Regulatory Requirements for Marketing a Therapeutic Product in Canada and in the United States (US)

Whether you are looking to market a drug, medical device, cosmetic, a natural health product or a dietary product it is important to understand all of the requirements that apply to your product from registering your product to through to GMP compliance establishment licensing/site registration and beyond.

Regulatory strategy and plans

Getting the regulatory strategy right, recognising the potential pitfalls and understanding the requirements for your specific product is of utmost importance.

For the market success of your product you need to know and comply with the regulations applicable on the markets you are targeting. These include directives and statutory requirements specific to the therapeutic product, and the overlapping regulations covering your product.

We analyse your particular projects and help you to fully understand the regulatory environment, taking into account precedents and current regulatory thinking. In close co-operation with your team, we develop the specific road maps that apply to your projects.

CANADA

REGISTRATION OF A THERAPEUTIC PRODUCT IN CANADA

Drug Products

The Drug Food and Cosmetic (FD&C) Act defines drugs, in part, by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals"

In Canada, a “drug product” can include everything from topical skin creams such as sunscreen products which declare an SPF through to prescription drugs which are used to treat acute health conditions. All drug products must be approved by Health Canada prior to their sale. For most classes of product, the applicant of the drug submission must provide scientific evidence which establishes the safety, efficacy and quality of the drug. Health Canada then evaluates the submission to determine whether the drug can be approved for sale in Canada. Submission requirements will vary by product type and will range from the simplest of submissions for over the counter (OTC) drugs through to more complex submissions for new drugs and prescription drugs or biological drugs.

Submissions for OTC drugs can be completed within a few days and are generally approved by Health Canada within a few months. Submissions for new drugs or prescription drugs can be completed within a few weeks to months and in some cases can take Health Canada up to a few years to approve. Once approved for sale, the applicant is issued a drug identification number (DIN) which must appear on product labelling. “New Drugs” are issued a “notice of compliance” and “Old Drugs” are issued a “drug notification form”.

If the drug does not meet the definition of a “new drug”, then it falls under “old drug” status and is approved via a “Drug Identification Number” or DIN submission. DIN Submissions generally contain proposed label copy along with attestations for meeting various labelling, formulation, or safety requirements.

NEW DRUGS
A new drug is a drug that is approved in Canada under the requirements of Division 8 of the Food & Drug Regulations. The definition of a “new” drug includes new drug substances as well as new indications, dosage forms or combinations of drugs, which have not been sold in sufficient time or sufficient quantity in Canada. When new drugs are approved for sale, the market authorization is issued via a Notice of Compliance (NoC).

OLD DRUGS
Old drugs are those drugs which are approved in Canada under the requirements of Division 1 of the Food & Drug Regulations. Drugs under Division 1 are generally older drugs that have been on the market for a number of years, such as acetaminophen. Often these drugs are available without a prescription. When old drugs are approved for sale, the market authorization is issued via a Drug Notification Form (DNF).

Types of drug submissions that are accepted for review by Health Canada

- Clinical Trial Application (CTA)
- Clinical Trial Application Amendment (CTA-A)
- Investigational New Drug Submission - veterinary drugs (INDS)
- New Drug Submission (NDS)
- Supplemental New Drug Submission (SNDS)
- Abbreviated New Drug Submission (ANDS)
- Abbreviated New Drug Submission - veterinary drugs (ABNDS)
- Supplemental Abbreviated New Drug Submission (SANDS)
- Supplemental Abbreviated New Drug Submission - veterinary drugs (ABSNDS)
- Notifiable Change Submission (NC)
- Drug Identification Number (DIN-A)
- Drug Identification Number – Biologics (DIN-B)
- Drug Identification Number –Disinfectants (DIN-D)
- Drug Identification Number – Category IV (DIN-F)
- Prescription to OTC Switch (Rx to OTC)
- Administrative manufacturer name/product name change/licensing agreements (ADMIN)

A Clinical Trial Application (CTA) must be filled by a sponsor to request approval to commence a human drug trial. Health Canada reviews the information contained in the CTA to ensure that the study design prevents participants from being exposed to undue risk. Good Clinical Practices (GCP) must be followed. If the results of the trial are good and the sponsor is satisfied that the benefits of the drug outweigh the potential risk, the sponsor may wish to fi le a New Drug Submission (NDS) to obtain approval of the drug for commercial distribution. CTA approval is required whenever a sponsor wishes to conduct human trials in Canada.

The New Drug Submission (NDS) contains specific information about both the drug substance and the drug product relating to safety, efficacy, and quality. The NDS includes the results of pre-clinical and clinical testing including information on the production of the drug substance and the drug product, along with information on packaging, labelling, stability, and validation. An NDS (or related filing) is required whenever a drug product meets the definition of a ‘new drug” as found in the Drug Regulations. The definition of a “new” drug includes new drug substances as well as “new” indications, dosage forms or combinations of drugs, which have not been sold in sufficient time or sufficient quantity in Canada.

An Abbreviated New Drug Submission (ANDS) is filed to obtain approval on a generic product. When the applicant can demonstrate that the product is as safe and efficacious as the innovator product, an ANDS is prepared. The generic product must be shown to be bioequivalent to the innovator drug or what is known as the Canadian Reference Product.

A Supplemental NDS (SNDS) is filled when the applicant wants to make significant changes to an already approved NDS or ANDS.

Less significant changes are fi led as **Notifiable Change (NC) Submissions (SNDS)** require pre-approval by Health Canada and are approved via a new Notice of Compliance (NOC). NC Submissions are subject to a target 90-day review and are approved via a "letter of no objection" meaning that Health Canada does not object to the implementation of the proposed change.

Submission evaluation and renewal of DINs are subject to cost recovery measures by Health Canada.

With expert knowledge of Canadian regulations MEDERA can be your one stop solution for your drug approval. Your products will be registered in record time with no hassle.

Controlled Substances and Precursor Chemicals Registration

A Controlled Substance is a substance that has higher-than-average potential for abuse or addiction. In Canada, they are divided into categories based on their potential for abuse or addiction. Controlled substances range from illegal street drugs to prescription medications.

Precursor Chemicals are chemicals that are essential to the production of a controlled substance. Precursor chemicals have a wide legitimate use in the production of consumer goods such as pharmaceuticals, fragrances, flavouring agents, petroleum products, fertilizers and paints. For example, ephedrine and pseudoephedrine, commonly used in cold and decongestant medicine, are precursor chemicals that are used to produce methamphetamine.

In Canada, Controlled Substances and Precursor Chemicals are regulated by the Controlled Drugs and Substances Act (CDSA) and its Regulations:

- Narcotics Control Regulations
- Benzodiazepines and Other Targeted Substances Regulations
- Part G of the Food and Drugs Regulations (Controlled Drugs)
- Part J of the Food and Drugs Regulations (Restricted Drugs)
- Marijuana Medical Access Regulations
- Industrial Hemp Regulations
- Precursor Control Regulations

The CDSA provides control over the possession, import, export, production, distribution and sale of narcotics, controlled drugs, targeted substances, and precursor chemicals used in the manufacture of controlled substances. All regulated activities are illegal unless permitted by regulation or permission of the Minister.

To legally handle and conduct activities with controlled substances and/or precursor chemicals in Canada, companies and research organizations must first obtain a licence. The licence authorizes the organization to possess and conduct activities using only the substances stipulated by the licence. As well, the licence is site specific. This means a separate licence is required for each site where the organization is to store and handle the controlled substance. The security for keeping controlled drugs is specific to a location and the issue of a licence is dependent upon the company conforming to proper security practices as well as other criteria.

MEDERA Consulting can help your firm with the following:

Controlled Substances

- Application for Permit to Import Controlled Drugs and Substances
- Application for Permit to Export Controlled Drugs and Substances
- Application for a Controlled Drugs and Substances Dealer's Licence
- Amendment (change) of a Controlled Drugs and Substances Dealer's Licence
- QPIC (Qualified Person in Charge) Services
- Direction on Physical Security Requirements
- Application for Destruction of Controlled Drugs and Substances
- Loss & Theft Reporting to Health Canada
- Application For An Exemption To Use A Controlled Substance For Clinical Studies
- Application For An Exemption To Use A Controlled Substance For Scientific Purposes
- Test Kit Registration

Precursor Chemicals

- Application for Transit and Transhipment Permit for Class A Precursors
- Application for Permit to Import Class A Precursors
- Application for Permit to Export Precursors
- Application for a Class A Precursor Licence
- Application for a Class B Precursor Registration
- RPIC (Registered Person in Charge) Services
- Direction on Physical Security Requirements

Medical Marijuana

• Application for Cultivation of a Cannabis (Marihuana) Licence for Scientific Purposes
•Direction on Physical Security Requirements

Low-Risk Veterinary Health Products (LRVHPs)

As of February 6, 2012 Health Canada's Interim Notification Pilot Program for Low-Risk Veterinary Health Products began accepting applications and started issuing Notification Numbers as of March 19, 2012! Previous to March 19, 2012 a Drug Identification Number (DIN) was required to sell Low-Risk Veterinary Health Products (LRVHPs).

Applications are to be submitted to North American Compendium (NAC), a third party administrator enlisted by Health Canada to manage the Interim Notification Program (INP), which will issue a Notification Number to Health Canada allowing for the sale of the Low-Risk Veterinary Health Products without a DIN.

To obtain a Notification Number the Pilot Program only requires that applicants attest in a formal application that they are meeting certain ingredient requirements, that they have adequate safety and efficacy data to support their product, and that they are manufacturing the product in accordance with GMPs.

MEDERA can assist in this application process by providing the following services.

- Review of retail labels and advertising materials for compliance
- Product Formulations (medicinal composition) and ingredients review

- Preparation of applications for submission to North American Compendiums
- Preparation of Safety/Efficacy dossiers to support product claims
- Assessment of manufacturers and importers for compliance with LRVHP GMPs

Experts at MEDERA can provide you support with the complex regulatory requirements and register your veterinary drug in record time.

Medical Device Products

Medical Devices Classification and Registration

Medical Devices are divided into 4 risk classes based on the level of risk associated with their use. Risk classification is determined by application of the "risk rules" which are found in the Medical Device Regulations.

Low risk devices such as toothbrushes, surgical instruments, and collection bags are classified as Risk Class I. Blood Pressure Monitors, Digital Thermometers, and Pregnancy Test Kits are classified as Risk Class II. Higher risk devices such as dental or breast implants, prosthetics, and drug test kits are classified as Risk Class III. Highest risk devices such as artificial hearts, heart pacemakers, skin grafts, and cardiovascular stents are classified as Risk Class IV.

All Risk Classes II, III and IV medical devices must be registered with Health Canada prior to their sale in Canada. As the risk class of the device increases, more data is required from the applicant to establish that the medical device is considered to be safe and effective for its intended use.

Upon approval of the submission by Health Canada, a Medical Device License (MDL) is issued to the applicant. Medical Device Licenses must be renewed annually.

In some cases, Health Canada may also issue a Medical Device License with Conditions whereby the applicant receives a submission approval but is still required to provide additional data to Health Canada to maintain the issuance of the license.

Submission review and license renewal are subject to cost recovery measures by Health Canada.

Types of Medical Device Submissions

- Risk Class II
- Risk Class III
- Risk Class IV
- License Amendments
- Private Label Medical Devices
- Private Label Medical Device License Amendments
- Investigational Testing Authorizations
- Changes to the Name of Licensed Devices
- Changes to Manufacturer Name/Address

Establishment Registration

There are two types of licenses issued by Health Canada for medical devices sold in Canada. The first is a license for the actual device itself and the second is a license for the establishment (company). The device license is called a Medical Device License (MDL) while the establishment license is called a Medical Device Establishment License (MDEL).

A MDEL is separate from a MDL and is issued for the activities of importing and selling medical devices for human use in Canada. A MDEL is issued by the Inspectorate based on an establishment certifying that they meet certain requirements and are then inspected for compliance.

Some establishments may be eligible for a reduced fee.

MEDERA has the right industry knowledge and market experience to help you stay on top of all regulatory requirements. We can provide you support with the complex regulatory requirements and register your medical devices in record time minimizing the risks of noncompliance.

Natural Health Products

All products regulated as an NHP must be registered, labelled and sold in compliance with the NHP Regulations.

NHP Registration

All natural health products must have a product license before they can be sold in Canada. To get a license, applicants must give detailed information about the product to Health Canada, including: medicinal ingredients, source, dose, potency, non-medicinal ingredients and recommended use(s).

Once Health Canada has assessed a product and decided it is safe, effective and of high quality, it issues a product license along with an eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM), which must appear on the label. This number lets you know that the product has been reviewed and approved by Health Canada.

In order to obtain approval of an NHP, an applicant must submit a Product License Application (PLA). Most submissions must include enough information to ensure that the product is safe, efficacious, and of high quality.

- Preparation of evidence reports based on scientific literature search, review and analysis that support the product's health claim(s)
- Preparation of Safety Summary Reports based on scientific literature search, review and analysis
- Careful scrutiny and submission of full text articles of scientific and clinical studies supporting the product's efficacy and safety
- Preparation of Quality Summary report stating the final product specifications, including the identity, purity, potency and quantity of the medicinal ingredients, and describing the unit process operations and the in-process quality control points used during manufacture
- Pertinent official product registration forms
- Full finished product testing through qualified third party laboratories licensed with Health Canada if required
- We provide Combination Rationales which is an essential component of the PLA submission as it explains why combining ingredients at their respective quantities in likely to be safe and efficacious within the context of the recommended conditions of use.

There are four levels to the review process at NHPD. In Level 1, the submission is assessed against very basic review criteria. If the submission is accepted for review, a Submission Receipt Acknowledgement (SRA) is issued. In Level 2, the submission is subject to a slightly more detailed assessment, and if applicable, a Processing Deficiency Notice (PDN) is issued. In Level 3, the submission is assessed for safety, efficacy, and quality. If applicable, one or more Information Request Notices (IRNs) are issued. Finally, at Level 4, a product license approval is

granted. The product license is issued with the 8-digit NPN (Natural Product Number) approval. For homeopathic products an 8-digit homeopathic medicine number is issued (DIN-HM).

NHP Submission Review Streams

- TPD Category IV/Labelling Standard
- Compendial
- Non-Compendial
- Traditional
- Non-Traditional
- Homeopathic

At MEDERA we have a range of NHP consulting solutions to offer. MEDERA can expedite preparation of your submissions and help you secure a submission control number. Contact us today to find out how we can help you spearhead your NHP registration projects and obtain more information on services offered.

Establishment Licensing

For NHPs, all sites involved in the manufacturing, packaging, labelling, or importation of an NHP must possess a valid site license (SL) issued by NHPD. For NHPs, distributors are required to comply with GMP but are exempt from the requirement to hold a site license. For Importers, when renewing their establishment or site licenses, they must also address the GMP compliance of foreign sites handling licensable activities. Requirements will vary based on drugs and NHPs, but acceptable evidence must be provided to Health Canada which supports the GMP compliance of the foreign site.

Good Manufacturing Practices (GMP)

Good Manufacturing Practices are found in Part C and Division 2 of the Drug Regulations and in Section 3 of the NHP Regulations.

The goals of GMP are to establish the following:

- Ensure that drugs and NHPs are manufactured, packaged, labelled, tested, or stored in an environment which does not compromise the product's safety or efficacy.
- That personnel with adequate training and expertise are available to carryout, supervise or approve various GMP activities.

Good Manufacturing Practices make sure proper standards and practices for the testing, manufacture, storage, handling and distribution of natural health products are met. Good Manufacturing Practices for NHPs cover:

- product specifications
- premises
- equipment
- personnel
- sanitation program
- operations
- quality assurance
- stability
- records
- sterile products
- lot or batch samples
- recall reporting

Good Manufacturing Practices are meant to ensure safe and high quality products while giving manufacturers, packagers, labellers, importers and distributors the flexibility to implement quality systems appropriate for their product lines and businesses.

MEDERA can assist you with any function of GMP Compliance. We will work with you to ensure that your client's NHP shipments have met the requirements of the Canadian NHP GMPs.

We can act as your QA/QC department (Quality Assurance Person or QAP) and review production documents and analytical test results to support product releases. We can handle your product releases on a full-time, part-time, or on an as-needed basis.

Cosmetics

PRODUCT ASSESSMENT AND CLASSIFICATION

Cosmetics fall under the Food and Drugs Act and its Cosmetic Regulations. Cosmetic products are required to comply with Health Canada's mandatory notification process, safety of ingredients and products, and product labelling.

While the regulations governing cosmetics are relatively straightforward there are potential pitfalls, particularly in the areas of proper classification and appropriate claims. MEDERA's experience, together with our ongoing relationships with cosmetic trade associations and government agencies, keeps us ahead of the curve with respect to any cosmetic regulatory affairs.

Our services in this area include:

- Cosmetic ingredient reviews
- Cosmetic label reviews
- Cosmetic claim and advertising reviews
- Cosmetic Notification Forms
- Advice on cosmetic GMPs

MEDERA offers a full range of regulatory solutions to assist firms in complying with the requirements of Health Canada. Our specialists can also advise you regarding the advantages and disadvantages of selling your product as a cosmetic as opposed to a drug or a natural health product (NHP).

LABEL AND INGREDIENT REVIEW

All cosmetic products must be labelled in compliance with the requirements of the Canadian Cosmetic Regulations. The 2004 Cosmetic Regulations introduced a requirement for declaration of ingredient listings on product labels, in accordance with prescribed declaration formats. Specific requirements are stated for compliance to International Nomenclature for Cosmetic Ingredients (INCI) and US requirements. MEDERA can review your ingredient listings to ensure INCI/US compliance.

It is important that therapeutic claims do not appear on the labels of cosmetic products or the product could be classified as a drug or natural health product.

Environmental assessment of new cosmetic ingredients may also be necessary under the New Substances Notification (NSN) Regulations of the Canadian Environmental Protection Act.

MEDERA will review your cosmetic labels to ensure that all claims are permissible for cosmetics and that all required information is present on labels and that ingredient listings are provided in the required formats.

COSMETIC PRODUCT NOTIFICATION

All cosmetic products must be registered with Health Canada within 10 days of first sale. MEDERA can prepare your cosmetic notifications and file these, on your behalf, with Health Canada.

MEDERA can as well help you obtain Certificates of Free Sale or COFS for products that are registered and sold in Canada to facilitate export of your products from Canada or facilitate registration of your products in other regulatory jurisdictions.

Contact us today to find out how MEDERA can work with you to ensure your cosmetics are notified to Health Canada and that they are labelled and sold in accordance with Health Canada

requirements. To receive our free white paper on marketing healthcare products in Canada, please click here.

GMP COMPLIANCE

The Cosmetic Regulations and the Food and Drugs Act require that cosmetics sold in Canada must be manufactured, prepared, preserved, packed and stored under sanitary conditions. The manufacturer must notify Health Canada that it is selling the product and provide a list of the product's ingredients.

Additionally, cosmetics must be packaged and labelled according to the Consumer Packaging and Labelling Act and Regulations, and all cosmetic ingredients are subject to the Canadian Environmental Protection Act.

Good Manufacturing Practice (GMP) is an important factor in helping to assure that your cosmetic products are neither adulterated nor misbranded. However, while FDA has provided guidelines for cosmetic GMP (Good Manufacturing Practice (GMP) Guidelines/Inspection Checklist), no regulations set forth specific GMP requirements for cosmetics. In contrast, the law requires strict adherence to GMP requirements for drugs, and there are regulations specifying minimum current GMP requirements for drugs. Failure to follow GMP requirements causes a drug to be adulterated. Each manufacturer, large or small, may have a unique means of achieving these outcomes.

MEDERA offers a full range of regulatory solutions to assist firms in complying with the requirements of Health Canada.

MEDERA will review your cosmetic labels to ensure that all claims are permissible for cosmetics and that all required information is present on labels and that ingredient listings are provided in the required formats.

Our specialists can also advise you regarding the advantages and disadvantages of selling your product as a cosmetic as opposed to a drug or a natural health product (NHP).

UNITED STATES

REGISTRATION OF A THERAPEUTIC PRODUCT IN UNITED STATES (US)

Drug Products

Types of Applications

Investigational New Drug (IND)

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

New Drug Application (NDA)

When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceuticals, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDA's are assigned an NDA number.

Abbreviated New Drug Application (ANDA)

An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

Over-the-Counter Drugs (OTC)

Over-the-counter (OTC) drugs play an increasingly vital role in America's health care system. OTC drug products are those drugs that are available to consumers without a prescription. There are more than 80 therapeutic categories of OTC drugs, ranging from acne drug products to weight control drug products. As with prescription drugs, CDER oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks.

Bringing Non-prescription Drug Products to the Market under an OTC Monograph

OTC drugs can be brought to the market following the NDA process as described above or under an OTC monograph. Each OTC drug monograph is a kind of "recipe book" covering acceptable ingredients, doses, formulations, labeling, and, in some cases, testing parameters. OTC drug monographs are continually updated to add additional ingredients and labeling as needed. Products conforming to a monograph may be marketed without FDA pre-approval. The NDA and monograph processes can be used to introduce new ingredients into the OTC marketplace. For example, OTC drug products previously available only by prescription are first approved through the NDA process and their "switch" to OTC status is approved via the NDA process. OTC ingredients marketed overseas can be introduced into the U.S. market via a monograph under a Time and Extent Application (TEA) as described in 21 CFR 330.14.

Code of Federal Regulations - Title 21 - Food and Drugs

The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government. Title 21 of the CFR is reserved for rules of the Food and Drug Administration. Each title (or volume) of the CFR is revised once each calendar year. A revised Title 21 is issued on approximately April 1st of each year and is usually available here several months later.

Biologic License Application (BLA)

Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm who manufactures a biologic for sale in interstate commerce to hold a license for the product. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.

Drug Establishment Registration

Section 510 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires firms that manufacture, prepare, propagate, compound, or process drugs in the U.S. or that are offered for import into the U.S. to register with the FDA. These domestic or foreign firms must at the time of registration, list all drugs manufactured, prepared, propagated, compounded, or processed for commercial distribution in the U.S. Foreign establishments must identify a U.S. agent at the time of their registration.

Registration information must be renewed annually. The Food and Drug Administration Safety and Innovation Act (**FDASIA**), signed into law on July 9, 2012, now requires drug firms to submit annual establishment registrations in the period from October 1st to December 31st of each calendar year. In addition at the time of annual registration, firms must list any drugs not previously listed.

Any additional updates to drug listing information must be submitted in June and December of each year. Drug establishment registration information allows FDA to identify all manufacturing facilities involved in producing drugs that are in commercial distribution in the United States, and drug listing information helps the FDA maintain a catalog of all drugs in commercial distribution in the United States. Drugs that are manufactured in establishments that are not properly registered and drugs that are not properly listed as required are misbranded and may be subject to regulatory action.

The Drug Establishments Current Registration Site (DECRS) is a database of current information submitted by drug firms to register establishments (facilities) which manufacture, prepare, propagate, compound or process drugs that are commercially distributed in the U.S. or offered for import to the U.S.

Establishments must be registered within 5 days of beginning operations. In addition, establishments must renew registration annually between October 1st and December 31st of each year.

Firms that send their initial or annual registrations during October 1st to December 31st period are considered registered until the end of following year. If a firm submits its initial, updated or annual registration outside this time frame, it is considered registered until the end of the current year and shall renew before December 31.

FDA Adverse Event Reporting System (FAERS) (formerly AERS)

What is FAERS?

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B). Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Who Reports to FAERS?

Reporting of adverse events and medication errors by healthcare professionals and consumers is voluntary in the United States. FDA receives some adverse event and medication error reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report adverse events and/or medication errors to the products' manufacturers. If a manufacturer receives an adverse event report, it is required to send the report to FDA as specified by regulations. The reports received directly and the reports from manufacturers are entered into FAERS.

MEDERA offers a wide range of consulting solutions to facilitate US registration of your drug products. MEDERA can handle the entire registration process from submission preparation through to managing the review process with FDA. We can also review submissions prepared by your staff to provide a critical review with the goal of identifying deficiencies so that FDA's review is more streamlined.

Dietary Supplements

FDA regulates both finished dietary supplement products and dietary ingredients. FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA):

- The manufacturer of a dietary supplement or dietary ingredient is responsible for ensuring that the product is safe before it is marketed.
- FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market.

Dietary Supplement Health and Education Act (DSHEA) of 1994 defines a dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include: 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, soft gels, gel caps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information 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 labeled a dietary supplement.

What is a "new dietary ingredient" in a dietary supplement?

The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined both of the terms "dietary ingredient" and "new dietary ingredient" as components of dietary supplements. In order for an ingredient of a dietary supplement to be a "dietary ingredient," it must be one or any combination of the following substances:

- a vitamin,
- a mineral,
- an herb or other botanical,
- an amino acid,
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or
- a concentrate, metabolite, constituent or extract.

Dietary Supplements Registration

Generally, manufacturers do not need to register their products with FDA or get FDA approval before producing or selling dietary supplements.* Manufacturers must make sure that product label information is truthful and not misleading.

Under FDA regulations at 21 CFR part 111, all domestic and foreign companies that manufacture, package, label or hold dietary supplement, including those involved with testing, quality control, and dietary supplement distribution in the U.S., must comply with the Dietary Supplement Current Good Manufacturing Practices (CGMPs) for quality control.

In addition, the manufacturer, packer, or distributor whose name appears on the label of a dietary supplement marketed in the United States is required to submit to FDA all serious adverse event reports associated with use of the dietary supplement in the United States.

FDA's responsibilities include product information, such as labeling, claims, package inserts, and accompanying literature. The Federal Trade Commission (FTC) regulates dietary supplement advertising.

A "new dietary ingredient" is one that meets the above definition for a "dietary ingredient" and was not sold in the U.S. in a dietary supplement before October 15, 1994.

Under DSHEA, a firm is responsible for determining that the dietary supplements it manufactures or distributes are safe and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading. This means that dietary supplements do not need approval from FDA before they are marketed. Except in the case of a new dietary ingredient, where pre-market review for safety data and other information is required by law, a firm does not have to provide FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products.

Also, manufacturers need to register themselves pursuant to the Bioterrorism Act with FDA before producing or selling supplements.

Registration of Food Facilities

Domestic and foreign facilities that manufacture, process, pack, or hold food for human or animal consumption in the United States are required to register their facility with FDA.

The FDA Food Safety Modernization Act (FSMA), enacted on January 4, 2011, amended section 415 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), in relevant part, to require that facilities engaged in manufacturing, processing, packing, or holding food for consumption including Dietary Supplements in the United States submit additional registration information to FDA, including an assurance that FDA will be permitted to inspect the facility at the times and in the manner permitted by the FD&C Act. The FD&C Act also requires food facilities to register with FDA to renew such registrations every other year, and provides FDA with authority to suspend the registration of a food facility in certain circumstances.

Adverse Event Reporting and Recordkeeping for Dietary Supplements

As required by the Dietary Supplement and Non-prescription Drug Consumer Protection Act the manufacturer, packer, or distributor whose name appears on the label of a dietary supplement marketed in the United States is required to submit to FDA all serious adverse event reports associated with use of the dietary supplement in the United States.

Serious adverse event reports received through the address or phone number on the label of a dietary supplement, as well as all follow-up reports of new medical information received by the responsible person within one year after the initial report, must be submitted to FDA no later than 15 business days after the report is received by the responsible person.

FDA recommends that all other serious adverse event reports received by the responsible person also be submitted to FDA within 15 business days of receipt.

MEDERA offers FDA regulatory consulting for companies involved in the production, packaging, labeling or holding of dietary nutritional supplements for distribution in the United States. Our function is to ensure that your business complies with the Dietary Supplement Health and Education Act (DHSEA) of 1994.

Medical Devices

Introduction

FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, re-label and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

Medical devices are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval. A description of device classification and a link to the Product Classification Database is available at "Classification of Medical Devices."

The basic regulatory requirements that manufacturers of medical devices distributed in the U.S. must comply with are:

- Establishment registration
- Medical Device Listing
- Premarket Notification 510(k), unless exempt, or Premarket Approval (PMA)
- Investigational Device Exemption (IDE) for clinical studies
- Quality System (QS) regulation
- Labeling requirements, and
- Medical Device Reporting (MDR)

Establishment Registration - 21 CFR Part 807

Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by FDA. All registration information must be verified annually between October 1st and December 31st of each year. In addition to registration, foreign manufacturers must also designate a U.S. Agent. Beginning October 1, 2007, most establishments are required to pay an establishment registration fee.

- Establishment Registration
- U.S. Agents

Medical Device Listing - 21CFR Part 807

According to 21CFR Part 807 manufacturers must list their devices with the FDA. Establishments required to list their devices include:

- manufacturers
- contract manufacturers that commercially distribute the device
- contract sterilizers that commercially distribute the device
- repackagers and relabelers
- specification developers
- reprocessors single-use devices
- remanufacturer
- manufacturers of accessories and components sold directly to the end user
- U.S. manufacturers of "export only" devices
- Medical Device Listing

Premarket Notification 510(k) - 21 CFR Part 807 Subpart E

If your device requires the submission of a Premarket Notification 510(k), you cannot commercially distribute the device until you receive a letter of substantial equivalence from FDA authorizing you to do so. A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent.

On October 26, 2002 the Medical Device User Fee and Modernization Act of 2002 became law. It authorizes FDA to charge a fee for medical device Premarket Notification 510(k) reviews. A small business may pay a reduced fee. The application fee applies to Traditional, Abbreviated, and Special 510(k)s. The payment of a premarket review fee is not related in any way to FDA's final decision on a submission.

Most Class I devices and some Class II devices are exempt from the Premarket Notification 510(k) submission.

Premarket Approval (PMA) - 21 CFR Part 814

Product requiring PMAs are Class III devices are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device.

Beginning fiscal year 2003 (October 1, 2002 through September 30, 2003), medical device user fees apply to original PMAs and certain types of PMA supplements. Small businesses are eligible for reduced or waived fees.

Investigational Device Exemption (IDE) - 21CFR Part 812

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA. Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with devices of non-significant risk must be approved by the IRB only before the study can begin.

Quality System Regulation (QS)/Good Manufacturing Practices (GMP) - 21 CFR Part 820

The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements.

Labeling - 21 CFR Part 801

Labeling includes labels on the device as well as descriptive and informational literature that accompany the device.

Medical Device Incident Reporting - 21 CFR Part 803

Incidents in which a device may have caused or contributed to a death or serious injury must to be reported to FDA under the Medical Device Reporting program. In addition, certain malfunctions must also be reported. The MDR regulation is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner.

U.S. Medical Device Establishments that are not exempt from U.S. FDA's registration and listing requirements must designate an Official Correspondent for U.S. FDA communications. As your Official Correspondent, MEDERA provide guidance on required

elements, formats and particularities of submissions including help in determining whether registration exclusions apply and, if not, we will prepare and submit your registrations with U.S. FDA and make changes, updates and cancellations as needed at no extra cost.

Most establishments that are required to register with the FDA are also required to list the devices and the activities that are performed on those devices.

MEDERA can assist you in determining your device's likely classification, prepares and submit your device listings to FDA and make changes, updates and cancellations as needed.

Many medical devices require clearance by the U.S. FDA before they can be sold in the United States. To obtain this clearance, companies must file an application and exhibits to demonstrate that the device is substantially equivalent to a device already legally marketed in the U.S., including substantial scientific and technical information provides verification of the structure, format and content of your 510(k) submission to help prevent incomplete submissions and costly delays. MEDERA will also communicate directly with the U.S. FDA on your behalf.

Cosmetics

Definitions

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines cosmetics by their intended use, as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance". Among the products included in this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any substance intended for use as a component of a cosmetic product.

Some products meet the definitions of both cosmetics and drugs. This may happen when a product has two intended uses. For example, a shampoo is a cosmetic because its intended use is to cleanse the hair. An antidandruff treatment is a drug because its intended use is to treat dandruff. Consequently, an antidandruff shampoo is both a cosmetic and a drug. Among other cosmetic/drug combinations are toothpastes that contain fluoride, deodorants that are also

antiperspirants, and moisturizers and makeup marketed with sun-protection claims. Such products must comply with the requirements for both cosmetics and drugs.

Product and Site Registration Requirements

Under the FD&C Act, cosmetic products and ingredients, with the exception of color additives, do not require FDA approval before they go on the market. Drugs, however, must generally either receive premarket approval by FDA through the New Drug Application (NDA) process or conform to a "monograph" for a particular drug category, as established by FDA's Over-the-Counter (OTC) Drug Review. These monographs specify conditions whereby OTC drug ingredients are generally recognized as safe and effective, and not misbranded. For more details please see the OTC drugs section of this document.

Among the many non-prescription drug categories covered by OTC monographs are:

- acne medications
- treatments for dandruff, seborrheic dermatitis, and psoriasis
- sunscreens

FDA maintains the Voluntary Cosmetic Registration Program, or VCRP, for cosmetic establishments and formulations. As its name indicates, this program is voluntary. The FD&C Act does not require cosmetic firms to register their establishments or list their product formulations with FDA. In contrast, it is mandatory for drug firms to register their establishments and list their drug products with FDA.

Cosmetic Labeling

A cosmetic product must be labeled according to cosmetic labeling regulations. OTC drugs must be labeled according to OTC drug regulations, including the "Drug Facts" labeling. Combination OTC drug/cosmetic products must have combination OTC drug/cosmetic labeling.

Good Manufacturing Practice Requirements

All cosmetics sold to consumers in Canada must be safe to use and must not pose any health risk. They meet the requirements of the applicable Cosmetics Acts and Regulations, including the Food and Drugs Act and the Cosmetic Regulations.

Section 16 of the Food and Drugs Act prohibits the sale of cosmetics that are manufactured, prepared, preserved, packaged or stored under unsanitary conditions, that may cause injury to the

health of the user, or that consist of any filthy or decomposed substance or any foreign matter. Section 18 of the Act prohibits the acts of manufacturing, preparing, preserving, packaging and storing a cosmetic under unsanitary conditions with the intention of sale. Under the Act, "unsanitary" means: "such conditions or circumstances as might contaminate with dirt or filth, or render injurious to health, a food, and drug or cosmetic."

In order to meet these safety and quality requirements, Health Canada encourages all cosmetic manufacturers to adhere to Good Manufacturing Practices (GMPs). Health Canada, along with its partners in the International Cooperation on Cosmetic Regulation (United States, European Union and Japan), endorse the use of the International Standards Organization (ISO) Guidelines on Good Manufacturing Practices for Cosmetics, ISO Standard 22716.

GMPs are manufacturing guidelines which are used to ensure product quality control and an effective approach to risk management. These guidelines set out standards for product manufacturing, testing, storage, handling and distribution, to ensure that each step of manufacturing is acceptable for quality and safety of the product.

Good manufacturing practice (GMP) is an important factor in helping to assure that your cosmetic products are neither adulterated nor misbranded. However, while FDA has provided guidelines for cosmetic GMP (Good Manufacturing Practice (GMP) Guidelines/Inspection Checklist), no regulations set forth specific GMP requirements for cosmetics. In contrast, the law requires strict adherence to GMP requirements for drugs, and there are regulations specifying minimum current GMP requirements for drugs. Failure to follow GMP requirements causes a drug to be adulterated. Each manufacturer, large or small, may have a unique means of achieving these outcomes.

The Cosmetic Regulations and the Food and Drugs Act require that cosmetics sold in Canada must be manufactured, prepared, preserved, packed and stored under sanitary conditions. The manufacturer must notify Health Canada that it is selling the product and provide a list of the product's ingredients.

Additionally, cosmetics must be packaged and labelled according to the Consumer Packaging and Labelling Act and Regulations, and all cosmetic ingredients are subject to the Canadian Environmental Protection Act.

Regulations as well as the Federal Register, VCRP Cosmetic Ingredient Dictionary, Guidance Documents, Labeling Guides, and Warning Letters issued by U.S. FDA. We can also assist you to register your cosmetic establishment with FDA as well as submit your Cosmetic Product Ingredient Statement (CPIS) filings to FDA.