Regulatory environment for nutraceuticals and functional foods

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Regulatory Environment for Nutraceuticals and Functional Foods

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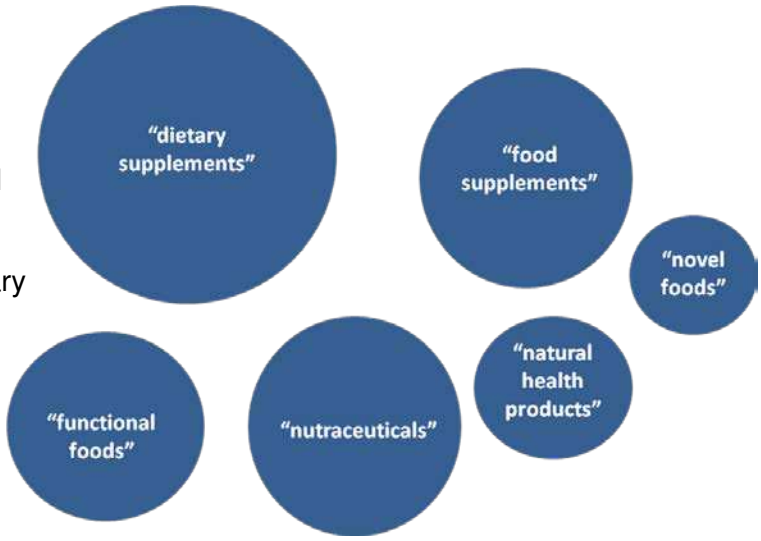
Contents

1 INTRODUCTION

A strategic regulatory plan, with timelines and budget estimates, is vital to product development in the area of nutraceuticals. This report provides information on the regulatory environment in Canada, the U.S., and the European Community. It highlights key agencies and documents, as well as areas of evolving policy, to assist firms with regulatory planning.[1] Although the key focus of this document is nutraceuticals and functional foods, other areas are covered since they are related and regulatory changes or developments could impact nutraceuticals. These areas include drugs for human and veterinary use, over-the-counter drugs, biologics and biosimilars, and cosmetics.

There is no global uniformity for regulating nutraceuticals. Approaches vary by country and Canada, the U.S. and Europe do not have regulations that specifically refer to "nutraceuticals" or "functional foods". Instead regulations refer to such categories as "natural health products", "dietary/food supplements" or "novel foods". Definitions vary and deciding where a product fits is often difficult and dependent on national perceptions.



Nutraceuticals sits at the boundary between drugs and food and depending on the claims made the "nutraceutical" may fall within either drug or food regulations.

Firms working in these industries will need to ensure that they understand how each country views their product and which regulations apply. Since working with regulations can be complex, expert advise may be required to fully understand the impact the regulatory environment will have on any given company or product.

The intent of this document is not to replace the advice and knowledge of a regulatory specialist but to give some initial insight into the regulatory process. For more in-depth coverage of this subject, check out the book:

> D. Bagchi, ed. (2008). *Nutraceutical and Functional Food Regulations in the United States and Around the World.* Elsevier.

[1] For an editorial in support of a strong and strategic regulatory plan, see G. Pekoe and A. H. Miller. (2009, July 22). Opinion: regulatory planning key for emerging technology companies. *Genetic Engineering & Biotechnology News.* http://www.genengnews.com/specialreports/sritem.aspx?oid=58652846

2 CANADA

2.1 Drugs / Pharmaceuticals

In Canada, the basic enabling legislation for the regulation of most pharmaceuticals and near pharmaceuticals (including non-prescription or over-the-counter drugs) is the *Food and Drugs Act* and *Food and Drug Regulations*. Health Canada's Therapeutic Products Directorate is the responsible division in most situations.

For purposes of regulations, drugs are classified as either Division 1 ("old" drugs, non-prescription drugs such as cough medications or products already on the market) or Division 3, 4, and 8 drugs ("new" drugs).

To bring a drug to market – to receive a Notice of Compliance or NOC – a manufacturer must first prove its safety and efficacy by passing through a multi-stage drug licensing process that consists of three key stages 1) clinical trial authorization, 2) submission review and 3) post market.

Clinical Trial Authorization Stage

In the first part of the regulated process, clinical trials, a phased approach is used, with phases 1 to 3 demonstrating safety and efficacy in an ever broader population of subjects and dosages. Trials may be stopped or fast-tracked depending on observed results and the urgency of the situation.

To begin the first stage of the Clinical Trials process, the manufacturer must first submit a Clinical Trial Application (CTA), supplying details on trial design and parameters, an investigator's brochure, a copy of the study protocol, informed consent documents, and clinical trial site information.

In support of its clinical trials process, and with an explanation of its forms and filing milestones and deadlines, Health Canada has published the following documents: *Guidance for clinical trial sponsors: Clinical Trial Applications*[2] and *Draft guidance for clinical trial sponsors: Clinical Trial Applications for comparative bioavailability studies for pharmaceuticals.*[3]

Submission Review Stage

At the conclusion of the Clinical Trials phase, the manufacturer then prepares a New Drug Submission, seeking permission to market the drug. A guidance document, *Guidance for industry: Management of drug submissions*, is available the Health Canada website.[4] New drugs (division 3, 4, and 8) go through the New Drug Submission review process.

[2] Health Canada. (2003, 2009). *Guidance for clinical trial sponsors: Clinical Trial Applications*. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php (PDF version, 45 p.)

[3] Health Canada. (2001, 2008). *Draft guidance for clinical trial sponsors: Clinical Trial Applications for comparative bioavailability studies for pharmaceuticals.* http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/ctabio_decbio-eng.php (PDF version, 32 p.)

[4] Health Canada. (1993, 2011). *Guidance for industry: Management of drug submissions*. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php (PDF version, 45 p.)

Post Market Stage

Post-market surveillance includes the mandatory reporting of adverse drug reactions and the regulatory management of any changes to the approved drug. Health Canada's MedEffect website is the vehicle for reporting adverse reactions and the site to search for reactions in their AR database, as well as to review published advisories and warnings. As for other stages in the drug licensing process, there is a Changes to a New Drug process to be followed and Health Canada publishes a guidance document for industry on how to report adverse drug reactions.[5]

Health Canada's proposed "Progressive Licensing Model" would revamp the current model, placing more emphasis on post-market events (with continuous monitoring and pharmacovigilance) and adopting more of a "life cycle" approach. There would also be more emphasis on risk-benefit assessment, with an eye to incorporating broader standards of evidence and reducing or increasing the evidentiary hurdles in proportion to the risk and benefit proposed by each new drug.[6] Keeping up-to-date on the progress of the Progressive Licensing Model should be a part of a firm's regulatory strategic program since changes such as this could have significant impact.

2.1.1 Non-Prescription (Over-the-Counter or OTC) Drugs

As noted above, Health Canada divides drugs into either "old" (Division 1, already in the market, including non-prescription painkillers cough medications, etc.) or "new" (Divisions 3, 4, and 8). Clinical trials for Division 1 may be somewhat less onerous, since the drugs are already in the market, but drugs in Divisions 3, 4, or 8 must pass through the entire approval process described above, whether prescription or OTC. Post-2004, several OTC products have been reclassified as "natural health products" and are being treated as such pursuant to the regulatory process overseen by the Natural Health Products Directorate.[7] Further information on natural health products is provided in section 2.4, below.

There have also been some recent changes to allowable advertising claims for non-prescription drugs. *"Schedule A" of the Food and Drugs Act* is a list of diseases and conditions that Health Canada has deemed too serious for self-diagnosis or treatment. In Canada, advertising of drugs to treat these diseases is prohibited. However, in December of 2007, amendments to the regulations and schedule allow OTC drug manufacturers to make claims to prevent these diseases (although not to treat or cure them).[8] Guidance on labelling non-prescription drugs is provided on Health Canada's Nonprescription Drugs: Labelling Standards page.

[5] Health Canada. (2011). *Guidance document for industry: Reporting adverse reactions to marketed health products.* http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php (PDF version, 43 p.)

[6] Health Canada. (2007, Sept. 19). *Progressive licensing model*. http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/index-eng.php

[7] Health Canada. (2010, Jan. 22). *Nonprescription drugs: Category IV monographs.* http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/cat-iv-mono/index-eng.php

[8] G. S. Jepson. (2009, January). "Drug, food and device regulation in Canada 2008: The year in review," *Regulatory Focus*, pp. 16-21. http://www.dww.com/dww/wp-content/uploads/2009/03/drug-regulation-2008.pdf

2.1.2 Biologics and Subsequent Entry Biologics (Biosimilars)

Biologics (microorganisms derived from humans or animals, and including classes of product such as blood or blood components, cytokines, monoclonal antibodies, proteins, vaccines, and gene therapy products) are considered a subset of drugs, but have a slightly different regulatory approach. This is due, in large part, to their molecular complexity and their sensitivity to changes in storage or the manufacturing process --- as a result, much more emphasis is placed on the manufacturing process and on quality control. While they still come under the responsibility of Health Canada, the regulatory wing is the Biologics and Genetic Therapies Directorate. The Directorate's Applications and Submissions page provides access to the forms, guidance documents, policies, and templates for regulatory submissions of these products.

A particular issue for the Directorate is the treatment of "subsequent entry biologics" (SEBs, also known as biosimilars or "follow-on protein products", especially in the U.S. and the European Community), biologics entering the market that are similar to already approved biologics that are ending their period of patent protection. Health Canada is considering the issue of whether or not to allow a reduced degree of evidentiary burden to SEB applicants, and how to prove similarity when the applicant does not have access to the originator's data on raw materials or information on proprietary manufacturing processes. In addition, the complexity of these products, and their frequently varied biological effect, present special challenges. The legal and pharmacological issues surrounding SEBs surface frequently in the literature, and Health Canada and other regulatory agencies are in the process of trying to reform regulations in order to deal with them.[9]

2.2 Nutraceuticals and Functional Foods

In Canada, natural health products are regulated as a sub-category of drugs. The *Natural Health Product Regulations*, promulgated in 2004, created definitions and classifications for such products, and set requirements for efficacy, safety and quality reviews. The regulations also required that the over 40,000 such products already on the market in Canada be assessed and obtain a licence and Natural Product Number (NPN) within a six year period. In some cases, because of the obvious backlog and bureaucratic burden created, this date has been extended and Health Canada has allowed products to be marketed, pending review.[10] The Natural Health Products Directorate of Health Canada is the responsible agency.

Products requiring a prescription continue to be regulated under the *Food and Drug Regulations (FDRs)*, and health food claims for functional foods are also managed under the authority of the *Food and Drugs Act*. Some products at the natural health product/food interface (e.g., foods with bioactive ingredients and general or specific health claims) create areas of confusion and controversy, however. Health Canada has sought public input in these gray/developing areas, and is in the process of determining policies which will establish rules and guidelines that reflect new realities, and protect

[9] Health Canada. (2006). Fact sheet: Subsequent Entry Biologics in Canada. http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006-eng.php ; see also, G. S. Jepson. (2009, January). "Drug, food and device regulation in Canada 2008: The year in review," *Regulatory Focus*, pp. 16-21. http://www.dww.com/dww/wp-content/uploads/2009/03/drug-regulation-2008.pdf

[10] S. Martyres, M. Harwood and E. R. Nestmann. (2008). Emerging policies and practices under the Canadian Natural Health Product Regulations. In D. Bagchi (ed.) *Nutraceutical and Functional Food Regulations in the United States and Around the World* (Chapter 12). Elsevier.

consumer health, in anticipation of an environment where these types of product are increasingly present in the market.[11] In 2010, Health Canada issued a guidance document to aid in determining whether a product should be classified as a food or natural health product.[12]

According to the regulations, natural health products (NHPs) may be defined by either substance or function. Substance components include plants, algae, bacteria, fungi, animal products (human or otherwise), and homeopathic medicines, including probiotics, amino or fatty acids, vitamins, and minerals. NHPs may also comprise extracts, isolates, or synthetic versions of the same substances. Excluded are antibiotics, substances administered by puncturing the dermis, substances regulated under the *Tobacco Act*, and several other substances regulated under the FDRs, such as radiopharmaceuticals, biologics and drugs. According to function components, NHPs can be manufactured, sold or used in the diagnosis, treatment, mitigation or prevention of a disease, disorder, or abnormal physical state in humans or to restore, correct, or modify organic functions in human, all in a way that maintains or promotes health.

Besides requiring a product review and licence for NHPs, the regulations also set up provisions for clinical trials (where no previous human data exist), labelling, site licensing and inspections (for sites where the product is manufactured in Canada, with similar information to be supplied for foreign locations), good manufacturing practices, and adverse events reporting.[13]

Health claims made pursuant to the Act and regulations are of 2 types: traditional uses and non-traditional uses, with more stringent evidence requirements, including clinical trials, descriptive studies and expert opinion reports for new or non-traditional uses.[14]

Regulation of health claims related to *foods*, including novel foods, are the province of the Food Directorate of Health Canada, pursuant to the *Food and Drugs Act* and *Food and Drug Regulations* and also of the Canadian Food Inspection Agency (with regard to labelling and advertising).[15] Existing claims are for probiotics as well as for the health effects of dietary fibre, calcium, folate, and foods free of saturated fats, sodium, and several other substances.

Health claims related to *foods* may be of three types:

[11] Health Canada. Health Products and Food Directorate. (2007, November). *Managing health claims for foods in Canada: Towards a modernized framework.* Discussion paper. http://www.hc-sc.gc.ca/fn-an/consult/_man-gest_health_claims-allegations_sante/index-eng.php (PDF version, 124 p.)

[12] Health Canada. Natural Health Products Directorate. (2010, June). *Classification of products at the food-natural health product interface: Products in food formats*. http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/food-nhp-aliments-psn-guide-eng.php (PDF version, 11 p.)

[13] Some useful summary brochures for aspects of the regulations are available from Quality & Compliance Inc: NHPD overview. *QuickNotes,* March 2009, 10 p. http://www.qualityandcompliance.com/pdfs/QuickNote%20-%20NHPD%20Overview_March%202009.pdf ; NHP product licensing. *QuickNotes, March 2009,* 6 p. http://www.qualityandcompliance.com/pdfs/QuickNote%20-%20NHP%20Product%20Licensing_March%202009.pdf ; NHP site licensing. *QuickNotes,* March 2009, 5 p. http://www.qualityandcompliance.com/pdfs/QuickNote%20-%20NHP%20Site%20Licensing_March%202009.pdf ; NHP good manufacturing practices. *QuickNotes,* Feb. 2009, 5 p. http://www.qualityandcompliance.com/pdfs/QuickNote%20-%20NHP%20GMP_February%202009.pdf ; Natural health products quality systems: Setup. *QuickNotes,* March 2010, 6 p. http://www.qualityandcompliance.com/pdfs/QuickNote%20-%20NHP%20Quality%20Systems%20Setup%20(March%202010).pdf

[14] Health Canada. Natural Health Products Directorate. (2006). *Evidence for safety and efficacy of finished natural health products.* http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/efe-paie-eng.php (PDF version, 56 p.)

[15] Canadian Food Inspection Agency. (2012, January 12) Guide to food labelling and advertising. http://www.inspection.gc.ca/english/fssa/labeti/guide/toce.shtml

- food claims (expressing the composition, quality, quantity or origin of a food product);
- nutrition claims (characterizing the amount of nutrient in a food, or its energy value; and,
- health claims (suggesting a relationship between an ingredient and health or disease risk reduction).

Depending on the nature of the claim, there are different regulatory requirements. Disease risk reduction claims have a higher evidentiary requirement, and currently only five such claims are allowed in Canada.[16] Canada has differed from the U.S. somewhat in its view on allowable health claims. For instance, in a review of 10 claims that were supported in the U.S. but not in Canada, Health Canada concurred with only five of the ten claims. In the case of beta-glucans from oats and psyllium and their link to prevention of heart disease, for instance, Health Canada has opted to review applications on a case-by-case basis, reviewing the food matrix and processing methods as well as nutrient content before granting a product specific claim. In the U.S., by contrast, all foods containing a certain amount of oats are eligible to make oat-related health claims.[17]

In 2007, Health Canada published an NHP regulatory review document[18], and engaged in broad stakeholder consultations regarding its own business process (and backlog) as well as needed reforms. Among the policy changes suggested were greater recognition of the cultural components of NHP usage, a regulatory path that is tied more closely to risk and benefit, and broader international consultations.

2.3 Cosmetics

Regulation of cosmetics and personal care products in Canada is also within the purview of Health Canada under the *Food and Drugs Act* and its *Cosmetic Regulations*, but may be managed in different ways. According to the departmental website:

- Products that have a therapeutic claim or that contain certain ingredients not permitted in cosmetics are considered to be drugs, for example sunscreens.
- Products containing natural therapeutic ingredients are considered natural health products (NHPs), for example many toothpastes.
- Items where ingestion is intentional and that do not have a therapeutic effect or claim are food products.
- Insect repellent lotions and sprays are pesticides.
- Products (such as creams, lotions, or shampoos) providing a therapeutic benefit to animals are veterinary drugs.[19]

[16] Health Canada. (2010, November 16). Questions and answers on health claims. http://www.hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/qa-qr_claims-allegations-eng.php
[17] Health Canada. (2009, July 9). *Position paper on five U.S. health claims considered for use in Canada.* http://www.hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/position_paper-enonce_position-eng.php (PDF version, 27 p.)
[18] Health Canada. (2007). *Charting a course: Refining Canada's approach to regulating natural health products.* http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/chart-course_tracer-voie-eng.php (PDF version, 47 p.)
[19] Health Canada. Consumer Product Safety. (2011, March 10). What is a Cosmetic? http://www.hc-sc.gc.ca/cps-spc/cosmet-person/cons/what-quoi-eng.php

In 2008, Health Canada issued a guidance document on the classification of products at the cosmetic-drug interface.[20] According to this document, the distinction (and the appropriate regulatory path) cannot be determined on the basis of risk alone, but should also be based on:

- representations made about the product (for instance, is it suggested as a treatment or prevention for a disease or condition? What are the dosing instructions?)
- its composition (for instance, does the substance have therapeutic or pharmacological activity?)
- its level and type of action (for instance, is it absorbed systemically?).

The Department has also published *Guidelines for cosmetic advertising and labelling claims.*[21] The document also lists claims that would drive a product into the "drug" category.

2.4 Veterinary Drugs, Biologics and Feeds

The Veterinary Drugs Directorate of Health Canada evaluates and monitors the safety and efficacy of veterinary drugs in Canada, in regulatory system that is similar to that used for human therapeutic products, i.e., requiring a demonstration of efficacy and safety, and with an evidentiary burden (toxicity and other studies), submission of labelling and documentation on good manufacturing practice. As with human therapeutic products, the veterinary regulations are pursuant to the *Food and Drugs Act* and *Food and Drug Regulations* of Canada. The Department's Applications and Submissions page provides resources such as guideline documents and regulatory policies for veterinary drug.

The Canadian Food Inspection Agency (CFIA) is responsible for regulating and licensing veterinary biologics and veterinary biologics manufacturing facilities in Canada, under the *Health of Animals Act* and its *regulations*. Biologics include "…vaccines, bacterins, bacterin-toxoids, immunoglobulin products, diagnostics kits, and any veterinary biologic derived through biotechnology." According to the Agency's website,

> To meet the requirements for licensure, veterinary biologics must be shown to be pure, potent, safe, and effective when used in the target species according to the manufacturer's label recommendations. In addition, the licensing submission must also contain supporting data demonstrating that the product can be manufactured and used without adversely affecting animal health, human health, food safety or the environment. [22]

CFIA forms, fee schedules and guidance documents related to veterinary biologics are available on their Guidelines and Forms page.

CFIA also regulates novel livestock feeds under the *Feeds Act* and its regulations. CFIA's Novel Feeds page has links to guidance documents and forms.

[20] Health Canada. (2008). *Guidance document: Classification of products at the cosmetic-drug interface.* http://www.hc-sc.gc.ca/cps-spc/pubs/indust/cosmet_drug_guide-drogue-ref/index-eng.php (PDF version, 12 p.)
[21] Health Canada. (2006). *Guidelines for cosmetic advertising and labeling claims.* http://www.hc-sc.gc.ca/cps-spc/alt_formats/hecs-sesc/pdf/pubs/indust/cosmet/guidelines-ld-eng.pdf
[22] Canadian Food Inspection Agency. (2011, October 13) *Veterinary biologics - FAQ.* http://www.inspection.gc.ca/english/anima/vetbio/queste.shtml

2.5 Canadian Reforms, Modernization Initiatives and Cooperation

In October of 2006, Health Canada published *Blueprint for Renewal*, which proposed many systemic and philosophical changes to Canada's drug regulation regime. Among the changes proposed were:

- More of a life-cycle approach to drug regulation
- More emphasis on post-marketing surveillance
- Greater leadership in health issues affecting certain populations (pregnant women, children, the elderly, etc.)
- Greater transparency and stakeholder involvement
- A move to regulatory interventions proportional to risk
- Better use of more types of evidence

Since that time, the Department has embarked on several policy reviews with its Progressive licensing project and its regulatory review of natural health products,[23] which are both initiatives of the Department's *Blueprint for Renewal*. Health Canada maintains a list of regulatory proposals that have been made into regulations and published in the Canada Gazette Part II. This should be consulted to understand recent changes to food and drug legislation. Prior to this stage, Health Canada will publish proposed regulatory amendments in the Canada Gazette Part I for public consultation. And prior to pre-publication in the Canada Gazette Part I are regulatory notices and/or proposals under early consultation.

In 2008, the government also introduced Bill C-51, An Act to amend the Food and Drug Act and to make consequential amendments to other Acts, which addressed certain aspects of NHP regulation. When a federal election was called in September of 2008, C-51 died on the order paper. Certain provisions have been reintroduced, however, in Bill C-6, An act respecting the safety of consumer products.

In an NHP progress report on the Health Canada website, the Department also notes that as of June 2010 over 22,000 natural health product licenses have been issued due to streamlining of procedures for low-risk products, and the grouping of similar applications. [24] An online electronic system for licensing has also been introduced as part of the Department's STEPS initiative (Standardized claims, Transparency, Electronic solutions, Process improvements, and Service delivery).[25]

Health Canada's cooperative agreements and initiatives are primarily with the European Medicines Agency (EMA) and the European Commission (EC). Canada participates in Mutual Recognition Agreements (MRAs), covering drug/medicinal products Good Manufacturing Practices (GMP) Compliance Programmes with the EC, Switzerland, the European Economic Area and Australia. Canada also participates with the U.S. and Mexico under a Trilateral Cooperation to increase

[23] Published as: Health Canada, Natural Health Products Directorate. (2007). *Charting a course: Refining Canada's approach to regulating natural health products*. http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/chart-course_tracer-voie-eng.php (PDF version, 47 pages).
[24] Health Canada. (2009, April 3). *Progress report: Natural Health Products.* http://www.hc-sc.gc.ca/dhp-mps/prodnatur/about-apropos/prog-rep-rap-etap-eng.php
[25] Health Canada. (2009, March 16). The S.T.E.P.S plan. http://www.hc-sc.gc.ca/dhp-mps/pubs/natur/nhprr-steps_erpsn-atsap-eng.php

communication, collaborate, and exchange information in the areas of drugs, biologics, medical devices, food safety and nutrition to protect and promote human health.

3 UNITED STATES

The US regulatory environment is significantly different from that of Canada. Firms interested in marketing products in both the US and Canada will need to carefully review the different treatments of their products under each regulatory structure. It is important to note that a product or substance that might be considered a food product in one country may be considered a drug in another. The issue of health claims is also significantly different in the US and Canada, with Health Canada tending to be more conservative and requiring greater evidence for claims made.

3.1 Drugs / Pharmaceuticals

In the United States, the Food and Drug Administration (FDA) of the Department of Health and Human Services provides oversight, and holds regulatory authority, for the safety and efficacy of drugs (human and animal). The FDA is also responsible for the regulation of food (human and animal), dietary supplements, cosmetics, medical devices, and biologics. The principal enabling legislation for FDA activity is the *Food Drug and Cosmetic Act* and its amendments. Regulations for the FDA are codified in *Title 21 of the Code of Federal Regulations (CFR)*. FDA's Laws, Regulations, Policies and Procedures for Drug Applications page provides links to CFR sections specific to new drug applications.

As in Canada, new drug applications must proceed through a pre-clinical study phase and clinical trials The investigational new drug (IND) phase is followed by a new drug application (NDA) stage which comprises the FDA's actual review of safety and efficacy, labelling, and manufacturing practices. According to an FDA webpage on the drug review process, the steps are as follows:

1. Preclinical (animal) testing.
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. [Clinical trial] Phase 1 studies (typically involve 20 to 80 people).
4. [Clinical trial] Phase 2 studies (typically involve a few dozen to about 300 people).
5. [Clinical trial] Phase 3 studies (typically involve several hundred to about 3,000 people).
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.

10. The FDA reviews information that goes on a drug's professional labelling (information on how to use the drug).
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or issue a complete response letter.[26]

Post-marketing requirements (sometimes referred to as "Phase 4 commitments") refer to the monitoring of adverse drug events and other pharmacovigilance conducted through MedWatch and other FDA programs.

In some cases of special urgency and/or well-demonstrated efficacy and safety, the new drug approval process may be fast-tracked. Both the FDA and its critics have been looking for ways to expedite the process, and so reduce the waiting time for the public for proven drugs, as well as the financial burden for manufacturers. The mean clinical phase times and approval phase times for new molecular entities and significant biologicals approved by the FDA between 2005 and 2009 was 6.4 years and 1.2 years. During this same period there was substantial variation in the mean clinical trial time depending on the therapeutic class. Infectious disease therapies such as AIDS antivirals had the shortest clinical trial time (4.6 years) while the longest clinical trial time was for central nervous system (CNS)-related conditions (8.1 years). The FDA approved on average 20 new molecular entities and significant biologicals for each of the five years from 2005-2009.[27]

The main watchdog within the FDA is the Center for Drug Evaluation and Research, or CDER. The following key process documents are available on CDER:

- Form and submission requirements for new drugs – Investigational New Drugs (IND) and New Drug Applications (NDA) stages, as well as forms for orphan drugs and generic drug products.
- Good manufacturing practice (GMP) documents for drugs.
- CDER and other FDA drug guidance documents.
- The CDER Manual of Policies and Procedures (with updates)

[26] U.S. Food and Drug Administration. (2010, Feb. 22). The FDA's drug review process: Ensuring drugs are safe and effective. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm

[27] K. I. Kaitin and J. A. DiMasi. (2011, February). Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade, 2000–2009. *Clinical Pharmacology & Therapeutics*, 89(2):183-188. doi:10.1038/clpt.2010.286. http://www.nature.com/clpt/journal/v89/n2/abs/clpt2010286a.html

3.1.1 Non-Prescription (Over-the-Counter or OTC) Drugs

Also regulated by FDA (the Office of Non-Prescription Products), non-prescription or over-the-counter drugs can follow one of two regulatory paths.

1. If a drug conforms to a pre-established FDA OTC drug monograph (if its ingredients are "generally recognized as safe" or GRAS) in one of more than 80 therapeutic categories, it may be marketed without FDA pre-approval.
2. If the drug does not match an OTC monograph or if the product contains a new OTC ingredient, it must proceed through the New Drug Approval (NDA) process. Drugs which switch status from prescription to OTC must also undergo NDA approval.

Industry guidance and rulings for OTC drugs can be found on CDER's Over-the-Counter (OTC) Related Federal Register Notices, Ingredient References, and other Regulatory Information page.

The U.S. Federal Trade Commission currently regulates advertising of OTC drugs, whereas the FDA is responsible for labelling of OTCs, as well as labelling and advertising of prescription drugs.[28]

3.1.2 Biologics and Biosimilars

Vaccines, blood products and other biologics are subject to approval via the Center for Biologics Evaluation and Research (CBER) of the FDA. As for other drugs, the proposed products must pass through an investigational new drug or IND phase (or may be exempted) and prepare a Biologics License Application or BLA. A premarket 510(k) form may be submitted when the manufacturer hopes to gain clearance by proving substantial equivalency to a device that is already marketed (thus obviated the need for the premarket approval process). Ultimately, new biologics will also need to undergo the New Drug Application (NDA) process. According to one source, the number of FDA approvals of biopharmaceutical products in recent years has dropped. This is probably not an indication that there are fewer applications in the area, since pipeline databases and other sources indicate that the number of bio-products vs. conventional pharmaceuticals has increased, but rather more indicative of the fact that for a variety of reasons, fewer products are making it past Phase 3 clinical trials. The same source notes that in 2007, few of these products demonstrated much innovation. Rather, they could be characterized as "incremental advances, me-too products, and those with rather specialized indications".[29]

Also, as in Canada, the FDA is currently grappling with how best to handle the regulatory and commercial issues related to biosimilars or follow-on protein products that require regulatory attention.[30]

[28] U.S. Federal Trade Commission. (2001, April). *Frequently asked advertising questions: A guide for small business.* http://www.ftc.gov/bcp/edu/pubs/business/adv/bus35.shtm

[29] R. Rader. (2008, March 18). Paucity of biopharma approvals raises alarms: Lower numbers, novelty, and economic impact indicate problems. *Genetic Engineering & Biotechnology News* 28 (6). http://www.genengnews.com/articles/chitem.aspx?aid=2403&chid=0

[30] U.S. Food and Drug Administration. (2010, June 22). Follow-on protein products: Regulatory and scientific issues related to developing. http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm085854.htm ; see also, A. Haberman. Resources. (2008, November). Meeting the challenges of manufacturing biosimilars. *Decision Resources Spectrum.* 26 p. Retrieved from Decision Resources database.

3.2 Nutraceuticals and Functional Foods

Under current U.S. regulations, functional foods can be classified as conventional foods, food additives, dietary supplements, medical foods, or foods for special dietary use. In most cases, two major instruments apply. They are the *Federal Food Drug and Cosmetic Act*, which regulates all foods and food additives, and the *Dietary Supplement Health and Education Act of 1994* (DSHEA), which covers supplements and their ingredients.

Functional foods are regulated as for all other foods, with a few notable exceptions related to food health claims. Three types of claims are allowed in the U.S. The first two are allowed without FDA pre-market approval, provided they are not false or misleading:

1) Nutrient content claims: for example, the product contains fats, sodium, sugar, etc.
2) Structure/function claims: for example, calcium is good for bones, fibre for digestive health, vitamins A/C/E for natural defenses, vitamin A for eyes, etc.
3) Health claims describe the relationship between a food and a disease or condition. Unlike structure/function claims, these must be pre-approved by the FDA, approved based on publicly available scientific evidence, authoritative statement, or qualified (emerging) health claims.[31] For claims that have been approved by the FDA, specific labeling or advertising language applies.[32]

The FDA also allows Dietary Guidance statements to promote better nutrition, for example, fruits and vegetables are good for one's health. Manufacturers who wish to make "significant scientific agreement" (SSA) or qualified health claims for a new product, however, must petition the FDA and provide documentary evidence in support of their claim.[33] To date, relatively few such food claims have been approved, although as noted above, the application of such claims has been interpreted more liberally in the U.S. than in Canada. When a manufacturer "oversteps", however, the FDA has been quick to respond. In a recent, well documented news story, the agency sent a warning letter to General Foods, manufacturer of Cheerios, advising them that their marketing practices for the cereal treated it like a drug intended for the treatment of disease, rather than a conventional, if functional, food.[34]

The DSHEA prescribed a somewhat different regulatory path for dietary supplements,

> vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information

[31] U.S. Food and Drug Administration. (2003, September). Claims that can be made for conventional foods and dietary supplements. http://www.fda.gov/Food/LabelingNutrition/LabelClaims/ucm111447.htm
[32] U.S. Food and Drug Administration. (2009, May 6). Guidance for industry: A food labeling guide: Appendix C: Health claims. http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/FoodLabelingGuide/ucm064919.htm
[33] U.S. Food and Drug Administration. (2006, May 12). Guidance for industry: FDA's implementation of "Qualified Health Claims": Questions and answers: Final guidance. http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm053843.htm
[34] FDA tells Cheerios cereal makers that their health claims contain "serious violations". (2009, May 13). *Medical News Today.* http://www.medicalnewstoday.com/articles/149857.php

> on their label must not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labelled a dietary supplement.[35]

Under DSHEA, the manufacturing firm is responsible to ensure that the supplements it makes or distributes are safe, and that no false or misleading claims are being made pursuant to their use. Only in the case of a new ingredient is pre-market approval required. More information for industry and listing of new, approved ingredients are provided in *New Dietary Ingredients in Dietary Supplements - Background for Industry*.

Good manufacturing practices for supplements are also regulated: in 2007, the FDA published rules to control manufacturing, quality control, facility, packing, labelling, and holding practices for dietary supplements, with staggered compliance dates, depending on the size of the firm.[36]

3.3 Cosmetics

Most cosmetic products (except those containing colour additives) do not require pre-market approval of the FDA. It is the responsibility of the manufacturer to determine the safety of products and ingredients before they are marketed. The FDA may prosecute companies that are in violation of U.S. laws, however – for instance, if their products are hazardous, adulterated, or misbranded. The two major instruments of law [37] are the *Federal Food Drug and Cosmetic Act* and the *Fair Packaging and Labeling Act*. The FDA also maintains a Voluntary Cosmetic Registration Program for post-market surveillance of cosmetic programs.

Issues arise, of course, when a product is at the cosmetic/drug interface. The FDA does not formally recognize a classification for “cosmeceuticals”. For the agency, a product is either a cosmetic or a drug, depending on its intended use, and according to factors such as product claims (made in labelling or advertising), consumer perception, or the presence of ingredients that have “therapeutic” uses. According to this interpretation, a product containing essential oils that will help the consumer sleep (aromatherapy) would be classified as a drug, and follow the regulatory path for drugs.[38]

[35] U.S. Food and Drug Administration. (2009). *Overview of dietary supplements.* http://www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm
[36] Quality and Compliance. (2009, February). FDA dietary supplement cGMP. NHP Compliance. *QuickNotes*. 9 p. http://www.qualityandcompliance.com/pdfs/QuickNote%20-%20Dietary%20Supplements_February%202009.pdf ; see also, U.S. Food and Drug Administration. (2009). *Current Good Manufacturing Practices (CGMPS): Dietary supplements.* http://www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/RegulationsLaws/ucm079496.htm
[37] U.S. Food and Drug Administration. (2009). *FDA authority over cosmetics.* http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ucm074162.htm
[38] U.S. Food and Drug Administration. (2002, July 8). Is it a cosmetic, a drug, or both (or is it soap)? http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ucm074201.htm ; see also, D. C. Steinberg. (2009, September 3). Labeling claims: Untangling the rules. *Global Cosmetic Industry*. http://www.gcimagazine.com/business/rd/claims/57039237.html?page=1

3.4 Veterinary Drugs, Biologics and Feeds

The responsible arm of the FDA is the Office of New Animal Drug Evaluation of the Center for Veterinary Medicine.

The approval process for veterinary drugs parallels the human drug regulatory path, with some differences:

- Animal feeds are regulated by the Division of Animal Feeds of the Center for Veterinary Medicine, as covered by the *Federal Food Drug and Cosmetic Act* (which defines food as "articles used for food or drink for man or other animals"). An assessment published in 1996 determined that the provisions of the *Dietary Supplement and Health Education Act of 1994* did not apply to animal feed, and that the *Federal Food Drug and Cosmetic Act* would still be in force as regards livestock nutrition. Therefore, supplements or additives to animal feeds "…are considered 'foods,' 'food additives,' or 'new animal drugs' depending on the intended use. The regulatory status of a product is determined by CVM on a case-by-case basis, using criteria provided in Guide 1240.3605 in Program Policy and Procedures Manual."[39]
- For new food additives not previously designated as GRAS, a manufacturer must petition the FDA for approval. Regulations for food additives in feeds are published in *Title 21, Part 570 of the Code of Federal Regulations* (PDF / 9 pages). Part 571 (PDF / 6 pages) prescribes the kinds of data that should be submitted by the petitioner and the required format for the petition itself. The petition should address areas such as human and target animal food safety, environmental impact, utility, chemistry, and labelling.
- Mills that manufacture medicated feed must be licensed per the *Animal Drug Availability Act of 1996* and its regulations.[40]

Additional information can be found in the animal and veterinary guidance documents listed on the Guidance for Industry page.

3.5 U.S. Reforms, Modernization Initiatives and Collaboration

In a comprehensive review and reform, the FDA's Critical Path Initiative, first announced in 2004, is examining "the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or 'proof of concept' into a medical product".[41] Some examples of technologies that have transformed the process include animal models of disease, biomarkers, quality assessment technologies, data mining and computer modeling, new statistical methodologies, and new designs for clinical trials. The agency will examine how and whether these new technologies should be incorporated into the approvals process. In the course of the project, the FDA hopes to

[39] U.S. Food and Drug Administration. (2011, February 16). *Product regulation.* http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/ucm050223.htm
[40] U.S. Food and Drug Administration. (2011, September 30). Medicated feeds. http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/default.htm
[41] U.S. Food and Drug Administration. (2009, September 14). *Critical Path Initiative: Frequently asked questions.* http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm077015.htm

develop better evaluation tools, streamline clinical trials, make better use of bioinformatics, and address the special needs of at-risk populations and urgent public health issues.

In May 2008, the FDA launched the Sentinel Initiative, a national electronic system that will enhance the agency's ability to track post-market events related to drugs, biologics and medical devices. As in Canada, the agency is placing new emphasis on the latter end, and not just the pre-approval phase, of the drug life cycle.

Greater emphasis is being placed on quality control within the manufacturing process (so-called "quality by design" or QBD initiatives)[42], especially as overseen by the office of New Drug Quality Assessment within CDER. This has also led to greater international cooperation through bodies such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), whose purpose is to "…make recommendations [for Europe, Japan, and the U.S.) towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new medicines."[43]

In August of 2009, the FDA and the European Medicines Agency (EMA) also announced an 18-month pilot project, dubbed the GCP Initiative, in which they will cooperate on good clinical practice inspections of clinical trial sites.[44] This marks the agencies' recognition of the increasingly global nature of clinical research. Previously, the two agencies have also collaborated on orphan and pediatric drug development.[45]

[42] U.S. Food and Drug Administration. (2007, May). *Pharmaceutical quality for the 21st century: A risk-based approach: Progress report*. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128080.htm
[43] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (2011). Vision. http://www.ich.org/about/vision.html
[44] FDA, EMEA plan joint clinical trial inspection pilot. (2009, August 5). *FDAnews Drug Daily Bulletin* 6 (151). http://www.fdanews.com/newsletter/article?articleId=119324&issueId=12887 ; see also, EMEA-FDA GCP Initiative. (2009, July 31). http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016820.pdf
[45] P. Walter. (2007, December 4). Cross pond collaboration on orphan drug development. *Chemistry and Industry 23* (8) ; see also, M. Rios. (2007, August). FDA, EMEA, EC extend regulatory collaboration efforts. *Pharmaceutical Technology 31* (8), 22. Both retrieved from Business Source Complete database.

4 EUROPEAN COMMUNITY

4.1 Drugs / Pharmaceuticals

In Europe, drug manufacturers who wish to market a new product must demonstrate safety and efficacy through a regulatory process that closely resembles the ones followed in Canada and the U.S. There several routes for approval, however:

- Companies may apply for a centralized review through the European Medicines Agency or EMA[46], the pharmaceutical regulatory and oversight body for the European Community. The EMA's evaluation is particularly intended for new technologies or those that present scientific, technical, or public health challenges. The centralized review is "…compulsory for products derived from biotechnology, for orphan medicinal products and for medicinal products for human use which contain an active substance authorised in the Community after 20 May 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes. The centralised procedure is also mandatory for veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth or to increase yields from treated animals." [47] A marketing authorisation from the EMA is valid for five years, and is renewable in five year increments.

- Companies may choose to use the "Mutual Recognition Procedure", seeking marketing authorisation by regulatory authorities in any one of the European Union's 27 member countries. Terms for the MRP were set out in *Directive 2001/83/EC*.[48] Under the MRP, a product must already have received authorisation in one member state. Through its local application, the company automatically launches a request for authorisation in all other member countries, and unless objections are lodged by any of the other countries on the basis of a threat to public health, the authorisation will be valid for all parties. The MRP procedure is used for most conventional medicinal products.[49] According to one analyst, this procedure has several advantages over the centralized approach, namely: the ability to launch a product in one country allows the manufacturer to provide cash flow and develop an effective marketing strategy before Europe-wide launch; a company may be able to conduct more cost-effective clinical trials in a particular country; the MRP enables co-marketing with partners in other countries; the MRP can

[46] From 1995 to 2004, the European Medicines Agency (EMA) was known as European Agency for the Evaluation of Medicinal (EMEA). Site was still available in Jan 2010 but was re-directed to new EMA site by May 2010.
[47] European Commission. (2011). *Procedures for evaluating medicinal products and granting marketing authorization.* *http://ec.europa.eu/health/authorisation-procedures_en.htm* ; see also, European Medicines Agency. (2009). About EMA http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp
[48] *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*. Consolidated PDF version, 2011-01-20. There will be regular amendments so check the Directive's permanent link for the latest version.
[49] European Commission. (2011). *The Mutual Recognition Procedure*. http://ec.europa.eu/health/authorisation-procedures-mutual-recognition_en.htm

pre-empt review of a drug by Member States that may be unlikely to approve it.[50]

- Companies may also opt for the decentralized procedure", introduced by *Directive 2004/27/EC*[51].This applies to conventional pharmaceutical products that have previously received authorization. Under this procedure, "…an identical application for marketing authorisation is submitted simultaneously to the competent authorities of the Reference Member State and of the Concerned Member States. At the end of the procedure, the draft assessment report, SPC, labelling and package leaflet, as proposed by the Reference Member State are approved."[52]

The European Commission also publishes a useful list of all guidelines informing the regulatory environment, from the clinical trials stage and evaluations through post-market vigilance. Each volume listed below includes links to forms and all enabling legislation, regulations, directives, and guidelines.[53]

- Volume 1 – EU pharmaceutical legislation for medicinal products for human use
- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
- Volume 3 - Scientific guidelines for medicinal products for human use
- Volume 4 – Guidelines for good manufacturing practices for medicinal products for human and veterinary use
- Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 – Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 – Guidelines for clinical trial

In addition there are specific rules for medicines for childeren, orphan medicinal products, herbal medicinal products and advanced therapies. The process is also somewhat different for subsequent entry biologics / biosimilars (see Section 4.1.2).

Post-market authorization, in spite of centralized approvals, drugs in Europe are subject to direct and indirect price controls in all countries except for Germany and the U.K. Direct price controls are negotiated by members states and the pharmaceutical companies, with the prices set according to

[50] A. Sahoo. (2008). *Drug approval trends at the FDA and EMEA.* Business Insights. 147 p. Retrieved from Business Insights database.

[51] *Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use*. PDF version, 2004-04-31. There may be eventual amendments so check the Directive's permanent link for the latest version.

[52] European Commission. (2011). *The decentralized procedure*. http://ec.europa.eu/health/authorisation-procedures-decentralised_en.htm

[53] European pharmaceutical regulation comes in the form of directives, regulations, and guidelines. Directives are legally binding for all member states, but national governments may choose how to enact the objectives of the directives – some local discretion is allowed. Regulations are also legally binding for all member states, but national governments may only apply national laws and regulations inasmuch as they support the regulations. Guidelines may be referred to in legislative framework or may fulfill a legal obligation set down elsewhere in Community law, but in most cases, they do not have the force of law.

factors such as the therapeutic value of the drug and the cost of comparable treatments. Indirect price controls set margins based on grouping, i.e., drugs with the same or related active ingredients or with similar therapeutic effect. As a result, drugs in jurisdictions with low margins are unlikely to see product launches in that country.[54]

4.1.1 Non-Prescription (Over-the-Counter or OTC) Drugs

Like their by-prescription only counterparts, non-prescription or over-the-counter drugs must also apply for marketing authorisation in Europe before they can be sold, per *Directive 2001/83/EC*.[55] In practice, most new drugs start their commercial life as prescription only, and then many switch to the OTC classification (using the centralised procedure) at a later date.[56]

As to whether a drug should be classified as prescription-only or not, certain criteria are set forth in article 71 of *Directive 2001/83/EC* (for instance, may the drug present a danger, even when used correctly, does it contain certain substances, must it be administered parenterally?); however, each member state is ultimately responsible for the classification decision in its jurisdiction.[57]

In Britain, the UK Medicines and Healthcare Products Regulatory Agency is currently pursuing an initiative to reduce the red tape surrounding regulation of OTC medicines in that country. Under the Better Regulation of Over the Counter Medicines Initiative (BROMI), the agency would introduce a new scheme for post-marketing authorisation self-certification in the case of minor changes to labelling and packaging.[58]

4.1.2 Biologics and Biosimilars

While biologics (kits, reagents, blood products, vaccines, etc.) in Europe are authorised under the centralised procedure described above, the community has designated a slightly different process for biosimilars, i.e., biologics similar to existing products that are facing patent expiration. The basis for biosimilarity was set out in *Directive 2004/27/EC* [59] of 2004, and annexes to the Directive also define criteria for pre-clinical tests and clinical trials, given that the exact raw materials and manufacturing

[54] Frost and Sullivan. (2008, December). *Drug approval process in Europe: An outlook.* 51 p. Retrieved from Frost & Sullivan database.
[55] *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*. Consolidated PDF version, 2011-07-21. There will be regular amendments so check the Directive's permanent link for the latest version.
[56] C. Morrison. (2009, June 14). In Europe, centralized OTC switch still has a few bugs. *EuroPharma Today*. http://www.europharmatoday.com/2009/06/in-europe-centralized-otc-switch-still-has-a-few-bugs-.html ; see also, Can successful Euro OTC switches help US fortunes? *EuroPharma Today*, January 14, 2010. http://www.europharmatoday.com/2010/01/can-successful-euro-otc-switches-help-us-fortunes.html
[57] R. E. Ferner and K. Beard. (2008, March 29). Over the counter medicines: Proceed with caution. *British Medical Journal 336*, 694-696. http://www.bmj.com/content/336/7646/694.full
[58] Medicines and Healthcare Regulatory Agency. (2006, May 23). Press release: Report of the better regulation of over the counter medicines initiative. http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON2023803
[59] *Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use*. PDF version, 2004-04-31. There may be eventual amendments so check the Directive's permanent link for the latest version.

process of the original may not be known. *Directive 2003/63/EC* [60] also defines which other data may be required, and the Committee for Medicinal Products for Human Use (CHMP) of the EMA has also published an overarching *Guideline on Similar Biological Medicinal Products*.[61] As in other regulatory jurisdictions, much more emphasis is placed on the manufacturing process, as opposed to the product.[62]

4.2 Nutraceuticals and Functional Foods

The European approach to regulation of nutraceuticals is quite complex. The *General Food Law Regulation, EC 178/2002* [63], applies to all foods, and there is no separate category for functional foods. Numerous rules may also apply, depending on the nature of the food/ingredient: for instance, there is a separate regulatory stream for dietetic foods, food supplements, novel foods, herbal medicines, and so on.[64] The European Food Safety Authority (EFSA), is responsible for oversight of much of this legislation and regulation. EMA is also implicated when a substance enters medicinal territory.

Some of the key reference documents include:

- Food supplements: *Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements*. Consolidated PDF version, 2011-12-05. There will be regular amendments so check the Directive's permanent link for the latest version. Guidance documents also available on the Europa Food Supplements page.

- Medicinal products: *Directive 2004/27/EC* applies to all medicinal products and defines criteria based for "medicinal" as being based on the claims made for the product, the pharmacological properties of the ingredients, a comparison with potentially similar licensed products in the market, and the presentation to the public made through labeling, packaging, promotional

[60] *Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use*. PDF version, 2003-07-01. There may be eventual amendments so check the Directive's permanent link for the latest version.
[61] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). (2005). *Guideline on similar biological medicinal products*. 7 p. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Additional biosimilar guideline documents can be found at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c&jsenabled=true
[62] Frost and Sullivan. (2008, December). *Drug approval process in Europe: An outlook.* 51 p. Retrieved from Frost & Sullivan database ; see also, F. Ehmann. (2008, September). Biosimilars in the European Union: Experience gained and perspectives. Slide presentation, *Biosimilars 2008 Conference*, Washington, DC. (42 slides). http://www.biosimilarstoday.com/2008/Ehmann.pdf
[63] *Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety*. Consolidated PDF version, 2009-08-07. There will be regular amendments so check the Regulation's permanent link for the latest version.
[64] P. Coppens, M. F. da Silva and S. Pettman. (2008). European legislation on dietary supplements and functional foods: Safety is key. In D. Bagchi (ed.), *Nutraceutical and Functional Food Regulations in the United States and Around the World* (pp. 173-197). Elsevier.

literature and advertisements.

- *Directive 2001/83/EC* determined that if a food could satisfy the definition of either a medicinal or a food product, medicinal regulations should apply, and the product must obtain a marketing authorisation..

- Novel Foods and Novel Food Ingredients: *Novel Food Regulation EC 258/97* [65] . Under the regulation, novel foods are classified as: Class 1: pure chemicals or simple mixtures with/without a history of food use in the EU; Class 2: complex novel foods with/without a history of food use in the EU; or Class 6: foods produced using a novel process resulting in a changed chemical composition or structure affecting purity, nutritional value or metabolism.[66] The Commission is in the process of revising the regulation of novel foods.[67] Their Novel Food Catalogue, a database of foods thus authorised or whose applications are pending/refused, may also provide some guidance on what constitutes a "novel food" in EFSA terms.[68]

- The Traditional Herbal Medicinal Products Directive 2004/24/EC [69] allows manufacturers of good quality herbal medications to register their products as medicines (rather than food supplements), and thus allows them to make some restricted claims. The medications s must be suitable for use without medical supervision.

- Botanicals: Botanicals present special challenges because of their complex nature and composition, especially as these affect quality and safety. Applicable directives have been interpreted to include Directive 2004/27/EC (definitions), the General Food Law Regulation 178/2002, article 2 (food vs. medicine), the Novel Food Regulation EC 258/97, Directive 89/398/EEC [70] (foods for particular nutritional Purposes), Directive 89/107/EEC [71] (food additives), Directive 2002/46/EC (food supplements), Regulation EC 1925/2006 [72] (addition of

[65] *Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients*. Consolidated PDF version, 2009-08-07. There will be regular amendments so check the Regulation's permanent link for the latest version.
[66] S. A. Ruckman. (2008). Regulations for nutraceuticals and functional foods in Europe and the United Kingdom. In D. Bagchi (ed.), *Nutraceutical and Functional Food Regulations in the United States and Around the World* (pp. 221-238). Elsevier.
[67] European Commission. (2008). *Novel foods: Review of Regulation (EC) 258/97.* http://ec.europa.eu/food/food/biotechnology/novelfood/initiatives_en.htm
[68] To search the Novel Food Catalogue database you need to click on the acknowledgement statement at the end of the page.
[69] *Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use*. PDF version, 2004-04-31. There may be eventual amendments so check the Directive's permanent link for the latest version.
[70] *Council Directive 89/398/EEC of 3 May 1989 on the approximation of the laws of the Member States relating to foodstuffs intended for particular nutritional uses*. Consolidated PDF version, 2003-11-20. There will be regular amendments so check the Directive's permanent link for the latest version.
[71] *Council Directive 89/107/EEC of 21 December 1988 on the approximation of the laws of the Member States concerning food additives authorized for use in foodstuffs intended for human consumption*. Consolidated PDF version, 2003-11-20. There will be regular amendments so check the Directive's permanent link for the latest version.
[72] *Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods*. Consolidated PDF version, 2009-12-21. There will be regular amendments so check the Regulation's permanent link for the latest version.

vitamins, minerals and certain other substances to food), and Directive 76/768/EEC [73] (cosmetic agents including some herbal products).[74] A good starting point is EFSA's page on botanicals. EFSA also published a guidance document on the safety assessment of botanicals used in food and supplements in July of 2009, and a compendium of botanicals known to cause toxic, addictive or psychotropic effects.

- Foods for Particular Nutritional Purposes (PARNUTS): framework directive is Directive 89/398/EEC, which sets up 9 sub-categories. Several of these categories have led to separate and specific Directives: Infant formulas and follow-on formulas, Directive 91/321/EEC; Processed cereal-based foods for infants and young children, Directive 96/5/EC, amended by Directive 2003/13/EC; Food used for energy-restricted, weight reduction diets, Directive 96/8/EC, as amended by Directive 2007/29/EC; and foods for special medical purposes, Directive 1999/21/EC. These directives are considered especially valuable for the functional food industry inasmuch as they relate functional properties to risk, consumer protection, manufacturer responsibility, and other issues in this area of growing commercial value.[75]

According to one article, instead of regulating a product group per se, European regulators have concentrated, in recent years, on risk analysis and on in restricting the claims which can be made pursuant to use of these products.[76] The EU's Regulation 1924/2006 [77] on nutrition and health claims made in food mandates the establishment of a public "register" of authorised health and nutrition claims for all member countries and also defines the nutrient profiles to be established for each claim. Nutrition claims state that a food has beneficial properties, such as "high in fibre"; while health claims state that health benefits can result from consuming a food component such as fibre or minerals. Health claims can be classified as those related to "function" or those related to "disease risk reduction". Function claims may be either general (covered in Article 13.1) or new (covered in Article 13.5). Risk reduction claims (covered in Article 14) are those claiming to reduce a risk factor in the development of a disease, e.g. plant stanol esters have been shown to reduce blood cholesterol, a risk factor in the development of heart disease. To make a new claim or modify an old one, companies must apply for authorisation to the EFSA.[78] Health claims assessed by the European Food Safety Authority (EFSA) for which the authorisation procedure is finished may be found in the EU Register on nutrition and health claims made on food. This includes both authorised and rejected health claims.[79]

[73] *Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products*, Consolidated PDF version, 2011-11-18. There will be regular amendments so check the Directive's permanent link for the latest version.
[74] O. P. Gulati and P. B. Ottaway. (2008). Botanical nutraceuticals (food supplements, fortified and functional foods) in the European Union with main focus on nutrition and health claims regulation. In D. Bagchi (ed.), *Nutraceutical and Functional Food Regulations in the United States and Around the World* (pp. 199-219). Elsevier.
[75] Coppens, M. F. da Silva and S. Pettman. (2008). European legislation on dietary supplements and functional foods: Safety is key. In of D. Bagchi (ed.) *Nutraceutical and Functional Food Regulations in the United States and Around the World* (pp. 173-197). Elsevier.
[76] I. Siro et al. (2008). Functional food: Product development, marketing and consumer acceptance: A review. *Appetite 51*, 456-467. Retrieved from ScienceDirect database.
[77] *Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods*, Consolidated PDF version, 2010-03-02. There will be regular amendments so check the Regulation's permanent link for the latest version.
[78] See Guidance for applicants on health claims. http://www.efsa.europa.eu/en/nda/ndaguidelines.htm
[79] As of 2012-02-27 there were 19 entries, 1 for new function claims and 18 for risk reduction claims.

4.3 Cosmetics

The EU's Cosmetics Directive 76/768/EC and its annexes sets out lists of ingredients that are prohibited, restricted, or allowed. There are also requirements for labelling, packaging, and market surveillance. The European Commission has also undertaken to develop and adopt a list of common criteria for claims that may be used for cosmetics.[80] A simplified and consolidated version of the 1976 Directive, with a reduction in red tape and greater emphasis on product safety, has also been proposed.[81] Responsibility for administration of the Cosmetics Directive rests with the Cosmetics Unit of the EC Directorates-General of Health and Consumers. They provide a list of guidance documents for the interpretation of the Cosmetics Directive that includes a guidance document on "Borderline" products.

4.4 Veterinary Drugs, Biologics and Feeds

Veterinary products in the EU must receive market authorisation as described above (see Volumes 4,5,6,7, and 9, in Section 4.1). Manufacturers may request the centralised procedure, mutual recognition, or the decentralised procedure, as for human pharmaceuticals. In the case of veterinary products, the assessments are conducted by the Committee for Medicinal Products for Veterinary Use (CVMP).

4.5 European Reforms, Modernization Initiatives and Collaboration

Like the FDA, and as part of the ICH Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the EMA has embarked on international harmonisation of procedures surrounding product registration.[82] They have also expanded their cooperation with the FDA in areas such as orphan and pediatric drugs and joint inspection of manufacturing facilities.[83] Cooperation with Health Canada covers the exchange of proposed legislation, regulations and guidance, staff exchanges, hosting of meetings in areas of mutual concern, and knowledge transfer in areas such as pharmacovigilance, licence suspensions, counterfeit drug seizures, restrictions on imports and distribution of pharmaceuticals.[84] Frost and Sullivan see such integration, collaboration and coordination as critically important in an era of global manufacturing/marketing of pharmaceuticals.[85]

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[80] D. C. Steinberg. (2009, September 3). Labeling claims – untangling the rules. *Global Cosmetic Industry* http://www.gcimagazine.com/business/rd/claims/57039237.html

[81] European Commission. (2008). *Review of Cosmetics Directive 76/768/EEC.* http://ec.europa.eu/consumers/sectors/cosmetics/documents/revision/index_en.htm

[82] EMEA pushes ahead with harmonization. (2009, July/August). *Manufacturing Chemist 80* (7), 8. Retrieved from Business Source Complete database.

[83] FDA and EMEA bond. (2008, July). *Pharmaceutical Technology Europe 20* (7), 8. Retrieved from Business Source Complete database ; see also, EMEA-FDA regulatory cooperation expanded. (2007, July 20). *Medical News Today*. http://www.medicalnewstoday.com/articles/74548.php, and most recently European Medicines Agency (2011). *Interactions between the European Medicines Agency and U.S. Food and Drug Administration September 2009-September 2010*. 16 pages. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/06/WC500107900.pdf

[84] Health Canada, European Commission and European Medicines Agency. (2009, April 2). *Implementation plan for regulatory cooperation on medicinal products following the exchange of letters between the EU (EC and EMEA) and Health Canada (HPFB).* 4 p. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018014.pdf

[85] Frost and Sullivan. (2008, December). *Drug approval process in Europe: An outlook.* 51 p. Retrieved from Frost & Sullivan database

5 COMMON ISSUES AND TRENDS

As has been seen in this report, all of the pharmaceutical/food regulatory agencies are in the process of addressing issues at the food/pharma interface. This has resulted in a proliferation of regulations and guidelines in these areas, and new sets of challenges for manufacturers who wish to obtain market authorisations in "gray areas". The overall trends are to controls and vigilance in areas hitherto unregulated (e.g., natural health products or food supplements), and greater emphases on good manufacturing practices and labelling requirements.

Funding shortfalls and burgeoning workloads, especially in new or developing areas such as natural health products regulation, have also led to substantial backlogs and slow turnaround times, especially for Health Canada and the FDA. Certain initiatives such as fast-track procedures (for orphan or critical drugs) and electronic filing may help ease the load and speed approval times, thus reducing applicant costs.

Biosimilars is another area of concern for all agencies, and one for which evolving policies may have repercussions for companies developing products in this area.

Other strategic areas where policy is changing and should be monitored are: post-market surveillance (adverse events reporting), special populations (children, the elderly, AIDS, etc.), and recognition of new technologies and types of supporting documentation. A cradle to grave approach to drug development, and progressive licensing schemes incorporating risk management philosophies and greater pharmacovigilance could mean more regulation for applicants, or it could mean less – if for instance, this translates into flexibility in the regulatory requirement, and requirements proportionate to risk. More recognition of biometric data and pre-clinical studies, adopted as part of modernization intiatives, may also help ease the burden.

Firms wishing to market products in Europe, US and Canada will need to take special care to understand how their products are considered under each regulatory structure. It is possible that one product or substance could be considered a food, a drug or a botanical depending upon the country regulations considered. Consequently, firms may need to seek professional expert advice to ensure they have correctly understood the regulations that apply to their products. It will also be important to keep up-to-date on changes to the regulatory process. Changes to the regulatory process and the regulations themselves are inevitable as countries try to ensure health is protected through regulatory control.

6 SOURCES CONSULTED

NRC-CISTI licensed sources:

- Business Source Complete
- Canadian Business and Current Affairs
- PubMed
- Business Insights
- Decision Resources
- Datamonitor
- Business Source Complete
- Frost & Sullivan

Canada:

- Health Canada. Therapeutic Products Directorate http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php
- Canadian Animal Health Institute http://www.cahi-icsa.ca
- Canadian Food Inspection Agency http://www.inspection.gc.ca
- Canada's Research-Based Pharmaceutical Companies (Rx and D) http://www.canadapharma.org/
- Consumer Health Products Canada (*formerly: Nonprescription Drug Manufacturers Association of Canada*) www.chpcanada.ca
- Canadian Health Foods Association http://www.chfa.ca/

United States:

- U.S. Food and Drug Administration http://www.fda.gov
- U.S. Federal Trade Commission http://www.ftc.gov
- Academy of Nutrition and Dietetics (*formerly: American Dietetic Association*) http://www.eatright.org
- Pharmaceuticals Research and Manufacturers of America http://www.phrma.org/
- The FDA Project [Harvard] http://people.hmdc.harvard.edu/~dcarpent/fdaproject.html

Europe:

- European Medicines Agency EMA http://www.ema.europa.eu/
- European Commission: Enterprise & Industry: The Rules Governing Medicinal Products in the European Union http://ec.europa.eu/health/documents/eudralex/index_en.htm
- European Food Safety Authority http://www.efsa.europa.eu/

Other:

- International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) http://www.ich.org/
- Quality and Compliance http://www.qualityandcompliance.com/
- Nutraceuticals World http://www.nutraceuticalsworld.com/
- International Food Information Council http://www.ific.org/
- Codex Alimentarius http://www.codexalimentarius.net/web/index_en.jsp
- Biosimilars Today Conference http://www.biosimilarstoday.com/
- Cosmetics Design Europe http://www.cosmeticsdesign-europe.com/

Books:

- D. Bagchi, ed. (2008).*Nutraceutical and Functional Food Regulations in the United States and Around the World.* Elsevier. (held at NRC-INH).

- T. Brendler, L. D. Phillips, and S. Spiess. (2009). *A Practical Guide to Licensing Herbal Medicinal Products.* Pharmaceutical Press. (held at NRC-INH)