

# Drugs

## From Research Lab to Pharmacy Shelf

Every year, more and more medications become available to treat disease.

Drugs are the fastest growing component of health care in Canada and have had a huge impact on improving the health of Canadians.

Approximately 22,000 drug products are on the market today. In 2006, pharmacists filled 422 million retail prescriptions.

Drugs are now the second largest health-spending category after hospitals and were forecast to make up 17% (\$25 billion) of total health expenditures in 2006, compared to 13% (\$10 billion) 10 years ago.

### 1. Research & Development

Research for new drugs begins with scientists developing various chemical or biological substances derived from molecules. Researchers are guided by close study of the disease process to help target cellular or genetic chemicals on which a drug might act. This phase can take up to four years.



### 2. Patent Protection

Manufacturers of newly discovered or invented drugs apply for patent protection early in the R&D phase.

In Canada, a patent is good for 20 years from the time of filing (following international standards) and gives the manufacturer the right to sell its drug without competition for that period. When a patent has expired, competing pharmaceutical companies are permitted to manufacture and sell generic versions of the drug. It takes a manufacturer about two to three years to develop a generic (chemically identical) copy of a patented drug, at a cost of about \$1 million.

### 3. Pre-clinical testing

Before a substance is tested on humans, it undergoes pre-clinical testing to determine how it actually works. Once the substance has been isolated and purified, it is administered to tissue cultures and to a variety of small animals to see if any significant changes occur (biochemical, physiological or behavioural). By looking at toxicology, adverse reactions and product stability, appropriate dosage forms and strengths are developed. This phase can take three to five years.

### 4. Clinical Trial Application (CTA)

If the drug has a desirable effect and is safe for animals, a Clinical Trial Application (formerly called an Investigational New Drug Application) is made to Health Canada, requesting permission to start clinical trials. The CTA includes information on test results; the drug's ingredients; dosage forms; data to support the proposed mechanism of action; toxic or carcinogenic effects found in animal studies; and the proposed methodology for the clinical trials. An average of 1,400 CTAs are made to Health Canada each year.

### Special Access Programme (SAP)

This Health Canada program provides access to drugs not currently available in Canada to practitioners treating patients with serious or life-threatening conditions where conventional therapies have failed, are unavailable or not suitable. Health Canada reviews the *Special Access Request Form* and, if approved, sends a Letter of Authorization to the drug manufacturer and the patient's physician. Pharmaceutical companies have the right to decide whether, and under what conditions, to provide the drug to the patient.

### 5. Clinical Trials

Clinical trials are used to assess a drug's benefits and risks for humans, i.e., whether a drug is safe; can prevent or treat disease; how well it works; and its effectiveness for other conditions. Types of clinical trials include disease treatment, prevention and screening, and quality of life. Clinical trials take place in three phases, each using an increasing number of test subjects.

**Phase I:** 20 to 100 healthy volunteers are used to assess the response and tolerance to different doses and to study how the drug is absorbed, metabolized and excreted by the body. This phase takes six to nine months; about 70% of investigational drugs survive Phase I.

**Phase II:** 100 to 300 patients with the target disease are used to identify short-term side effects and ideal dosages. This phase can take six months to three years.

**Phase III:** 1,000 to 3,000 patients with the disease are used to confirm effectiveness and further study side effects. To eliminate bias, a double blind study is generally used in which patients and investigators do not know which treatment the patient is receiving — the drug or a placebo. This phase can take one to five years and tries to finalize the ideal dosage regimen for different types of patients. Only about 10% of investigational drugs tested will make it to Phase III clinical trials.

A clinical trial may be stopped if the drug is shown to be either unsafe or have dramatic benefits. If the drug is unsafe, it is dropped or sent back for further development. If it appears to have dramatic benefits, it may be fast-tracked through the Health Canada authorization process.

### 6. Health Canada's Drug Review Process

All drugs sold in Canada — both those manufactured here and those imported from other countries — must be authorized for sale by Health Canada. Within the Health



Products and Food Branch (HPFB), the Therapeutic Products Directorate (TPD) reviews and authorizes new pharmaceuticals and medical devices, and new indications for already authorized products, for their safety, efficacy and quality. The Natural Health Products Directorate (NPHD) regulates natural health products — vitamin/mineral supplements and herbal products — when a therapeutic claim is made. The Biologics and Genetic Therapies Directorate (BGTD) evaluates biological and radiopharmaceutical drugs.

If a new drug passes Phase III clinical trials, a New Drug Submission (NDS) may be prepared which includes information on test data; the disease treated; type of patients who could benefit; length of treatment; and the goal (e.g., a cure, improved quality of life). New drugs usually require pre-clinical, clinical, chemistry and manufacturing data.

About 4,400 drug submissions are made to Health Canada each year but only about 80 are for new drugs. (The rest are for new uses, formulation changes, generic drugs, name changes, etc.) Health Canada reviews the submitted information and evaluates the drug's safety, efficacy and quality. Biological drug reviews also include on-site evaluation of the production process and, in some cases, lab analysis of samples sent by manufacturers. Health Canada is now implementing the Therapeutics Access Strategy in an effort to improve the drug review process and eliminate the backlog of pharmaceutical submissions. (The backlog was reduced by 65% in 2003/04 and should be cleared by March 2005.)

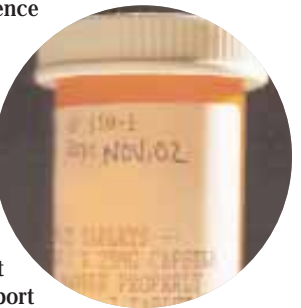
A Priority Review Process is in place that allows for earlier review of drug products for life threatening or severely debilitating conditions (e.g., cancer, AIDS, Parkinson's disease) when there is no effective drug on the Canadian market.

To gain Health Canada authorization, generic manufacturers are required to provide TPD with an Abbreviated New Drug Submission (ANDS) demonstrating that the generic formulation of the drug is bioequivalent to the brand formulation. Generic manufacturers must also clear all patent issues before being allowed to market their product.

### 7. Notice of Compliance (NOC)

At the completion of the review, if Health Canada has authorized the new drug and its manufacturing process under the *Food and Drugs Act and Regulations*, it provides a NOC. This indicates official approval and permits the drug to be marketed in Canada. A Drug Identification Number (DIN) is also issued to all drugs authorized for marketing.

If there is insufficient evidence to support the safety, efficacy or quality claims, a marketing authorization for the drug will not be granted and a Notice of Deficiency or Notice of Non-Compliance is issued. Drug companies can then submit further information to support their claims and can appeal a decision not to authorize a drug.



The *Natural Health Products Regulations* came into force in January 2004, with a six-year transition period. The *Regulations* place specific requirements on companies that manufacture, package, label, import or distribute the over 25,000 NHPs on the market to ensure they are safe for over-the-counter use and have proper labeling. They also require reporting of adverse reactions to Health Canada. Once a product has been assessed and granted market authorization by Health Canada, its label will have a natural product number (NPN) or in the case of a homeopathic medicine, DIN-HM.

## 8. Drug Scheduling

Canadian provinces (except Québec) use a national drug scheduling model to align the provincial drug schedules and ensure consistent conditions of sale across the country. At the request of the manufacturer, scheduling recommendations are made to provincial regulatory authorities by the National Drug Scheduling Advisory Committee (NDSAC). A set of factors are used to determine the schedule under which a drug can be sold; these include potential for dependency, adverse reactions, interaction, etc.

Canada uses four categories (in comparison, the U.S. uses five):

**Schedule I** — available only by prescription and provided by a pharmacist

**Schedule II** — available only from a pharmacist; must be retained in an area with no public access

**Schedule III** — available via open access in a pharmacy (over-the-counter)

**Unscheduled** — can be sold in any store without professional supervision

The Drug Strategy & Controlled Substances Program (DSCSP) manages the 1997 *Controlled Drugs & Substances Act* which controls the import, production, export, distribution and possession of narcotics and controlled substances. These substances are classified according to three schedules.

Pharmacists must follow standards of practice as set by their provincial regulatory authority. The National Association of Pharmacy Regulatory Authorities (NAPRA) has developed a national model that sets out the level of professional intervention and advice necessary for the safe and effective use of drugs by consumers.

## 9. Price Review

**Patented Drugs:** The Patented Medicine Prices Review Board (PMPRB) regulates the prices charged by manufacturers of patented medicines (prescription and nonprescription) to ensure they are not excessive. This quasi-judicial body operates under the Patent Act and is independent of Health Canada. Patentees are required to file price and sales information twice a year for each dosage strength form of all patented medicine. Following a public hearing, if PMPRB finds that a price is excessive, it can order the patentee to reduce it. (This has only occurred eight times in the past six years.) As a reference, PMPRB collects comparative price data from the U.S. and six European countries.



Pricing of patented drugs is also impacted structurally by the “buying power” of provincial formularies and large private drug plans. In order to control costs, provincial formularies are selective in the drugs they list, with the implication that drug companies consider this in their pricing decisions.

**Generic Drugs:** Generic versions are available for many drugs whose patent has expired, and cost on average about 45% lower than the brand name equivalent. PMPRB does not have the authority to regulate the price of non-patented drugs, which includes generic drugs. Generic drug prices are, in fact, “structurally” set by provincial regulations, notably the *Ontario Drug Benefit Act* and the *Ontario Drug Interchangeability & Dispensing Fee Act*. These Acts permit the Ontario government to limit the prices of generic drugs it will reimburse. The “70/90” rule of the *Ontario Drug Benefit Act* requires a first-entry generic drug to be priced at no higher than 70% of the brand drug, while subsequent products are limited to 90% of the first generic.

## 10. Advertising

Health Canada is the regulatory authority for drug advertising. Unlike the U.S., Canada permits only limited Direct-to-Consumer Advertising of prescription medications (only the drug’s name). Advertising in professional journals within the health care sector contains prescribing information.

Drug advertisements are reviewed and pre-cleared by two independent agencies — Advertising Standards Canada (ASC) and the Pharmaceutical Advertising Advisory Board (PAAB) — to determine compliance with the *Food and Drugs Act* and the various advertising codes. Pre-clearance is voluntary, although most companies comply.

## 11. Distribution

Community pharmacies purchase their pharmaceuticals either from the manufacturer itself or from drug wholesalers (who buy from the manufacturer and must operate a warehouse). Hospital pharmacies (and some community pharmacies) generally use group-purchasing organizations to buy drugs at negotiated rates.

## 12. Listing on Provincial Formularies

Each province decides what drugs it will reimburse (i.e., list on their formulary) for residents eligible under a provincial drug plan. (Public drug plans account for about 45% of expenditures on prescription drugs.) Drug accessibility varies widely between the provinces, which use a number of factors when deciding to list a specific drug, e.g., effectiveness analyses, cost, government priorities and patient advocacy. Some drugs receive a restricted listing if special monitoring is required or their cost is high.

While new drugs now go through the Common Drug Review to receive a listing recommendation, generic and existing/revised drugs are submitted directly to the various drug plans to request listing.



The Common Drug Review (CDR), which was initiated in 2002, is a single, rigorous process for reviewing and recommending new, approved drugs for listing on F/P/T formularies. The CDR Directorate is housed at the Canadian Coordinating Office for Health Technology Assessment (CCOHTA). The CDR consists of an appraisal of the best clinical evidence and a listing recommendation from the Canadian Expert Drug Advisory Committee (CEDAC). The drug plans continue to make the final formulary listing decision. (Québec does not participate in the CDR.) A target timeframe of 20-26 weeks has been set for the review process. While private drug plans are not involved with the CDR, they have access to the recommendations when making their own listing decisions.

## 13. Post-Market Surveillance

Since clinical trials are controlled and involve a limited number of patients, they generally detect only frequent or common adverse reactions (AR). Even after a new drug is authorized for sale, the manufacturer continues to monitor its safety and study alternative uses.

Health Canada maintains regulatory control and monitors AR (defined as undesirable effects from a product used at prescribed dosages). Under the *Food and Drugs Act*, drug manufacturers are required to report serious AR of which they are aware.

Health Canada’s Marketed Health Products Directorate (MHPD) is responsible for coordinating the consistency of post-market surveillance of drugs and natural health products. It monitors adverse events and investigates complaints and problem reports. Should a product’s safety, efficacy or quality come into question, in collaboration with other Health Canada directorates, MHPD will take appropriate action ranging from informing the public and health care community of new product safety information, to removing the product from the market. The HPFB Inspectorate is responsible for compliance and enforcement via product investigations and inspections of clinical trials and drug production sites. In 2002/03, Health Canada received 9,500 domestic AR reports and 106,650 foreign reports. However, these are considered to represent only a small percent of the adverse reactions that actually occur.



The Canadian Adverse Drug Reaction Information System (CADRIS) is a database that contains suspected adverse reactions to pharmaceuticals, biologics and natural health products reported to Health Canada’s Canadian Adverse Drug Reaction Monitoring Program (CADRMP). AR reports are submitted voluntarily by health professionals or consumers either directly to Health Canada or via market authorization holders.

### SOURCES

1. Health Canada
2. Rx&D — *Drug Development Process*
3. Canadian Association for Pharmacy Distribution Management
4. Canadian Coordinating Office for Health Technology Assessment
5. Canadian Generic Pharmaceutical Association
6. Canadian Institute for Health Information. *National Health Expenditures in Canada*. December 2006
7. IMS Health Canada
8. National Association of Pharmacy Regulatory Authorities
9. National Drug Scheduling Advisory Committee
10. Pharmaceutical Advertising Advisory Board
11. Fraser Institute Occasional Paper, *Generic Drugopoly*, August 2004
12. CD Howe Report. *Rx for Canada, Close the Internet Pharmacies*. October 2004

January 2007

*The Canadian Pharmacists Association is the national organization of pharmacists, committed to providing leadership for the profession and improving the health of Canadians.*