).

Site Licenses

- Anyone in Canada who wishes to manufacture, package, label or import a natural health product for sale must have a site license
- all sites in distribution chain (i.e. including distributors and wholesalers) must adhere to Good Manufacturing Practices (GMPs)
- Responsibility of Canadian importers to provide evidence that imported products that are manufactured, packaged and/or labelled in foreign sites meet Canadian GMPs for natural health products or equivalent standards

Activities that Require a Site License

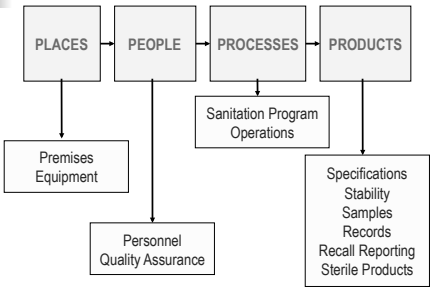


Acceptable Evidence for Foreign Sites

One of the following types of evidence is required:

- Quality Assurance Report demonstrating compliance to Canadian GMPs for natural health products
- Certificate of Compliance issued by a recognized Regulatory Authority
- Recent Inspection Report from a Recognized Regulatory Authority

Canada's Good Manufacturing Practices for Natural Health Products



Products

Specifications
- Should have specifications for raw materials, packaging materials, and finished products

Stability
- Determine the expiry date and ensure that every finished product meets its specifications and label claims at the expiry date

Samples
- A sample of each lot of a finished product should be retained

Records
- Required records should be maintained (ex. list of all ingredients, testing records, lot or batch information)

Recall reporting
- A recall program should be in place and product recall information should be submitted to Health Canada within three days of initiating a recall

Priority Approach to Compliance and Enforcement

Priority 1 - NHP substances in HPFB's New Drug List	June 1, 2004
Priority 2 - Isolates, amino acids, fatty acids, and concentrated volatile (essential) oils	Jan 1, 2005
Priority 3 - Algal, bacterial, fungal, probiotics and animal materials	June 1, 2005
Priority 4 – Plants, plant materials, extracts and volatile (essential) oils	June 1, 2007
Priority 5 - Vitamins and Minerals	Jan 1, **2008**
Priority 6 - Homeopathic Medicines	June 1, **2008**

The Dietary Supplement Market in the USA

- The DS market is large and diverse
  - Nearly 29,000 DS available for sale in the U.S.
  - The market has more than quadrupled since 1994 and is expected to continue growing
  - Main bases of appeal of DS include
    - Weight loss, regain lost vigor,
    - Used in place of prescription drugs
      - Lower prices, no prescription needed
    - Used to enhance digestion
    - 60% consumers take vitamins daily
    - Many customers prefer holistic or natural products
    - Some are taken based on ethnic practices

Dietary Supplement Health and Education Act of 1994

- DSHEA ensured that most DS's would not require pre-market testing for safety (and efficacy)
  - DSHEA defines DS's as non-food additives and as
  - Non-pharmaceutical drugs
  - Statutory definition of DS was expanded to include fish oils, ginseng,
  - DS manufacturers are not required to register with the FDA
    - Or to report adverse events
    - Note that the Bioterrorism Act of 2002 gives the FDA regulatory authority over food and DS manufacturers
  - Basically the standards for judging DS are the same as they have been since 1906
    - Can only be removed from the market if the FDA determines that a DS contains a poisonous or deleterious substance

Definition of Dietary Supplement

- Product (other than tobacco) that is intended to supplement the diet
- Contains one or more of the following dietary ingredients:
  - Vitamin
  - Mineral
  - Herb or other botanical
  - Amino acid

Definition of Dietary Supplement

- Dietary ingredients (continued):
  - Other dietary substance used by man to supplement the diet by increasing total dietary intake (e.g., glandulars, organ tissues & enzymes)
  - A concentrate, metabolite, constitute, extract, or combination of any of the above dietary ingredients

Dietary Supplement Forms

- Tablet
- Capsule
- Liquid
- Powder
- Softgel
- Gelcap

Other Requirements for Dietary Supplements

- Cannot be represented as a:
  - Conventional food
  - Sole item of a meal
- Must be intended for ingestion
- Must be labeled as a dietary supplement

Excluded As Dietary Supplements

- Articles approved or authorized for investigation as a new drug, antibiotic, or biologic that were <u>not</u> first marketed as a dietary supplement or as a food

Structure-Function Claims 21 CFR 101.93

- May make claims about:
  - Nutritional deficiency disease
  - Structure/function
  - Mechanism of effect on structure/function
  - General Well Being
- Must be an allowed claim
- Must have substantiation it is truthful and not misleading
- May not claim to treat/cure/prevent disease
- Must use mandatory disclaimer

NOTIFICATION REQUIREMENTS: Ingredients: New Dietary Ingredients (NDIs)

- NDI: Those ingredients that were not marketed in the U.S. prior to October 15, 1994
  - Note : There is no authoritative list of dietary ingredients that were marketed before October 15, 1994

NDI Premarket Notifications

- Manufacturers or distributors must submit a notification to FDA 75 days before a new dietary ingredient is marketed or introduced for marketing in the U.S.
- This notification must meet the requirements of 21 CFR § 190.6.

(http://www.cfsan.fda.gov/~lrd/cfr190-6.html)

FDA Guidelines relevant to Dietary Supplements

- The FDA issued in August 2007 GMP guidelines for the manufacturing of dietary supplements
  - No performance testing required

USP Monographs relevant to Dietary Supplements

- The USP has a separate section for Dietary supplements (2000 and higher)
- General Chapters under 1000 are FDA enforceable

USP Performance Test Scheme

Dietary Supplements

<561> Articles of Botanical Origin
<563> Identification of Articles of Botanical Origin
<565> Botanical Extracts

<2040> Disintegration and Dissolution of Nutrition Supplements
<2091> Weight Variation
<2750> Manufacturing Practices of Dietary Supplements
<2090> Weight Variations of Dietary Supplements

Regulating Herbal Medicines in Europe

Until 2004:

Different national regulations

31 March 2004:

Directive 2004/24/EC as regards traditional herbal medicinal products

Definition similar to Canada

Directive 2004/24/EC
Traditional Herbal Medicinal Product: Criteria THMP(1)

- Indications without prescription
- Specified strength and dosage
- Oral, external and/or inhalation preparation
- Period of traditional use has elapsed:
  - at least 30 years, including at least 15 years within the European Union

Traditional herbal medicinal product: Criteria (2)

- Data are sufficient:
  - Not harmful in the specified conditions of use
  - Pharmacological effects or efficacy are plausible on the basis of long-standing use and experience

Documents for the application of traditional herbal medicinal products

- Results of pharmaceutical tests
- Summary of Product Characteristics
- Information relating to combinations
- Registrations in other countries
- Evidence to the medicinal use of at least 30 with at lease 15 years in the EU

Labelling / Package Leaflet / Advertisement

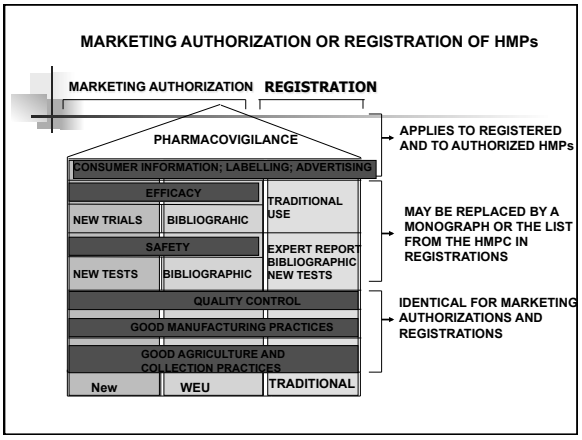
"Traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use"

Scientific Committees at EMEA (European Medicines Agency)

- CHMP (formerly CPMP): Human Medicines
- CVMP: Veterinary Medicines
- COMP: Orphan Products
- HMPC: Herbal Medicinal Products

Tasks of the HMPC

- Check evidence of long-term medicinal use of a traditional herbal medicinal product
- Prepare lists of herbal substances for registration as traditional herbal medicinal products
- Establish community monographs for traditional and other herbal medicinal products



Conclusions: Laws Regulating Natural Health Products in Canada

- Safety first!
- Evidence based claims
- Probiotics included
- Product and Site license required
- GMP mandatory but adapted to Natural Health Products (different from Drugs)

Conclusions: Laws Regulating Dietary Supplements in the USA

- Dietary Supplement Health and Education Act of 1994 - Outdated
- Defined the term dietary supplement
  - Included dietary supplements under the FD&C Act's adulteration provisions
  - Established requirements for new dietary ingredients
  - No topical allowed (Drug or Cosmetic only)
- USP and FDA have added Standards

Conclusions: Laws Regulating Dietary Supplements in Europe

- Three different Registration or Market Authorization Options
- Most restricting regulation due to one GMP Guideline

Any Questions