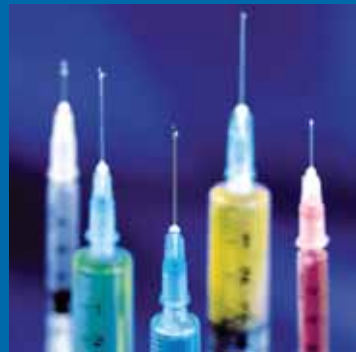




Access to Therapeutic Products

The Regulatory Process in Canada



Access to Therapeutic Products

The Regulatory Process in Canada

Our Mission is to help the people of Canada
maintain and improve their health

Health Canada

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Introduction

Therapeutic products such as pharmaceutical drugs, vitamins, vaccines and medical devices play an important role in helping Canadians lead healthy lives. More than 22,000 pharmaceutical products and 40,000 medical devices are available in Canada. Canadians trust that the products they use have passed Health Canada's rigorous safety standards and will help to deliver desired health outcomes.

This publication describes how therapeutic products in Canada make their way from the laboratory to the marketplace. It explains how Canada's regulatory system facilitates access to safe medical devices, natural health products and drugs, including pharmaceuticals, radiopharmaceuticals, biologics and genetic therapies (for definitions, see Annex I).

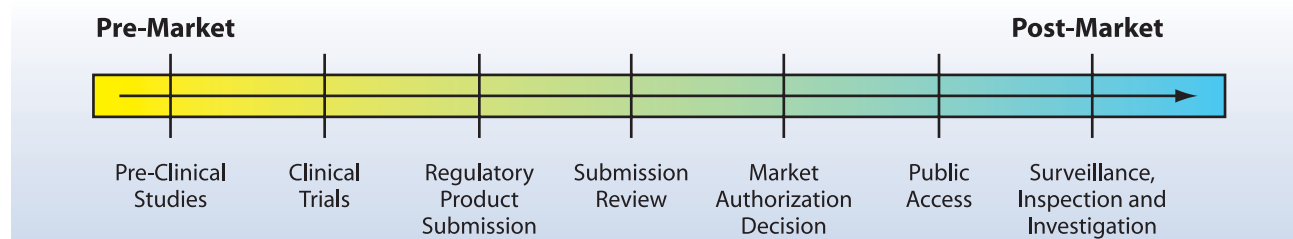
Access to Therapeutic Products in Canada

From a public policy perspective, the rationale for rapid access to safe, effective therapeutic products is simple. Good health benefits everyone. In opinion polls, individuals say it contributes significantly to their quality of life. And governments value it because the nation as a whole benefits socially and economically when everyone enjoys the best possible

health. Health Canada therefore works to help the people of Canada maintain and improve their health. In collaboration with provincial and territorial governments, it develops health policy, enforces health regulations, promotes disease prevention and encourages healthy living. And it works closely with other federal departments, agencies and stakeholders to reduce health and safety risks to Canadians.

The *Food and Drugs Act* and Regulations authorize Health Canada to regulate the safety, efficacy and quality of therapeutic products. The following pages describe the steps and the stakeholders involved. The stages and activities range from pre-clinical trials to post-authorization surveillance, inspection and investigation. Participants in the regulatory process include patients and consumers, health care professionals, research scientists, industry, academic institutions, pharmacies, hospitals, regulatory scientists and policy makers.

Improving access to therapeutic products in Canada is a high priority for Health Canada. That includes not only getting them to market, but also removing barriers that affect public access to health products once they



make it to the marketplace. This involves studying such factors as how medicines and therapies are prescribed, how they are used, and how much information is available about them.

Federal Government Commitments

In recent years, the government has promised to facilitate earlier access to safe, effective and affordable therapeutic products. The 2002 Speech from the Throne advocated “speeding up the regulatory process for drug approvals to ensure Canadians have faster access to the safe drugs they need, creating a better climate for research on drugs.” Further analysis and recommendations come from the Romanow Commission’s *Report on the Future of Health Care in Canada*. In their First Ministers’ Health Accords, federal, provincial and territorial leaders undertook to work together to provide Canadians with continued access to new, appropriate and cost-effective drugs. Budget 2005 provided \$170 million over five years to enhance the safety and effectiveness of drugs and other therapeutic products.

The Regulatory Process

New therapeutic products can be sold in Canada once they have successfully passed a review process to assess their safety, efficacy and quality. Responsibility for this review process rests with Health Canada’s Health Products and Food Branch (HPFB).

Health Canada’s Therapeutics Access Strategy (TAS) — The Vision

To provide Canadians with improved access to safe, high-quality, therapeutically effective and appropriately used therapeutic products in a timely and cost-effective manner.

TAS received \$190 million over five years from the 2003 federal budget. For information on progress, refer to *Regulation and Beyond: Progress on Health Canada’s Therapeutics Access Strategy*, available at http://www.hc-sc.gc.ca/hcs-sss/pubs/care-soins/2005-therap-strateg/index_e.html

Health Canada has several initiatives underway in response to these commitments, including the Therapeutics Access Strategy (TAS), the National Pharmaceuticals Strategy and new tools to improve the safety and transparency of the regulatory system for therapeutic products.

Taken together, these initiatives (and other related work such as the renewal of federal health protection legislation) serve to improve Canadians’ access to drugs and other therapeutic products.

The HPFB evaluates and monitors the safety, efficacy and quality of thousands of human and veterinary drugs, medical devices, natural health products and other therapeutic products available to Canadians, as well as the safety and quality of food in Canada. The Branch also contributes to the health and

well-being of Canadians in a variety of other ways, which include developing nutrition policies and standards. (To view the HPFB's organization chart, see Annex II).

Health Canada's Health Products and Food Branch — Minimizing Risk, Maximizing Safety

When it comes to approving therapeutic products, HPFB strives to find the best possible balance between benefits and risks. Public safety is priority number one.

Pre-market review — Before a therapeutic product is authorized for sale in Canada, the manufacturer must provide HPFB with scientific evidence of its safety, efficacy and quality, as defined by regulations. Scientists then review the evidence to determine whether the risks associated with the product are acceptable in light of its potential benefits. If they are, and if the product has been proven to be effective under specified conditions, it is approved for sale in Canada.

Post-market surveillance, inspection and investigation — Once therapeutic products reach the market, the Branch monitors them for safety, efficacy and quality. Reports of suspected problems are received from manufacturers, health care professionals and consumers, and the Branch evaluates them and takes appropriate action if a serious health risk is identified. Such actions can range from issuing warnings to the public and the health care community to removing a product from the market.

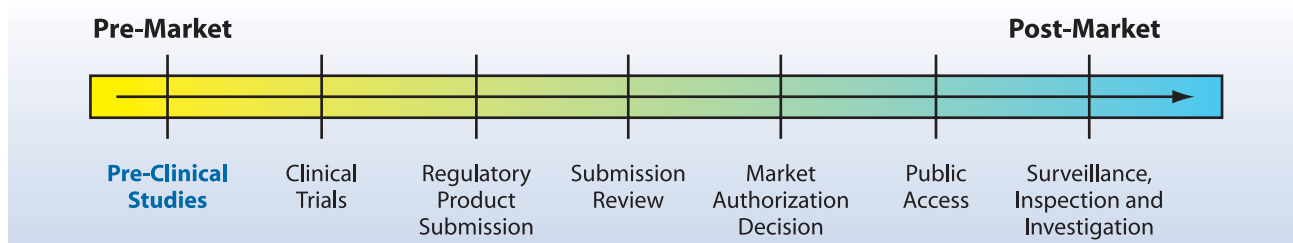
Among its other functions, the Branch also conducts inspections, investigates products, and licenses laboratories and manufacturing facilities. It uses formal risk management principles and scientific methods to arrive at its decisions, with a view to optimizing public safety, product availability and product quality.

Working with others — The Branch has developed strong partnerships with other levels of government, academia and stakeholders and ensures that their perspectives are included in its assessment of the health benefits and risks of every therapeutic product it reviews. HPFB also works with international organizations, including regulatory authorities in other countries, to harmonize regulatory standards and processes for therapeutic products.

Pre-Clinical Studies

As a first step in drug development, pre-clinical studies are carried out to evaluate the safety of a drug and its potential use. These studies are carried out *in vitro* (test tube testing) and *in vivo* (using animals) to assess the performance of the drug, including assessment of the existence and extent of

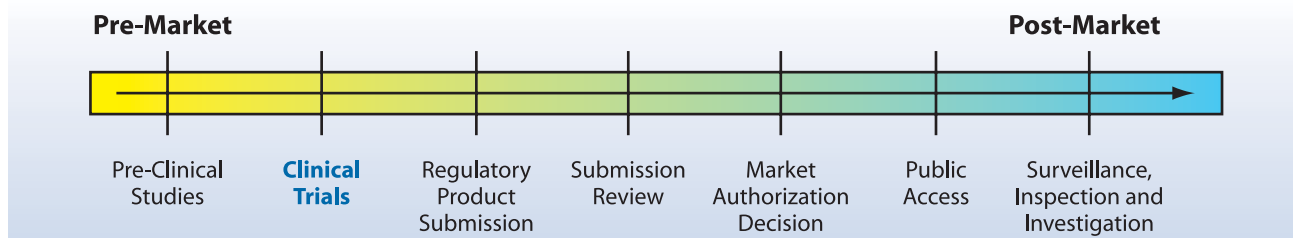
toxic effects. The pre-clinical studies provide important information on the potential use of the drug prior to testing on humans in clinical trials. If the pre-clinical studies are promising, the sponsor¹ must apply to the HPFB for authorization to conduct a clinical trial involving human subjects in Canada.



Clinical Trial Authorization

Clinical trials are conducted by sponsors to gather information on a product's safety and efficacy in humans. Before a clinical trial begins in Canada, HPFB reviews the information submitted in the Clinical Trial Application to ensure that the trial is properly designed and that participants are not exposed to undue risk.²

Clinical trials in Canada must be conducted in accordance with internationally accepted principles of good clinical practice. For drugs and natural health products, these principles are set out in Good Clinical Practices (GCP), an international quality standard. Clinical trial requirements are set out in the *Food and Drugs Act* and Regulations. For medical



¹ The person or organization who takes responsibility for the application.

² In the case of natural health products, clinical trials are required only when certain new and untested claims are made.

devices, investigational testing requirements are set out in Canada's *Medical Devices Regulations*.

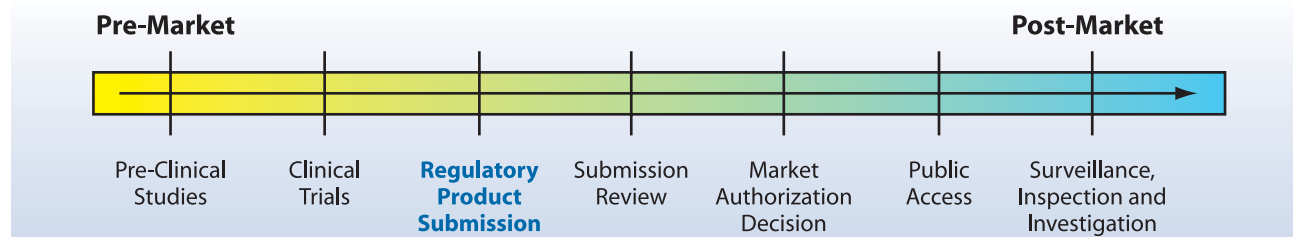
HPFB has the authority to conduct inspections of clinical trials for drugs and natural health products. Currently, two per cent of the clinical trials conducted in Canada for drugs are inspected annually. Canada's approach to verification of proper conduct of clinical trials is similar to that of other jurisdictions. However, when complaints or concerns are brought to the attention of HPFB, an investigation is launched to determine the facts and, if required, action is taken to bring the clinical trial into compliance.

Good Clinical Practices (GCP)

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the ethical principles established by the *World Medical Association Declaration of Helsinki*.

Product Submission



Drug Submissions

If the results of the clinical trial studies indicate that a new drug has potential therapeutic value that outweighs the risks (e.g., adverse effects or toxicity) associated with its proposed use, the manufacturer may seek authorization to sell the product in Canada by filing a New Drug Submission with HPFB. (The clinical trials need not have been conducted in Canada.)

A New Drug Submission (NDS), which typically involves between 100 and 800 binders of data, contains scientific information about the product's safety, efficacy and quality. It includes the results of both the pre-clinical and clinical studies, details on the production of the drug and its packaging and labelling, and information about its claimed therapeutic value, conditions for use and side effects. New drugs are commonly referred to as brand-name products because they have been created by companies and patented rather than reproduced by competitors.

An Abbreviated NDS (ANDS) is used for a generic product. The submission must meet the same quality standards as an NDS and the generic product must be shown to be as safe and efficacious as the brand-name product. An ANDS, which typically involves between 10 and 20 binders of data, includes scientific information that shows how the generic product performs compared with the brand-name product, as well as providing details on the production of the generic drug, its packaging and labelling. The generic drug must be shown to deliver the same amount of medicinal ingredient at the same rate as the brand-name product. This comparison is usually done through comparative bioavailability studies.

A Supplemental NDS (SNDS) must be filed by the manufacturer if certain changes are made to already-authorized products. Such changes might include the dosage form or strength of the drug product, the formulation, method of manufacture, labelling or recommended route of administration. An SNDS must also be submitted to HPFB if the manufacturer wants to expand the indications (claims or conditions of use) for the drug product.

A Drug Identification Number (DIN) application must be filed for those products that do not meet the definition of a 'new drug'. In such circumstances the substance for use as a drug has been sold in Canada for a sufficient time and quantity to establish the safety and effectiveness of that substance for use as a drug. DIN application requirements are outlined in regulations, and the information requirements are further clarified in policies and guidelines that are posted on Health Canada's Web site.

Natural Health Product Applications

To sell a natural health product in Canada, the applicant must submit a product licence application and demonstrate that the product meets legal requirements for safety, efficacy and quality when it is used under the recommended conditions.

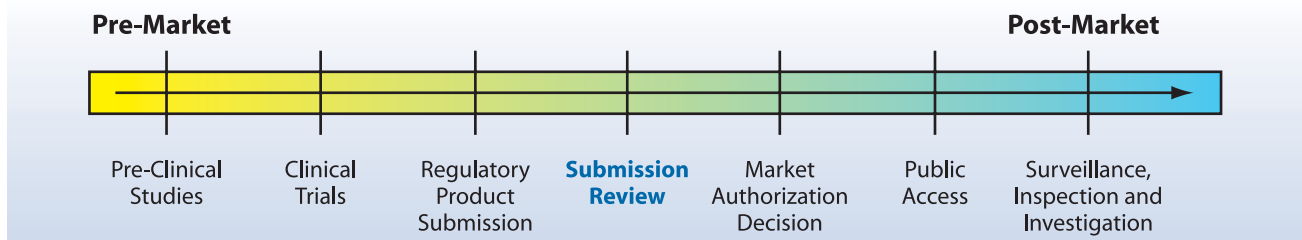
Medical Device Applications

In Canada, medical devices are divided into four classes based on the level of risk associated with their use (see Table 1). Class I devices present the lowest potential risk and do not require a medical device licence for their sale in Canada. A typical example is thermometers. However, manufacturers of Class I devices must ensure they are designed and manufactured to be safe as defined under the *Medical Devices Regulations*. Manufacturers of Class II, III and IV devices must obtain a medical device licence before their products can be legally sold in Canada. As the risk level of the device increases, more data is required from the manufacturer to demonstrate that it is safe and effective for its intended application.

Table 1: Classes of Medical Devices

	Risk	Examples
Class I	Lowest risk	Reusable surgical scalpel, Band-Aids, culture media
Class II	Low risk	Contact lenses, epidural catheters, pregnancy test kits, surgical gloves
Class III	Moderate risk	Orthopedic implants, glucose monitors, dental implants, haemodialysis systems, diagnostic ultrasound systems
Class IV	High risk	HIV test kits, pacemakers, angioplasty catheters

Review of Product Submission



Upon receipt of a New Drug Submission, Natural Health Product Application or Medical Device Application, HPFB:

- screens the submission content to ensure that it is complete and of suitable quality to be reviewed;
- performs a thorough review of the submitted information, sometimes using external reviewers and expert advisory committees. This involves evaluating the safety, efficacy and quality data to assess the potential benefits and risks of the product;
- reviews the information that the manufacturer intends to provide to health care practitioners and consumers about the product (e.g., on the label or in the product monograph); and
- requests additional information from the manufacturer if necessary. If there are deficiencies in the submission and the shortcomings are not addressed, the product may not be granted market authorization.

Priority Review and Notice of Compliance with Conditions

Priority review status may be granted to New Drug Submissions and Class III and IV medical device applications intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses or conditions where:

- no product is currently marketed in Canada; or
- the new product represents a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is better than that of existing therapies.

Submissions granted priority review status are subject to the same quality, safety and efficacy requirements as non-priority submissions, but are processed more quickly with shorter performance target times.

In certain circumstances, a Notice of Compliance with Conditions, may be granted to expedite access to potentially life-saving drugs (with the same eligibility criteria as priority review drugs) under the Notice of Compliance with Conditions (NOC/c) policy.

An NOC/c authorizes the manufacturer to market a drug on condition that the manufacturer undertake additional studies to confirm the clinical benefit. Conditions associated with approval allow HPFB to monitor the safety and effectiveness of the drug through enhanced post-market surveillance.

Target Review Times

Different classes of therapeutic products have different target times for completion of reviews. For example, target review times are shorter overall for medical devices than they are for other therapeutic products. HPFB sets specific target times (measured in calendar days) for various steps in the review process for therapeutic products (see Table 2).

Table 2: Performance Targets for First Decision Concerning Market Authorization*

New Drug Submission		Target Times (calendar days)
Processing		10
Priority:	Screening	25
	Review	180
Notice of Compliance with Conditions:	Screening	25
	Review	200
Standard:	Screening	45
	Review	300
Abbreviated New Drug Submission (Generic):	Screening	45
	Review	180
Medical Devices		Target Times (calendar days)
Class II:	Screening and Review	15
Class III:	Screening	15
	Review	60
Class IV:	Screening	15
	Review	75
Priority (Class III and IV):	Screening and Review	45

Information on performance is available at http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/performance_rendement_2004_e.html

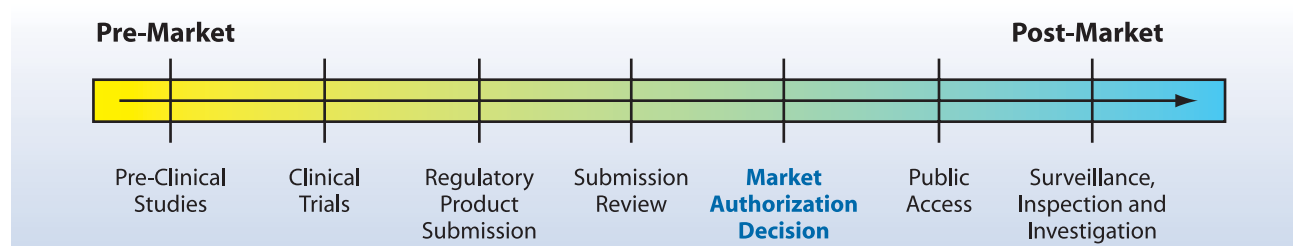
* Performance targets for natural health products are under development.

Table 3 shows the number of therapeutic product submissions to HPFB in 2005.

Table 3: Number of Therapeutic Product Submissions to HPFB (2005)

Type	Description	Number
New Drug Submissions (NDS)	New pharmaceuticals, radiopharmaceuticals, biologics and genetic therapies for human use	63
Abbreviated NDS (ANDS)	Generic drugs	139
Supplemental NDS/ANDS	New uses, new formulations	227
Notifiable Changes	Name change, licensing agreements mergers, buy-outs	1,219
Drug Identification Number Applications	Products that are not considered new drugs	995
Clinical Trial Applications	Scientific studies using test populations, designed to test the safety, efficacy and quality of drugs on human subjects	1,982
New Medical Device Licence Applications — Class II	Low-risk devices such as contact lenses, pregnancy test kits, surgical gloves	2,598
New Medical Device Licence Applications — Class III	Moderate-risk devices such as dental implants, glucose monitors	664
New Medical Device Licence Applications — Class IV	High-risk devices such as HIV test kits, pacemakers	112
Amendment Applications (Class II, III and IV)	Changes to a licensed medical device such as a change in design, indications or additions/deletions of identifiers	1,577
Faxback Amendment Applications (Class II, III and IV)	Device name change, manufacturer name or address changes or non-significant additions/deletions to device identifiers	5,895
Investigational Testing Applications	Clinical trials using medical devices on human subjects	131

Market Authorization Decision



Drug Submissions

If, at the completion of a new drug review, HPFB concludes that the benefits outweigh the risks and that the risks can be mitigated and/or managed, the product is issued a letter known as a Notice of Compliance (NOC) and a Drug Identification Number (DIN), as required in the *Food and Drugs Act* and Regulations. This allows the manufacturer to sell the product in Canada.

If, upon completing its review, HPFB finds that the submission fails to comply with the requirements set out in the *Food and Drugs Act* and Regulations, it will issue a Notice of Non-Compliance (NON). This notice outlines HPFB's concerns and generally requests additional information. The manufacturer must respond by a specified date.

The *Patented Medicines (Notice of Compliance) Regulations* provide a link between the *Patent Act* and the regulatory review process under the *Food and Drugs Act* and Regulations. The objective of these regulations is to encourage investment in drug research and development by preventing competitors from infringing the patent rights of brand-name drug manufacturers while still allowing generic drugs to enter the market as soon as the patent expires.

Natural Health Product Applications

Natural health products are issued a product licence if the application is determined to meet regulatory requirements. Each natural health product approved to be marketed is assigned a Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM).

Medical Device Applications

Upon completion of the review of a Class III or IV medical device, HPFB may issue a Medical Device Licence allowing the manufacturer to sell the device in Canada. HPFB may also issue a Medical Device Licence with Conditions when there is reasonable assurance that the device is safe and effective but supplemental information is required to support this conclusion. The applicant must provide the requisite information by a prescribed date.

Identification Numbers

With the exception of radiopharmaceuticals, blood and blood products, all drugs marketed in Canada must have a Drug Identification Number (DIN). The DIN is an eight-digit number located on the label of prescription and non-prescription drug products that have been authorized for sale in Canada.

A similar identification system is used for Class II, III and IV medical devices (Device Identifiers). Natural health products are assigned an eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM).

These numbers make it easier to identify, follow, recall, inspect and monitor therapeutic products marketed in Canada.

Appeal Procedure

A manufacturer may appeal a decision made by HPFB on a submission. An appeal allows both parties to formally discuss issues related to the decision. The parties may clarify and justify their positions using the information available when the decision was made.

Special Access Programme

HPFB's Special Access Programme (SAP) allows health care professionals to gain limited access to drugs, natural health products and medical devices that have not been authorized for sale in Canada.

Special access can be requested for emergency use or if conventional therapies have failed, are unsuitable or are unavailable to treat a patient. The SAP can also respond to specific health crises, such as an outbreak of a communicable disease.

The SAP is not intended to be a mechanism to promote or encourage the early use of therapeutic products where the degree of risk and efficacy may not be known or to circumvent

the regular therapeutic product review process, but rather to provide compassionate access to therapeutic products on a case-by-case basis.

Establishment Licensing for Drugs and Natural Health Products

The purpose of Establishment Licensing is to ensure that manufacturers comply with Good Manufacturing Practices (GMP) or equivalent standards for drugs and natural health products. All establishments engaged in fabrication, packaging or labelling, importation, distribution, wholesale, or operation of a testing laboratory are required to hold an establishment licence unless expressly exempted under the *Food and Drugs Act* and Regulations. The HPFB regularly inspects establishments to verify whether they are in compliance with GMP. Importers must demonstrate that the products they import originate from sites that comply with GMP.

Good Manufacturing Practices (GMP)

GMP include standards to ensure that drugs are produced and controlled consistently. Key elements of this international standard include:

- qualified and trained personnel;
- adequate premises and space;
- suitable equipment and services;
- correct materials, containers and labels;
- approved procedures and instructions;
- adequate testing; and
- suitable storage and transport.

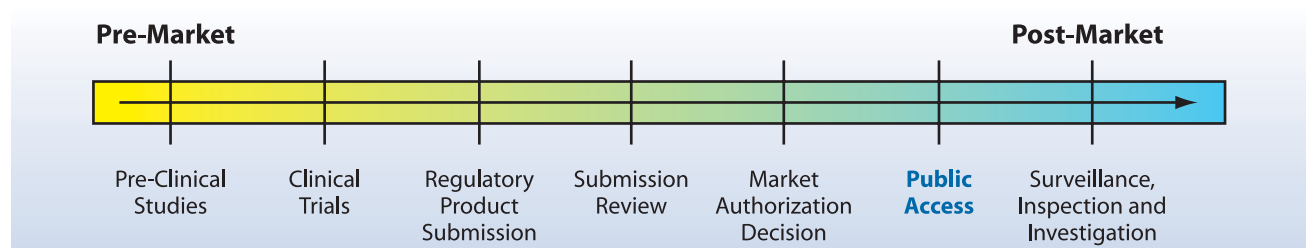
Medical Device Establishment Licensing

The Medical Device Establishment Licensing requirements in the *Medical Devices Regulations* ensure that HPFB is made aware of establishments that are importing or selling and manufacturing medical devices. Some exceptions apply. Establishments must meet regulatory requirements related to:

- distribution records;
- complaint handling;

- recalls;
- mandatory problem reporting; and
- having documented procedures in place for handling, storage, delivery, installation, corrective action and servicing of any Class II, III or IV devices they import or distribute.

Public Access



Labelling

Once a therapeutic product is approved for the Canadian market, it must be packaged and distributed with information that will help consumers make an informed choice about its use. Labels serve this purpose, as does any literature that accompanies or belongs to the therapeutic product. This includes the product monograph, the label on the product package and the label on the product container.

Since October 2004, the specifications for drug product monographs have changed. These monographs must now include a new consumer information section clearly

explaining what the medication is for, how to use it and what the potential side effects are. There is also a new section intended to give health care professionals the information they need to counsel patients.

A compendium of natural health product ingredient monographs is available on Health Canada's Web site. It is used as a tool for the timely and efficient preparation of natural health product applications by manufacturers as well as timely and efficient evaluation by HPFB of the safety and efficacy of many commonly used medicinal ingredients that make up natural health products.

Medical devices also have a label that must include such information as the name of the device, the name and address of the manufacturer, and the product expiry date.

Summary Basis of Decision

To increase the transparency of the drug and medical device review process and provide people with ample information on the risks and benefits of authorized products, Health Canada issues a Summary Basis of Decision (SBD) for every new therapeutic product it authorizes. The intent is to help people make informed choices.

The SBD is a document that outlines in technical language the risk-benefit analysis and scientific considerations that have factored into HPFB's decision to grant market authorization for a drug or medical device. The document, published on Health Canada's Web site, includes regulatory, quality, efficacy and safety information.

Public Databases on Authorized Therapeutic Products

(1) Patent Register

The Patent Register provides an alphabetical listing of drug products and associated patents, patent expiry dates and other related information.

[http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_drugs_patent_e.html]

(2) Notice of Compliance Database

The Notice of Compliance (NOC) database provides searchable information on drugs that have been authorized for use in Canada. Information in the database includes brand name, DIN, manufacturer, medicinal ingredient(s), submission class, therapeutic class, product type and NOC date.

[http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_drugs_noc_e.html]

(3) Medical Devices Active Licence Listing Database

The Medical Devices Active Licence Listing (MDALL) database provides product information for all licensed Class II, III and IV medical devices offered for sale in Canada. Information available in the database includes company name, company identification, licence name, licence number, device name, device identifier, device class, issue date and revision date.

[http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic_e.html]

(4) Drug Product Database

The Drug Product Database (DPD) provides product-specific information on human and veterinary drug and disinfectant products that are commercially available in Canada. The DPD contains approximately 25,000 marketed products, including brand name, DIN, company, active ingredient(s), route of administration, pharmaceutical form, package sizes, therapeutic classification, pharmaceutical standard and veterinary species.

[http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index_e.html]

Price Review — The Patented Medicine Prices Review Board

The Patented Medicine Prices Review Board (PMPRB) is an independent quasi-judicial administrative agency created in 1987 under the *Patent Act*. Its mandate is two-fold:

- **Regulatory:** to ensure that the manufacturers' (ex-factory) prices of patented medicines sold in Canada are not excessive. The PMPRB reviews the price at which a drug product is sold by the manufacturer to all purchasers, including wholesalers, pharmacies, hospitals and others.
- **Reporting:** reports annually to Parliament through the Minister of Health on drug price trends of all medicines; on cost drivers and drug utilization for public drug plans; and on the research and development performance of pharmaceutical patent-holding manufacturers.

The PMPRB is responsible for regulating the price charged by patentees for prescription and non-prescription patented drugs sold in Canada to wholesalers, hospitals or pharmacies for human and veterinary use to ensure that they are not excessive. The PMPRB regulates the price of each patented drug product, including the price for each strength of each dosage form of each patented medicine sold in Canada.

Under the Patented Medicines Regulations, patentees are required to file price and sales information twice a year for each strength of each dosage form of each patented medicine sold in Canada for price regulation purposes. Patentees are also required to file research and development expenditures once a year

Progress on the National Pharmaceutical Strategy – NPS

In October 2005, as part of the NPS, First Ministers gave the PMPRB responsibility to monitor and report on the prices of non-patented (prescription) drugs. For more information, go to http://www.scics.gc.ca/cinfo05/830866004_e.html

for reporting purposes. Manufacturers must inform the PMPRB of their intention to sell a new patented medicine but are not required to obtain approval of the price before they do so.

Patentees are required to comply with the *Patent Act* to ensure that prices of patented medicines sold in Canada are not excessive. In the event that the Board finds, after a public hearing, that a price is excessive in any market, it may order the patentee to reduce the price and take measures to offset any excess revenues it may have received.

Provincial and Territorial Governments

While Health Canada, through HPFB, is responsible for regulating the manufacturing, sale and import of therapeutic products, health care is a responsibility shared with provincial and territorial partners.

The provincial and territorial governments are responsible for:

- managing and delivering health care services;
- planning and evaluating the provision of hospital care, physician care and allied health care services;

- providing public drug benefit plans to certain segments of their population — all provinces and territories provide coverage to seniors and those receiving social assistance;
- managing drug formularies (a list of drugs for which public reimbursement from government drug plans is available) — in some cases, drugs have a restricted status limiting coverage to particular types of patients or situations; and
- the practice of medicine/pharmacy and the regulation of health professionals.

Review of drugs and medical devices at the provincial level includes:

- assessing whether a brand-name drug and its generic competitor are interchangeable. If products are deemed to be interchangeable, provincial reimbursement is typically limited to the price of the lower-cost generic;
- reviewing the therapeutic value and cost-effectiveness of new drugs and medical devices on behalf of most federal, provincial and territorial drug plans by the Canadian Coordinating Office for Health Technology Assessment (see below); and
- prior to including a drug or medical device in a formulary and thereby making it eligible for coverage, provinces typically assess how such a decision will affect the public purse.

The federal government oversees drug benefit programs for the following client groups:

- First Nations and Inuit;
- veterans;
- Canadian Forces members;
- members of the Royal Canadian Mounted Police;
- certain designated classes of migrants; and
- inmates of federal penitentiaries and some former inmates on parole.

Canadian Agency for Drugs and Technologies in Health (CADTH)

Since 1989, CADTH (formerly known as the Canadian Coordinating Office for Health Technology Assessment) has provided Canadian health care decision makers with unbiased, reliable information about health technologies, focusing on evaluations of clinical effectiveness and cost-effectiveness. As Canada's health technology agency, the goal of CADTH is to increase access to and use of evidence as a basis for informed decisions about technology use in Canada's publicly funded health care system.

The Common Drug Review (CDR) began in the fall of 2003. CDR involves a single process to assess new drugs for potential coverage by participating federal, provincial and territorial drug benefit plans. CADTH develops evidence-based clinical and pharmaco-economic reviews to assess a drug's cost-effectiveness.

These reviews are used by the Canadian Expert Drug Advisory Committee, an independent advisory body of professionals in drug therapy and evaluation, as the basis for its recommendations on what drugs to include in the formularies of the participating drug plans. Federal, provincial and territorial governments (with the exception of Quebec) examine the CDR recommendations but retain the final say over which drugs to include in their respective formularies.

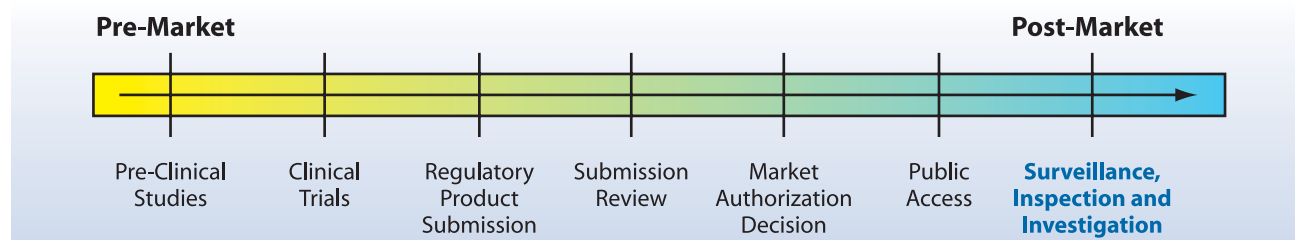
In 2004, CADTH expanded once again by adding the Canadian Optimal Medication and Prescribing Utilization Service (COMPUS). COMPUS is the Canadian centre for nationally coordinated information and education on best practices in drug

Expanding the Scope of the CDR

As part of the NPS, in October 2005, First Ministers directed the CDR to expand its scope to include recommendations for reimbursement to all drugs and to work towards a common national formulary, which is expected to lead to more consistent access to drugs across Canada. For more information, go to http://www.scics.gc.ca/cinfo05/830866004_e.html

prescribing and use. Three prescribing areas have been identified as priorities: (1) proton-pump inhibitors (used for the treatment of gastrointestinal problems); (2) diabetes management; and (3) anti-hypertensives (used for the treatment of high blood pressure).

Post-Market Activities



Regulation of therapeutic products in Canada continues even after the product has reached the marketplace.

Surveillance and Inspection

Under the *Food and Drugs Act*, manufacturers are responsible for monitoring the safety of their products. Manufacturers are required to report any new information they receive

concerning serious side effects (adverse reactions), including any failure of the product to produce the desired effect.³

There is a prescribed format and timeline for reporting adverse reactions to HPFB (see below). Manufacturers must also notify HPFB about any studies they have that provide new safety information.

³ Reporting requirements for lack of efficacy apply to “New Drugs” as defined in Division 8 of the *Food and Drugs Act*.

HPFB also inspects manufacturing plants and other sites where activities involving products covered under the *Food and Drugs Act* are conducted to verify compliance with regulatory requirements. Imported therapeutic products must meet the same standards as those manufactured domestically before they can be made available in Canada. Activities include inspection of specific incoming shipments and close cooperation with the Canada Border Services Agency.

Adverse Reaction Reporting

All therapeutic products have potential benefits and potential risks. Before a product goes to market, what we know about its safety and efficacy is limited. Relatively few patients participate in clinical trials compared with the number of users required to detect uncommon adverse reactions. What’s more, clinical trial participants are a select and homogeneous group that meets specific criteria. Clinical trials are therefore not necessarily representative of the real world and the real degree of risk to users is not always discovered in pre-market studies. It is therefore necessary to continue monitoring the safety and effectiveness of therapeutic products even after they reach the marketplace if we are to fully understand their health benefits and the potential risks associated with their use. This “post-market” surveillance and assessment contributes new

and up-to-date information that can only be realistically acquired after a product is widely used under real life conditions.

Adverse Reaction Reports

An Adverse Reaction Report contains information about the affected patient, the suspected association between the therapeutic product and the adverse reaction, and the treatment and final outcomes of the product use. The identities of both the patient and the person reporting are kept confidential by HPFB.

Patients, health professionals, manufacturers and health product regulatory authorities work together to monitor adverse reactions and medical device incidents. The most common source of information about adverse reactions is voluntary reporting by health professionals and consumers (see Table 4).

To facilitate such reporting, HPFB has toll-free telephone and facsimile numbers. Adverse reaction reports are collected in seven regional Adverse Reaction Centres and a National Adverse Reaction Centre. Regional centres undertake an initial review of the information, which is then sent to the national centre to be analysed and disseminated.

Table 4: Number of Adverse Drug Reaction (ADR) Reports Received Annually by HPFB

Year	1999	2000	2001	2002	2003	2004
Number of Domestic ADR Reports Received	5 688	7 361	7 389	8 566	9 209	10 238
Number of Foreign ADR Reports Received	41 243	53 004	81 057	106 654	136 961	138 609

Medical Device Incident Reports

Manufacturer reports are the most common source of information on medical device incidents. Both mandatory and voluntary incident reports for medical devices are made to HPFB (see Table 5). A mandatory problem report is required for any incident involving a medical device sold in Canada when the incident:

- takes place in Canada or abroad;
- relates to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use; and
- results in a patient's death or in a serious deterioration in the health of a patient, user or other person, or could do so if the incident were to recur.

Mandatory reporting is intended to reduce the recurrence of adverse incidents related to defective medical devices and to provide HPFB with information to effectively investigate such incidents and manage the risk posed by problematic devices.

Getting the Word Out on Adverse Reactions

In deciding whether to communicate product health risk information to health care providers and the public, HPFB considers the strength of the available evidence, the immediacy of the risk and how a product is used. Such decisions are made on a case-by-case basis.

The Canadian Adverse Reaction Newsletter, a quarterly publication, alerts health professionals to potential health concerns based on the review of drug-related case reports submitted to HPFB. The newsletter is an effective and timely way of disseminating information on suspected adverse reactions before comprehensive risk-benefit evaluations and regulatory decisions are undertaken.

The newsletter and advisories are distributed as an attachment to the Canadian Medical Association Journal. This ensures distribution to the Canadian Medical Association's 64,000 members. The newsletter is also available to health care professionals, pharmacists and the public on HPFB's Web site. HPFB maintains an electronic mailing list to provide immediate notice of publication of the newsletter or issuance of an advisory.

Table 5: Number of Medical Device Incident Reports Received Annually* by HPFB

Year	1998	1999	2000	2001	2002	2003	2004
Number of Incident Reports Received	290	670	1 147	1 318	1 046	1 150	964

* This table includes both voluntary and mandatory reports. Mandatory problem reporting requirements came into effect in July 1998.

For all therapeutic products, Health Professional Communications and Public Advisories are posted on Health Canada's *MedEffect* Web site to alert consumers to new safety information. In addition, a plain language bulletin, *It's Your Health* and fact sheets are regularly published by Health Canada to draw attention to common adverse reactions or other safety concerns that may be prevented by such measures as attention to diet or through changes in behaviour.

Compliance Verifications and Investigations

When HPFB responds to national and international complaints and problems related to therapeutic products, results can range from minor modifications to major redesigns or recalls. There can be changes to packaging, labelling and manufacturing. HPFB also monitors recalls of therapeutic products by foreign or domestic manufacturers in Canada. When HPFB receives a complaint, the information is reviewed to determine whether corrective action is

necessary. It is the responsibility of the company to determine what corrective action is needed and to take the necessary steps to ensure compliance. HPFB monitors the actions taken until it has verified that the company is in full compliance.

Compliance verifications may involve such matters as:

- labelling and advertising violations;
- product contamination;
- tampering allegations;
- product ineffectiveness (in the case of drugs and medical devices) and product failure (in the case of medical devices);
- sale of regulated therapeutic products without authorization by HPFB; and
- counterfeit drugs or fraudulent products.

Investigations are supported by chemical, physical and microbiological laboratory analytical services.

User Fees

HPFB levies three types of user fees relating to therapeutic product regulatory activities:

- i) a fee to evaluate the documentation submitted by a manufacturer to demonstrate the safety, efficacy and quality of a product;
- ii) fees for maintaining the right to market a product; and
- iii) a fee for an establishment licence that certifies the type of operations and category of products that the establishment is authorized to handle.

Exemptions from Fees

Currently, user fees are not levied for clinical trial applications or HPFB's Special Access Programme. Fee reductions may be granted where charging the full fee would result in economic hardship to the manufacturer.

User Fees Act

Canada's new *User Fees Act* (UFA) became law on March 31, 2004. The UFA establishes a link between performance and new fees, and subjects this process to parliamentary oversight. Currently, HPFB is developing a

new external charging regime. As part of this process, HPFB is taking steps to ensure that its performance standards, reporting and related fees are internationally comparable.

International Cooperation and Harmonization

The HPFB participates in international regulatory cooperation work, sharing resources and knowledge with other governments around the world. HPFB is a significant contributor to international harmonization efforts, especially through the creation and implementation of technical guidance and standards for the development, registration and control of therapeutic products.

The ICH produces technical guidances that each member region can incorporate into its national regulatory function. HPFB has been active in the development and implementation of ICH guidances since the organization's inception in 1990. Participation in ICH is a cost-effective means for Canada to introduce internationally recognized standards for evaluating the quality, safety and efficacy of drug products.

The International Conference on Harmonisation

Drug regulation harmonization activities are centred around drug registration — the standards specifying the type, quantity and sometimes the manner of generating the data necessary to support the evaluation of a drug's safety, quality and efficacy.

The ICH is one of the most important and successful harmonization initiatives in the drug sector, with the development of more than 40 technical guidances on drug registration requirements, electronic transmission standards, a medical dictionary of regulatory terms and, most recently, a common format for marketing applications.

The main international standardization body for drugs is the International Conference on Harmonisation (ICH), which consists of the regulatory authorities and the major industrial pharmaceutical research regions of the United States, the European Union and Japan. Canada, the World Health Organization and countries of the European Free Trade Association serve as observers.

This format, the ICH's "Common Technical Document" (CTD), is facilitating greater regulatory communication and improving submission quality. The purpose of this initiative is to streamline submission requirements on a global level to maintain consistency in regulatory requirements and introduce greater efficiency for industry in filing applications.

Communication has been further improved with the introduction of an electronic format for the CTD (e-CTD). This has established an international electronic standard for regulatory interchange and integrated electronic submissions within a broader electronic review environment for drug regulatory authorities. The CTD and e-CTD has made it easier for submissions to be filed in Canada and other countries at the same time.

Global Harmonization Task Force

Canada is also a founding member of the Global Harmonization Task Force (GHTF). The GHTF was established in 1992 as a joint regulatory–industry project. Its purpose is to encourage the convergence of regulatory practices to ensure the safety, effectiveness/ performance and quality of medical devices in different jurisdictions; promote technological innovation; facilitate international trade; and provide a forum for information exchange.

The GHTF works to achieve its objectives by disseminating guidance documents on basic regulatory practices. These documents, which are developed by four different GHTF study groups, can be adopted and implemented by national regulatory authorities.

Collaborative Activities

In November 2003, HPFB signed a Memorandum of Understanding (MOU) and Confidentiality Agreement with the US Food and Drug Administration (USFDA). In April 2004, an MOU was signed with Australia’s Therapeutic Goods Administration (TGA).

These MOUs build on existing collaborative efforts between HPFB and both the USFDA and the Australian TGA. In general, they will better enable the regulatory authorities to share information on the post-market safety of therapeutic products, the review and evaluation of new product submissions, and product investigations and enforcement activities. It also sets the stage for other, more specific, collaborative projects for exchanging regulatory information, including expert visits, joint training initiatives, participation on scientific advisory bodies and development of guidance documents.

Other examples of collaborations with international counterparts include:

- participation in the World Health Organization (WHO) Adverse Drug Reaction Reporting Network and the WHO pilot procurement project for securing quality sources of HIV/AIDS, anti-malarial and anti-tuberculosis drugs for use in developing countries;
- collaborating with the WHO’s Traditional Medicines Initiative;

- participating in the European Pharmacopoeia and the United States Pharmacopoeia expert committees for establishing standards for the quality of therapeutic products; and
- developing Mutual Recognition Agreements with Canada's trading partners respecting, for example, mutual recognition of Good Manufacturing Practices compliance programs for therapeutic products.

Mutual Recognition Agreements (MRA)

Mutual Recognition Agreements (MRAs) are legally binding, negotiated agreements between governments governing specific regulated products. Canada is a signatory to several MRAs covering drug/medicinal product Good Manufacturing Practices.

MRAs are an effective way to enhance international regulatory cooperation, maintain high standards of product safety and quality, help reduce the regulatory burden for industries, and reduce barriers to trade.

Conclusion

Ensuring timely access to therapeutic products in Canada requires a strong regulatory system that puts health and safety first.

Globalized markets and human migration are making the regulator's role increasingly complex. Public health issues such as Severe Acute Respiratory Syndrome (SARS), West Nile Virus and Bovine Spongiform Encephalopathy (mad cow disease) are fundamentally transforming the regulatory environment in Canada and abroad. Technological and scientific advances are also altering this environment and changing the role played by regulatory organizations.

HPFB is responding to these challenges by participating in a variety of initiatives, including the Government of Canada's Smart Regulation initiative, Health Canada's Therapeutics Access Strategy and the renewal of federal health protection legislation. HPFB's goal is to strengthen the regulatory process to enhance public access to safe and effective therapeutic products. By focusing on all aspects of product access, from availability and cost to cost-effectiveness, appropriate prescribing and informed use, HPFB strives to contribute to better health outcomes for Canadians.

Annex I: Glossary

These plain language definitions are intended for general understanding, and are not necessarily the formal definitions used by Health Canada or those that appear in legislation or regulations.

Adverse reaction: Any undesirable effect of a health product. This can range from a minor effect such as a skin rash to a life-threatening one such as liver damage.

Bioequivalence: A high degree of similarity in the rate and extent of absorption into the systemic circulation of two comparable pharmaceutical products from the same dose, that are unlikely to produce clinically relevant differences in therapeutic effects or adverse effects, or both.

Biologics: A subset of therapeutic products that are made from biological starting material, including those obtained by recombinant DNA procedures. They include vaccines, blood and blood products, and many hormonal products such as insulin.

Clinical trial: A scientific study, using a test population, designed to test the safety, efficacy and quality of drugs or medical devices on human subjects.

Common Drug Review (CDR): A single common process for reviewing new drugs to assess potential coverage under Canadian public drug benefit plans, established in September 2001 by federal, provincial and territorial health ministers.

Common Technical Document (CTD): A common international format that may be used by drug sponsors to submit information supporting new drug applications to regulatory authorities for review. The United States, the European Union, Japan, Australia and now Canada all use this format.

Drug: Any substance used in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, and in restoring, correcting or modifying organic functions in humans or animals.

Drug review process: Drugs are only approved for sale in Canada once they have gone through the drug review process. Drug applications are carefully reviewed by scientists in the Health Products and Food Branch of Health Canada. These scientists assess the safety, efficacy and quality of a drug. If the benefits of the drug outweigh the risks, the product is given authorization to be marketed in Canada.

Effectiveness: Whether a drug achieves its desired effect in the real world.

Efficacy: Whether a drug has the ability to bring out the intended beneficial effects in a controlled environment, for example, with no interactions with other drugs or diseases.

Guidance documents: Manuals, policy interpretations, guidelines and other texts that support a better understanding of regulations and how to participate in the regulatory process.

Health Products and Food Branch (HPFB):

A science-based organization within Health Canada that regulates products, including pharmaceuticals, radiopharmaceuticals, biologics and genetic therapies, medical devices, natural health products, veterinary drugs and food, as required by the *Food and Drugs Act* and Regulations.

Inspection: An independent evaluation, conducted by an objective, unbiased inspector or inspection team, to assess an establishment's compliance with set standards or regulations. Inspections are normally conducted on a multi-year cycle or as required.⁴

International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) (ICH):

A global project dedicated to reducing duplicate testing of new medicines, to make better use of resources, safeguard public health and avoid unnecessary delays in making new medicines available.

Labelling: Includes any legend, word or mark attached to, included in, belonging to or accompanying any therapeutic product and is commonly understood to mean all packaging and product inserts, including the drug product monograph.

Medical device: Any article or instrument used in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, and in restoring, correcting or modifying organic functions in humans or animals. Devices also include those used in the prevention, diagnosis and care of pregnancy and do not include a drug.

Natural health products: Include vitamins, minerals, traditional medicines, medicines made from plants, bacteria and fungi, probiotics, amino acids and essential fatty acids (such as Omega-3). *Also refer to definition of drug.*

New Active Substance (NAS): A therapeutic substance that has never before been approved for marketing in any form.

New Drug Submission (NDS): The formal process of applying for market approval of a new drug product. A new drug is any drug that has not been sold in Canada for sufficient time and in sufficient quantity to establish its safety and effectiveness under use or its recommended conditions for use.

Patent: An instrument issued by the Commissioner of Patents in the form of letters patent for an invention. The patent provides its holder and its holder's legal representatives with the exclusive right to make, construct, use and sell the invention for a designated period.

Performance metrics: The criteria by which performance is measured, based on specific target goals.

Pharmaceuticals: Mostly synthetic products that are made from chemicals, pharmaceuticals include prescription and non-prescription drugs, disinfectants, and low-risk products such as sunscreens, antiperspirants and toothpaste.

⁴ Health Canada. GMP Inspection Policy for Canadian Drug Establishments. January 2004.

Post-market surveillance: The process of tracking drugs and other therapeutic products, already approved and on the market, to assess signals and safety trends once these products are in use among a wider population.

Product monograph: A factual, scientific document, devoid of promotional material, that describes the properties, claims, indications and conditions of use for a drug and that contains any other information that may be required for optimal, safe and effective use of the drug. Product monographs are submitted to HPFB as part of a new drug submission.

Quality: An accepted standard of production methods and manufacturing facilities, including the premises, equipment, in-process controls and tests during fabrication, packaging and labelling, to ensure consistent results in final products that are safe, efficacious, pure and stable.

Radiopharmaceuticals: A pharmaceutical, biological or drug that contains a radioactive entity. Radiopharmaceuticals are primarily used for various imaging functions but can also be used in a therapeutic capacity.

Risk: Chance of harm: a health hazard. All therapeutic products that offer benefits are accompanied by risks. Although risks can be controlled and managed, they cannot be fully eliminated. Risk varies by product and changes through the product life cycle. The definition of risk within the context of safety, quality and efficacy of therapeutic products continues to develop globally and through international harmonization initiatives.

Risk communication: The exchange of information about health risks between experts, other interested parties and the public.

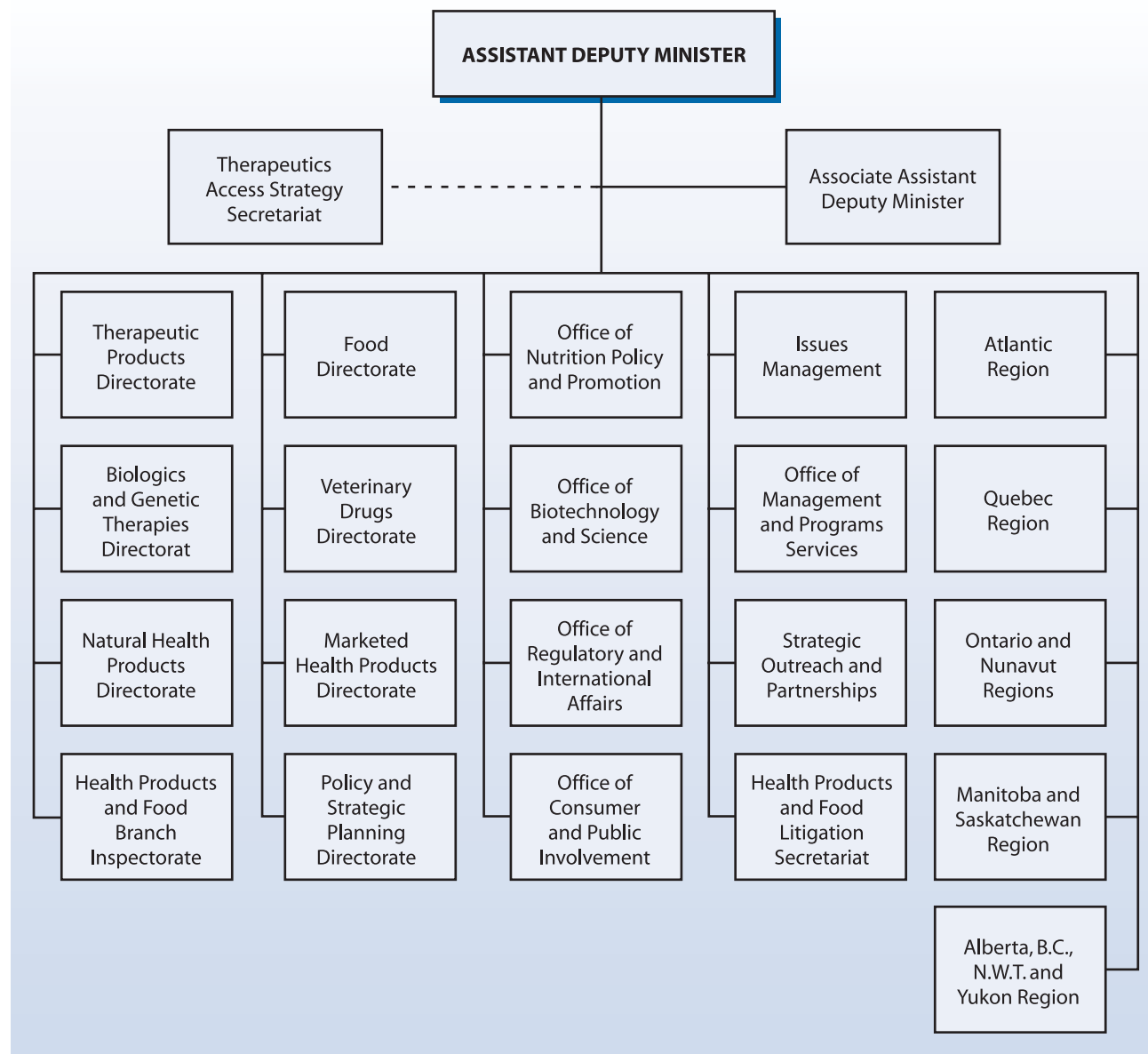
Safety: The relative risk of harm. Safety is aimed at defining the type, level and scope of adverse events, reactions and hazards to be balanced against the benefits of a health product so that an appropriate risk-benefit assessment can be developed and an appropriate therapeutic index for a health product can be established.

Stakeholder: An individual, group or organization that is affected by or interested in an issue or policy. Stakeholders, interested parties and affected parties are segments of the public. Stakeholders may include health professionals, academia, industry and patients.

Summary Basis of Decision (SBD): A public document that outlines in technical language the risk-benefit analysis and scientific considerations that have factored into HPFB's decision to grant market authorization for a drug or medical device. The document provides regulatory, quality (chemistry and manufacturing), efficacy and safety information.

Therapeutic products: A broad range of products, including drugs (pharmaceuticals, radiopharmaceuticals, biologics and genetic therapies), natural health products and medical devices.

Annex II: Health Products and Food Branch: Organization Chart



Annex III: Further Sources of Information

Organizations

Health Canada

<http://www.hc-sc.gc.ca/>

Health Products and Food Branch, Health Canada

<http://www.hc-sc.gc.ca/hpfb-dgpsa/>

Canada's *Food and Drugs Act* and Regulations

<http://laws.justice.gc.ca/en/F-27/index.html>

Therapeutic Products Directorate

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/aboutus_e.html

Biologics and Genetic Therapies Directorate

http://www.hc-sc.gc.ca/hpfb-dgpsa/bgt-dpbtg/aboutus_e.html

Natural Health Products Directorate

http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/index_e.html

Marketed Health Products Directorate

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/about-mhpd_e.html

Health Products and Food Branch Inspectorate

http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/index_e.html

Provincial and Territorial Government Health Ministries and Links

http://www.hc-sc.gc.ca/hcs-sss/medi-assur/ptrole/ptmin/index_e.html

Canadian Agency for Drugs and Technologies in Health

<http://www.cadth.ca/index.php/en/home>

Patented Medicine Prices Review Board

<http://www.pmprb-cepmb.gc.ca/>

Public Policy Forum — Strengthening Canada's Regulatory Process for Therapeutic Products

http://www.ppforum.ca/ow/ow_e_05_2003/ow_e_05_2003_cons.htm

Canadian Health Network

<http://www.canadian-health-network.ca>

