

Chapter 9

Authorization for Marketing: Safety and Efficacy

Introduction

Many drugs are highly effective in combating disease, lengthening life, and improving the comfort and quality of life for the ill. However, this effectiveness is sometimes accompanied by toxic effects, especially when drugs are taken in combination. Such adverse reactions do not often occur in all the consumers of a drug, but rather in exceptional individuals or a particular category of patients. One category of special concern is pregnant women.

Pharmaceutical manufacturers and distributors wish to avoid adverse drug reactions from their products because of humanitarian concerns and a sense of responsibility and also because adverse reactions may cause claims for compensation and produce unfavourable publicity for their brands and for pharmaceutical products in general.

The multiplication of drugs and the increase in their potency since the 1930s has inevitably produced some toxic effects which proved fatal or crippling for numbers of individuals. These catastrophes led to the extension of government controls on drug consumption by making many drugs unobtainable without a physician's prescription and by increasing the stringency with which new drugs are evaluated before allowing them to be placed on the market. During the 1940s and 1950s the evaluations focused on the safety of drugs. In the 1960s and thereafter regulatory authorities have also been concerned with the therapeutic efficacy of new drugs.

Countries vary with respect to the precise mechanism used to regulate the introduction of new drugs and to monitor the performance of existing drugs. Some governments require pharmaceutical firms which propose to market new drugs to submit extensive information on chemical composition, method and place of manufacture, and results of animal tests and of clinical tests on humans. In many countries each stage of clinical testing may require authorization before the final review; in others, for instance Switzerland, clinical testing can proceed without governmental review and a single comprehensive review takes place when the firm seeks authorization to put the drug on the market. Some countries require that the clinical data be generated domestically; others, Canada amongst them, require no domestic data if data

are available from foreign tests carried on under conditions that are adequate in the eyes of the responsible health protection agency.

In some countries the regulatory authorities take into account the judgements made by the regulatory authorities of other countries which have full procedures for drug evaluation and may base their clearance of drugs for marketing on decisions made abroad, thereby avoiding the duplication of reviews, their considerable costs for both firms and governments, and possible delays in introducing the new drugs. The high respect in which the Canadian regulatory authorities are held in some countries in Africa and South America means that proof of Canadian clearance is sufficient to obtain clearance for marketing in those countries.

Stages in the Clearance Process

The process of clearance for marketing that prevails in Canada can be taken as a representative example. The major stages of the process are indicated in Table 9.1. Processes are similar in the United States, France, the United Kingdom, and many other countries.

When a new chemical entity has been discovered and is judged potentially effective, it is tested on tissue cultures and on various species of animals so as to obtain information on its toxicity and on its pharmacological effects. These results are used to help predict its potential toxicity and efficiency in humans. This is the preclinical phase. At the same time the manufacturer determines whether the active ingredient can be produced on a large scale with adequate control of quality.

The next stage is clinical testing. The firm presents a Preclinical New Drug Submission (usually called an Investigational New Drug Submission [IND] following U.S. nomenclature) seeking permission to administer the drug to humans, usually a small number of healthy volunteers, through the agency of a qualified medical researcher. The purpose of these tests is primarily to determine the safety of the new product for humans or its metabolism. The Preclinical New Drug Submission (PNDS) contains detailed information on the product, including its method of manufacture, and on results of animal tests as well as identifying the medical researcher and the detailed protocols under which he will carry out the research.

The Health Protection Branch reviews the submission, balancing the risk in human experimentation against the advantages expected of the new drug, and, if satisfied, issues an approval for the PNDS. Phase 1 clinical trials then proceed. Upon their completion, the firm submits additional information and a protocol requesting authorization to proceed to clinical trials on a small number of sick volunteers to test for therapeutic effects of the new drug in addition to safety. This is Phase 2 research which proceeds after approval by the Health Protection Branch. Phase 3 research on a larger sample of patients follows additional protocols and approval. Each phase may include many

Table 9.1
Stages in the Development and Approval of
a New Drug in Canada

Research	Regulation
Discovery of new drug: chemical synthesis or extraction, analysis, formulation.	Preclinical New Drug Submission (PNDS): all available information on new drug. Review by Health Protection Branch (HPB) of Health and Welfare Canada. If approved company may proceed to clinical testing.
Phase 1 clinical research	Protocols: detailed description of proposed clinical tests on humans; each is reviewed and approved by HPB and is subject to ethical review of research institution and informed consent of subjects. Phase 1 protocol: toxicology, small sample of healthy subjects.
Phase 2 clinical research	Phase 2 protocol: therapeutic effect, toxicology, small sample of patients.
Phase 3 clinical research	Phase 3 protocol: therapeutic effect, toxicology, large sample.
Marketing	New Drug Submission (NDS): complete information on new drug including full report on clinical tests. If approved receives Notice of Compliance (NDS/NOC) and Product Monograph.
Phase 4 clinical research: no approval is required.	

Note: Research reported for PNDS and NDS need not be done in Canada.

different and successive protocols, each of which must be approved by the Health Protection Branch. Phase 1 and Phase 2 research is the most scientifically interesting.

Upon completion of this clinical research, the firm submits a New Drug Submission (NDS) requesting permission to market the drug. This NDS is an exhaustive set of documents, often of several hundred volumes, which includes details of all the experiments conducted on the drug both in foreign centres and

in Canada; the name of the manufacturer of the active ingredient; the brand name that will be given to the product; a full description of the drug and its uses; information that will be distributed to physicians, pharmacists and, in some cases, to consumers; and other material.

When the Health Protection Branch issues a Notice of Compliance for the New Drug Submission the drug can be sold and receives "new drug status." The Notice of Compliance is accompanied by a Product Monograph which is based on the material submitted to the regulatory authority in the NDS and essentially summarizes the information. The Monograph is written by the firm, but amended at the suggestion of the Health Protection Branch which gives final approval to the Monograph. Its purpose is to provide information to health professionals about the use and all precautions associated with the product and it summarizes and references all published and unpublished studies of the drug. It may also contain sections destined to inform consumers. The Product Monograph becomes public when the Notice of Compliance is issued.

After receiving clearance for marketing, a drug may be subjected to post-marketing studies. These are Phase 4 clinical trials. They do not require approval if the drug is studied at the same dosage levels and for the indications described in the Product Monograph. A drug remains on "new drug status" for many years to permit the Health Protection Branch to control its sales until entirely satisfied of its safety and efficacy. Few drugs cleared since 1963 have been removed from "new drug status." There are virtually no controls on "old" drugs.

If experience or experimentation (the latter requiring a new PNDS and approvals of protocols) should lead to the use of a drug for medical conditions other than those for which the drug was originally approved, a Supplementary NDS must be submitted to the Health Protection Branch and go through a new approval process.

The Objectives and Effects of Drug Regulation

The consideration that must and does dominate in devising and applying regulatory processes is to reach the right balance between the benefits society derives from assurance of the safety and efficacy of new drugs and the cost of the process. The cost is partly that of administration to the taxpayer and partly the cost of administration and compliance to manufacturers. But in an important and unmeasurable degree the cost also resides in the delay in the general availability of drugs that turn out to be beneficial in their effect.

A secondary consideration is the way in which the length of the clearance process affects the amount of pharmacological research and development carried out in the country. Most governments are eager to stimulate research because it provides employment in the scientific sector, increases the familiarity of physicians with new drugs to the benefit of patients, and opens possibilities for industrial development.

Since the early 1960s an increased amount of information has been required by the review processes of most countries to determine the efficacy and safety of drugs. This in turn has required more animal and clinical testing. In consequence, the delay between the discovery of a drug and its clearance for introduction on the market has been extended by several years and the costs for pharmaceutical manufacturers have been raised. These increased costs have been accompanied by a decrease in the number of new chemical entities introduced on the market, despite increased real expenditures on research and development by the world-wide pharmaceutical industry. The precise reasons for the decrease in the number of new chemical entities (NCEs) is much debated, but three factors are recognized as central: the exclusion of drugs judged to be ineffective by the regulatory authorities, the decreased stock of unexploited scientific knowledge, and the increase in the cost of introducing new drugs owing to the more stringent regulatory requirements.

Differences amongst countries in the costs imposed by the stringency of regulatory requirements and the efficiency of their administration are believed to be sufficiently great to exert an influence on the location of clinical research. The earlier a firm knows whether a drug will be a success or will be withdrawn, the lower the costs it will incur. Consequently, the role of regulation affecting the time it takes pharmaceutical firms to obtain clearance for clinical trials is crucial.

The Canadian Regulatory Process

Canadian standards to ensure the safety and efficacy of new drugs and for reviewing the safety of existing drugs are generally considered to be extremely strict. The entire program of research in clinical trials is presented in a Preclinical New Drug Submission. It is reviewed by the regulatory authorities and, if acceptable, receives an approval. Thereafter each protocol reporting on research in Phase 2 and Phase 3 is reviewed and approved before the next step in trials is undertaken. This is followed by the New Drug Submission and decision on approval for marketing.

The resources available to the Health Protection Branch for this regulatory process have not increased substantially over the years, whereas the number of Preclinical New Drug Submissions, New Drug Submissions, Supplementary New Drug Submissions, and protocols has increased. The consequence has been lengthening delays by government in responding to submissions in all categories (except protocols) and an accumulated backlog of submissions, delay in the availability of new drugs for the ill, and detriment to the attractiveness of doing clinical research in Canada.

The second greatest area of concern expressed to the Commission, after the current provisions of the Patent Act, pertains to the delays and the characteristics of the Canadian process for approving drugs for investigation and marketing.

Table 9.2
Mean Clearance Duration for Approval
for Preclinical Studies (PNDS), 1981-July 1984

Year	Patent-holding Firms		Generic Firms		Hospitals & Institutes	
	N	Duration*	N	Duration*	N	Duration*
1981	29	4.9 (2.3)	10	4.7 (3.8)	5	1.4
1982	27	5.7 (3.7)	5	2.2 (.8)	4	1.8
1983	34	4.7 (2.7)	10	5.5 (2.8)	6	1.7
1984 (7 months)	20	5.1 (2.8)	5	6.2 (2.8)	8	2.2
Mean 1981-84:		5.1		4.8		1.8

*PNDS mean clearance delay (\pm standard deviation) in months, excluding submissions cleared in more than 12 months.

Table 9.2 shows the number of PND Submissions that have received approvals during the past four years classified by type of firm originating the PNDS. (Submissions cleared in more than 12 months are omitted from the data, because they are assumed to have been inadequately prepared by the submitting firm.) The table reveals that patent-holding firms make substantially more submissions than generic firms and research institutions and that the delay between the submission of the PNDS and the receipt of approval to proceed with clinical trials is much the same for the two types of firms, but lower for the research institutes. The submissions of research institutes are usually simpler than those of the firms.

It should be emphasized that not all the period between Preclinical New Drug and New Drug Submissions and the relevant approval is attributable to time taken by the Health Protection Branch. In the process of review, requests for further information are normally directed to the firms, which in turn take time to respond. About a quarter of the total days required for New Drug Submissions is accounted for by the firms themselves. For PNDSs and protocols it is somewhat less than half the number of days.

The mean delay between the dates of PNDS and of approval is about five months. Similar delays apply to the approval of protocols, several of which may be needed in each phase of research. This means that if a firm wished to have a complete program of research for a new chemical entity encompassing many clinical trials in each of Phases 1, 2, and 3, the process would involve two to three years of regulatory delay. In reality, delays for clinical research for individual new drugs in Canada are not that long, because firms do most of their research elsewhere and submit data obtained in other countries for the New Drug Submission.

The result of the lengthy approval process in Canada and of the policy of accepting foreign data is reflected in the fact that no clinical trials were carried

out in Canada in support of 11 out of the 66 New Drug Submissions that received approval in the period from January 1981 to July 1984. It can be seen from Table 9.3 that 18 of the 30 major drugs in that sample of drugs cleared in the period 1956 to July 1984 were unsupported by clinical data produced in Canada. Most of these 18 cases were drugs introduced in Canada before 1970.

The Canadian authorities do not require that domestic data from clinical research be submitted with applications for permission to market new chemical entities. They accept data from foreign trials when it is judged of adequate quality. This policy avoids the waste of resources that would be involved in obliging firms to duplicate in Canada research that had already been carried out elsewhere. It also reduces delay in the introduction of new drugs to Canadian physicians and patients when already existing foreign data can be used, or when new data can be obtained from countries with lesser delays. Safety and speed of introduction are the objectives of these reviews, not the stimulation of clinical research through unnecessary demands.

The Commission believes that the Health Protection Branch should continue its policy of accepting data of adequate quality from foreign clinical trials when these are presented in a New Drug Submission.

The partial nature of the clinical research programs in Canada is evidenced by the smaller numbers of the more basic Phase 1 and Phase 2 trials compared to Phase 3 and Phase 4. The proportions of clinical research in terms of expenditure in Phases 1, 2, 3, and 4 in Canada were found to be 7, 14, 57, and 22 per cent respectively over the five years from 1979 to 1983 in the Commission's survey of the largest firms in the industry.

Table 9.4 provides data on the months required for the issuance of Notices of Compliance for New Drug Submissions during the past four years. The average length of time for a new chemical entity submitted by a patent-holding firm is just over two years, whereas for a compulsorily licensed generic firm seeking clearance for a copy of an already existing drug the mean period was nine months. Information on generic drugs is already available and familiar to the regulatory authorities.

Table 9.5 shows the minimum period that would have been required in the period 1981 to 1984 between presenting a Preclinical New Drug Submission and the eventual issuance of an NDS Notice of Compliance permitting the marketing of the new drug. The average period required for obtaining approval for a Preclinical New Drug Submission related to a new chemical entity of a patent-holding firm was 4.7 months; for the New Drug Submission it was 24.6 months. The period during which the clinical research proceeded between the PNDS approval and the New Drug Submission averaged 33.1 months. The sum of these three average periods is 62.4 months. This is a minimum, because the calculation omits the delays that would occur if a firm requested permission for doing Phase 1, 2, and 3 trials in sequence. It is also a minimum because exceptionally long PNDSs have been left out of the calculation. The corresponding total lag for generic firms is 28.1 months.

Table 9.3

**Comparative Data for Innovator and First Generic Firm:
29 Major Drugs, 1956-84**

Generic Name	Brand Name*	Submission PNDS (1)	Clearance PNDS (2)	PNDS: Lag in Clearance (months) (2)-(1) (3)	Submission NDS (4)	Clearance NDS/NOC (5)
PERPHENAZINE	TRILAFON (Schering) PHENAZINE (ICN)	—	— Old Drug	—	05-12-56 Unknown	23-01-57 18-11-74*
TRIFLUORO- PERAZINE	STELAZINE (SKF) NOVORIDA- ZINE (Novopharm)	—	— Old Drug	—	04-01-58 No NDS	20-06-58
SPIRONOLAC- TONE	ALDACTONE (Searle) NOVOSPIRO- TAN (Novopharm)	— 08-05-80	— 26-01-82	— 20	19-11-59 09-09-82	08-12-59 09-02-84
AMITRIPTYLINE	ELAVIL (MSD) LEVATE (ICN)	—	— Old Drug	— —	20-12-60 No NDS	28-02-61
DIAZEPAM	VALIUM (Roche) VIVOL (Horner)	— 25-02-69	— 29-04-69	— 2	05-01-62 14-01-70	08-02-62 12-05-70
CLOXACILLINE	ORBENIN (Ayerst) NOVOCLOXIN (Novopharm)	— 06-11-75	— 26-01-76	— 2	25-06-63 17-03-76	27-09-63 04-01-79
FLUOCINOLONE	SYNALAR (Syntex) FLUODERM (K-Line)	—	— Old Drug	—	26-03-62 No NDS	05-10-63
BETAMETHASONE	CELESTODERM (Schering) BETADERM (K-Line)	—	— Old Drug	— —	13-04-64 No NDS	16-02-65
OXAZEPAM	SERAX (Wyeth) OXPAM	— 07-06-78	— 19-09-78	— 3	12-03-64 31-01-79	21-06-65 21-06-79
INDOMETHACIN	INDOCID (MSD) NOVOMETHA- CINE (Novopharm)	— 17-07-75	— 22-01-77	— 18	03-07-64 22-10-79	22-09-65 08-10-80
HALOPERIDOL	HALDOL (McNeil) NOVOPERIDOL (Novopharm)	No PNDS 07-02-79	— 24-07-80	— 17	05-01-65 28-07-81	21-02-66 13-04-84

NDS: Lag in Clearance (months) (5)-(4) (6)	Date of Marketing (7)	Market Exclusivity ^b (months) (8)	Market Exclusivity ^c after 1969 (months) (9)	Date of Licence Application (10)	Date Licence Granted (11)	Patent Exclusivity ^d (months) (11)-(7) (12)	Period of Research (months) (4)-(2) (13)
1	1957	180	30			180	—
5	01-73			01-74	11-74		—
5	1958	168	24			144	—
	1972			08-69	04-70		—
1	12-59	291	166			204	—
16	03-84			06-75	12-76		8
8	1961	124	13			120	—
9	06-71			08-70	06-71		—
1	1962	96	0			96	—
4	1970			07-69	04-70		9
3	1963	144	60			144	—
34	02-75			11-74	12-75		2
7	1963	192	108			168	—
	1979			04-76	04-77		—
10	1965	168	108			168	—
	1979			03-78	06-79		—
15	06-65	168	109			168	—
5	06-79			06-78	31-06-79		4
14	09-65	181	125			109	—
12	10-80			11-73	10-74		33
13	03-66	217	167			128	—
33	04-84			04-75	11-76		12

Table 9.3 (continued)

**Comparative Data for Innovator and First Generic Firm:
29 Major Drugs, 1956-84**

Generic Name	Brand Name ^a	Submission PND5 (1)	Clearance PND5 (2)	PND5: Lag in Clearance (months) (2)-(1) (3)	Submission NDS (4)	Clearance NDS/NOC (5)
TRIAMTERENE + HYDROCHLORO- THIAZIDE	DYAZIDE (SKF)	—	—	—	26-06-64	16-03-66
	NOVOTRIAM- ZIDE (Novopharm)	19-11-79	04-02-80	3	04-09-80	16-09-81
ALLOPURINOL	ZYLOPRIM (B.W.)	—	—	—	06-10-64	25-03-66
	PURINOL (Horner)	18-11-76	17-03-77	5	08-08-77	16-03-78
FUROSEMIDE	LASIX (Hoechst)	—	—	—	13-12-65	15-06-66
	NOVOSEMIDE (Novopharm)	26-05-75	08-08-75	3	18-12-75	23-07-76
CLOFIBRATE	ATROMID-S (Ayerst)	—	—	—	28-12-64	07-11-67
	NOVOFIBRATE (Novopharm)	18-12-75	01-11-76	11	12-04-77	22-06-78
PROPRANOLOL	INDERAL (Ayerst)	15-06-64	29-10-64	5	19-08-66	08-07-68
	APO-PRO- PRANOLOL (Apotex)	11-10-77	16-02-79	16	12-11-79	01-04-80
FLURAZEPAM	DALMANE (Roche)	—	—	—	23-10-68	16-12-70
	NOVOFLURAM (Novopharm)	01-12-77	21-06-78	7	27-02-79	28-04-80
CEPHALEXINE	KEFLEX (Lilly)	25-03-69	23-11-69	8	20-01-70	07-01-71
	NOVOLEXIN (Novopharm)	14-02-77	11-01-78	11	26-05-78	15-08-78
RIFAMPIN	RIFADIN (Dow)	02-08-68	11-09-69	13	16-02-71	10-02-72
	ROFACT (ICN)	16-12-75	20-02-76	2	03-10-75	17-05-77
SALBUTAMOL	VENTOLIN (Glaxo)	19-02-69	05-07-70	15	19-01-72	20-10-72
	NOVOSALMOL (Novopharm)	09-07-81	08-11-82	16	20-09-83	14-09-84
IBUPROFEN	MOTRIN (Upjohn)	27-12-67	30-10-70	34	05-06-70	08-12-72
	APO-ABU- PROFEN (Apotex)	10-09-81	08-01-82	4	20-04-82	08-09-83

NDS: Lag in Clearance (months) (5)-(4) (6)	Date of Marketing (7)	Market Exclusivity ^b (months) (8)	Market Exclusivity after 1969 (months) (9)	Date of Licence Application (10)	Date Licence Granted (11)	Patent Exclusivity ^d (months) (11)-(7) (12)	Period of Research (months) (4)-(2) (13)
21	1966	180	132			156	—
12	1981			04-78	01-79		7
17	1966	144	96			132	—
7	1978			12-76	08-77		5
6	06-66	122	75			83	—
7	08-76			05-72	05-73		4
35	01-68	125	97			81	—
14	06-78			01-74	10-74		5
23	07-68	141	119			131	22
5	04-80			06-78	06-79		9
26	03-71	110	110			69	—
14	05-80			09-75	12-75		8
12	11-71	96	90			60	2
3	1979			03-75	11-76		4
12	02-72	63	63			41	17
19	05-77			01-75	07-75		4
9	10-72	141	141			81	18
12	10-84			07-79	07-79		10
30	12-72	129	129			125	0
16	09-83			03-82	05-83		3

Table 9.3 (continued)

**Comparative Data for Innovator and First Generic Firm:
29 Major Drugs, 1956-84**

Generic Name	Brand Name ^a	Submission PNDS (1)	Clearance PNDS (2)	PNDS: Lag in Clearance (months) (2)-(1) (3)	Submission NDS (4)	Clearance NDS/NOC (5)
CLORAZEPATE	TRANXENE (Abbott)	—	—	—	02-08-72	24-04-73
	NOVOCLOPATE (Novopharm)	18-11-82	07-03-83	4	21-12-83	11-84
TRIMETOPRIM	BACTRIM (Roche)	03-03-70	10-07-70	4	27-10-72	16-08-73
	APO-SULFATIM (Apotex)	31-08-78	21-02-79	6	13-06-79	30-10-79
AMOXICILLIN	AMOXIL (Ayerst)	29-09-71	29-09-72	12	17-07-73	07-02-74
	AMOXICAM (ICN)	20-09-76	22-11-76	2	25-01-77	30-01-78
NAPROXEN	NAPROSYN (Syntex)	09-04-70	07-05-70	1	21-11-73	14-06-74
	NOVONAPROX (Novopharm)	28-04-81	11-08-81	4	14-12-81	04-08-82
LORAZEPAM	ATIVAN (Wyeth)	03-03-71	17-12-71	9	14-05-75	14-02-77
	NOVO-LORA (Novopharm)	19-01-83	26-07-83	6	21-03-84	in review
CIMETIDINE	TAGAMET (SKF)	30-05-75	23-09-75	4	07-09-76	31-05-77
	PEPTOL (Horner)	01-10-79	24-01-80	3	14-05-81	03-09-81
METOPROLOL TARTRATE	LOPRESOR (Geigy)	11-06-73	15-05-74	11	19-08-76	27-06-77
	APO-METO- PROLOL (Apotex)	27-05-82	04-03-83	9	11-08-83	26-06-84
KETOPROFEN	ORUDIS (Rhône-Poulenc)	05-09-72	02-10-73	13	22-01-75	29-11-77
	APOKE- TROFEN (Apotex)	19-10-83	in review	—	—	—

^a The first name is the brand name of the original patent holder; the second is that of the first generic competitor.

^b Date of marketing of innovator less date of marketing of generic firm.

^c Number of months of exclusivity after April 1970, the first date on which a compulsory licence was issued after change in Patent Act.

^d Date of marketing of innovator less date of licence of generic firm.

Note: Dates show day, month, and year in that order.

NDS: Lag in Clearance (months) (5)-(4) (6)	Date of Marketing (7)	Market Exclusivity ^b (months) (8)	Market Exclusivity ^c after 1969 (months) (9)	Date of Licence Application (10)	Date Licence Granted (11)	Patent Exclusivity ^d (months) (11)-(7) (12)	Period of Research (months) (4)-(2) (13)
8	05-73	139	139			115	—
11	12-84			02-81	12-82		9
10	08-73	75	75			63	27
4	11-79			08-77	11-78		4
7	01-74	48	48			48	10
12	02-78			08-76	04-77		2
7	06-74	98	98			60	42
9	08-82			04-78	06-79		4
21	03-77					75	41
—	—			10-82	06-83		
8	06-77	51	51			37	12
4	09-81			07-79	07-80		4
10	06-77	87	87			87	27
22	09-84			10-83	01-85		5
34	12-77					62	15
—	—			02-81	02-83		—

Table 9.4

**Mean Clearance for Notice of Compliance (NOC)
for New Drug Submissions (NDS), 1981-July 1984**

Year	Patent-holding Firms		Generic Firms	
	N	Duration*	N	Duration*
1981	21	28.6 (25.7)	9	8.3 (3.6)
1982	17	31.9 (34.6)	9	6.7 (3.4)
1983	16	15.9 (12.1)	12	6.8 (5.1)
1984 (7 months)	12	19.2 (13)	9	12.6 (8.9)
Mean 1981-84:		24.6 (24.6)		8.9 (6.0)

* Mean clearance delay (\pm standard deviation) in months.

A Comparison of Canadian and Foreign Clearance Processes

An impression of the stringency of the Canadian regulatory process can be obtained by comparing it with that of other countries. The comparison can be made in terms of the requirements that are imposed on firms seeking clearance in different countries and by comparing the actual duration of the processes. This latter measure is affected by the requirements, but also by the efficiency of administration and the resources devoted to it and by differences in the extent to which clinical research is carried out in each country by the firms applying for clearance.

Canadian requirements differ from those of other countries with respect to the duration of toxicological studies in animals that are required in preparation for a Preclinical New Drug Submission. Canada requires studies of 18 months; the United States requires 12 months; the United Kingdom, France, and West Germany require six months.

A Preclinical New Drug Submission in Canada must contain full reports on the chemical, pharmacological, and toxicological aspects of the preclinical research, and must provide complete clinical protocols. The Health Protection Branch must approve the submission, a process that takes about five months. In the United States the documentation provided in an Investigational New Drug Submission (IND) is the same as in Canada, but the Federal Drug Administration has only 30 days in which to review the safety aspects of the proposed clinical research. It may veto the proposed clinical research. This occurs in one or two per cent of the cases. The research proceeds automatically if no refusal is given. As the research proceeds in the two to four months following the IND, the Federal Drug Administration reviews the research program and advises the manufacturer of possible shortcomings in anticipation

Table 9.5
Duration of Clearance and Clinical Research Leading to
Notices of Compliance (NOC) for New Drug Submissions (NDS),
Issued from 1981 to July 1984

Year	Patent-holding Firms				Generic Firms			
	Duration*				Duration*			
	PNDS**	NDS	Clinical R & D	Total	PNDS**	NDS	Clinical R & D	Total
1981	5.3	28.6	25.7	56.6	6.2	8.3	11.6	26.1
1982	4.7	31.9	29.8	66.4	5.4	6.7	7.5	19.9
1983	4.1	15.9	44.6	64.6	5.0	6.8	10.1	21.9
1984 (7 months)	3.7	19.2	34.6	57.5	9.0	12.6	9.5	31.1
Mean 1981-84:	4.7	24.6	33.1	62.4	6.0	8.9	13.2	28.1

* Mean values in months.

** PNDS submissions cleared in 12 months or less.

of data that would be needed to meet NDS requirements. In the United Kingdom the content of the Preclinical New Drug Submission contains only a summary of preclinical studies and of the chemical and pharmacological aspects of the research and only an outline of clinical protocols. The Department of Health and Social Services has 35 days in which to veto proposed studies, otherwise the studies proceed. In France the firm's data must be reviewed by an expert selected by the company from an officially approved list. The regulatory authorities must be notified of the planned research and must acknowledge it within 30 days. In West Germany the authorities need only be notified that the clinical study is being undertaken.

Clinical research protocols also require five months to receive approval in Canada. In the United States, France, and West Germany a firm only notifies the authorities that the trials are taking place. In the United Kingdom protocols must be approved within one month.

The average time required for a Notice of Compliance for a New Drug Submission is 24.6 months in Canada. It is six months in the United Kingdom and France. In the United States it is 12.3 months for drugs making major or modest therapeutic advances and 19.5 months for drugs with minor advances. The United States has an accelerated process for new drug entities that are considered to be major therapeutic advances. Moreover, on 11 December 1984 new regulations were approved in the United States for the Federal Drug Administration permitting approval based solely on foreign clinical data (as in Canada) and permitting simultaneous review of applications by different offices in the FDA.

It is difficult to gauge the importance of differences in the regulatory process in causing the differences between countries in the amount of clinical research that takes place. However, it is obvious that the greater amount of time required for approval of research must make it difficult for firms to include Canadian projects in their multinational research activities. The delays are especially disadvantageous to Canadian research when projects are carried on simultaneously in several centres in order to obtain large samples and a variety of populations. Patent-holding firms in Canada report that several clinical studies have been cancelled owing to regulatory delay. The estimate of several firms that a change in regulations, bringing them more into line with those of other countries, would raise clinical research by at least 50 per cent is credible.

The potential for increased clinical research in Canada is suggested from British experience. Until March 1981 the British authorities required Preclinical New Drug Submissions similar to those presently required in Canada and the United States, namely, containing all available data. Since that date the submissions consist of a summary of no more than 50 pages and no raw data are presented. The authorities respond within 35 days, but may require a longer period or a full submission in cases of doubt. For most drugs the summary is used. Between 1980 and 1983 the number of Preclinical New Drug Submissions for new chemical entities in the United Kingdom rose from

40 to 120, compared with an increase in the United States from 136 to 144 over the same period. In Canada the numbers were 40 and 34. The change in the United Kingdom induced firms to carry out more clinical research there rather than following their previous practice of shifting part of their clinical investigations to the Continent where the requirements for clearance had been less restrictive.

The average duration of clinical research on a new chemical entity in Canada from 1981 to 1984 was 33 months as shown in Table 9.5. The corresponding figure for the United States was 69 months. The difference reflects the greater level of research activity in the United States where a full program of research for a new drug is frequently carried out. The relatively low level of clinical research per new drug in Canada is doubtless explained by many factors, but the much longer approval process in Canada and the much longer additional delay that would occur due to the necessity to approve protocols if there were full research programs, must inevitably play a substantial role in causing the difference. Otherwise Canada has distinct advantages—from the generally high quality of clinical research in Canada, its location with respect to United States' centres, and the low cost of clinical research compared to that in the United States.

The Acceleration of the Clearance Process in Canada

It is evident that Canadian requirements for the marketing of drugs cause longer delays than prevail in other countries, thereby postponing the benefits that the public receives from therapeutic advances and reducing the profitability of new drugs for innovative firms. The length of the procedure also reduces the attractiveness of Canada as a location for clinical research. The question is whether these drawbacks are justified or not in view of the risk of adverse drug reactions from the earlier introduction of new drugs. In this connection it is interesting to report that the Canadian Medical Association's brief to the Commission stated that "Evidence is accumulating that in countries with lengthy approval mechanisms the standard of drug safety is not noticeably higher than in those countries such as the United Kingdom where approval procedures are much shorter."

Whereas the general availability of drugs on prescription in Canada requires strict standards centrally imposed for the protection of the public, clinical trials are performed by highly qualified medical investigators whose programs of research are approved and monitored by research committees and by ethics committees of universities, hospitals, and institutes which evaluate hazards and ensure the awareness and consent of subjects. The scientific community in Canada is small; researchers have high standards and are known to each other so that the risks to volunteers and patients from clinical research would not be increased by a more rapid clearance process for Preclinical New Drug Submissions. The risks are greatest after a new drug has been released for marketing and a large number of patients are exposed to its effects in a less controlled environment than during clinical trials.

For these reasons *the Commission recommends that Preclinical New Drug Submissions should consist of a summary of information on the new drug, certified in Canada by a qualified health professional, and of a protocol of the proposed clinical studies, and that approvals for Preclinical New Drug Submissions should be automatic within one month of receipt unless the Health Protection Branch finds reason not to grant them or requires further information from the firms concerned. The approval for the PNDS would also apply to the protocols for Phases 1, 2, and 3 which would not require further approval after filing for notification unless by explicit decision of the Health Protection Branch.* Such a system functions effectively in the U.K. today.

It is important as well that the final review of information on a new drug in the NDS/NOC process should be more expeditious than it is at present. Whether or not it receives additional resources, the Health Protection Branch will need to review and reform its requirements, range of activities, and procedures to achieve this. It is evident that if resources are to be freed to review NDSs, some activities of the Branch will have to be abandoned or curtailed and that any inefficiencies that may exist in present procedures owing to lack of coordination, common standards, and communication with industry will have to be ironed out. Though it cannot judge the merits of any single measure needed to speed up the NDS process, the Commission is satisfied that changes could reach the objective without increasing risk to patients.

Possible measures to relieve pressure on resources include giving firms the responsibility for distributing emergency drugs to physicians under carefully monitored conditions once the Health Protection Branch has decided that particular drugs qualify for such limited distribution. Firms might be allowed to add contra-indications, adverse reactions, and precautions to Product Monographs simply by notification, thus avoiding the burden of a Supplementary New Drug Submission (NDS/S) review. Such a change would also increase safety. Firms might be allowed to change the manufacturing procedures or the manufacturer of the final dosage form, upgrade specifications, or extend expiration dates by means of notification and not of an NDS/S as today. Fifty professionals and technicians would be freed if the Health Protection Branch ceased duplicating the quality control activities of manufacturers of biological products (an activity it follows for no other pharmaceutical product) and relied on establishing standards and inspection. Any testing that the regulatory system may require should be the responsibility of the firms seeking authorization of their products.

Changes can also doubtless be made to reduce the absorption of resources in the duplication of activities and review of inessential material. One example of duplication is that the submission of a compulsory licensee must contain a literature review that duplicates one already in the possession of the Branch in the original patentee's NDS/NOC. Another is that each generic manufacturer of the same drug must produce his own Product Monograph. The Health Protection Branch might also be able to use resources more effectively if given the power to request synopses of material submitted by firms and to refuse to review inadequately prepared submissions.

The Health Protection Branch should consider withdrawing from the review of ethics in drug research related to PNDSs, because ethical review committees now exist in research institutions and have responsibility for ethics in research. It also should consider limiting its role in the review of PNDS research to indicating the data it foresees as necessary for the eventual NDS, as is done in the United States, and leaving the responsibility for the design of research entirely to the clinical investigators.

The objective of such changes in the procedures, structure, or activities of the Health Protection Branch would be to enable the Branch to respond to an NDS or an NDS/S within a reasonable period of time.

The Commission recommends that the Health Protection Branch reorder its activities so as to be able to respond to New Drug Submissions and to Supplementary New Drug Submissions without fail within 120 days.

In view of the risk of adverse drug reactions following an NDS/NOC and the release of new drugs for general distribution to a large number of patients, the Commission recommends that regulations should permit the Health Protection Branch to impose post-market studies on the manufacturer as a condition of permission for marketing. Such authority does not now exist. It would provide the Branch with greater control over new drugs and perhaps aid in hastening the clearance process itself.

The Commission also recommends that Notices of Compliance be issued for New Drug Submissions and Supplementary New Drug Submissions for pharmaceutical products and medical devices that have not received them in Canada but which have already received Notices of Compliance in the United States and either France or the United Kingdom without review in Canada until the backlog of submissions has been absorbed and procedures reformed to provide clearance delays no longer than 120 days.

The Commission is aware that the apparent productivity of different divisions in the Health Protection Branch with respect to the clearance time required for both Preclinical and New Drug Submissions varies widely by a factor of more than two to one for PNDSs and by up to four to one for NDSs. It may be that these data are to some extent misleading if administrative practices vary between divisions, for instance if some divisions require one submission for each of a series of identical trials in different hospitals and others require one for all of them together. It is also the case that reviews and decisions in some therapeutic fields inherently require more time than in others. Confidence in the efficiency of the administration would be increased by the standardization of administrative practices respecting the recording of submissions, if that does not already exist, and the strengthening of the divisions with the greatest workload by shifting personnel.

The Commission believes that the period required for the clearance of new drugs in Canada should be reduced. Such a reduction would permit the earlier introduction of beneficial new drugs. It would raise the profitability of the

industry, because new drugs are introduced at higher prices than those they supplant. It would probably increase the amount of clinical research in Canada, though admittedly the extent of this response cannot be estimated. Nevertheless, if more research were to become available, new career opportunities for pharmacists, biologists, physicians, statisticians, chemists, and others would be created as well as permitting members of Canadian universities to contribute their basic research more directly to the attainment of applied objectives thus increasing the contact between universities and industry.

The Use of Committees of Non-governmental Experts

The United Kingdom and France give the responsibility for the final decision as to the acceptability of a drug for marketing to committees of experts composed of pharmacologists, chemists, physicians, and others with special pharmaceutical knowledge. In the United States use is made of advisory committees of experts in the process of review. In contrast, Canada makes very little use of experts from outside the federal government in its evaluation and clearing of drugs.

The rationale for committees of non-governmental experts is that they can draw on the knowledge of all the most highly trained individuals in the country, that they give a voice to persons who can gauge the value of introducing new drugs directly from their own experience as physicians who prescribe drugs to their patients, and that they distance the final decision from the most immediate political pressures. However talented the staff of a government agency, an expert committee drawn from universities, hospitals, research institutions, and industry has a better chance to make a properly balanced judgement on a particular drug. For example, medical practitioners know from daily experience the usefulness of improved products and may be more sensitive to the advantages of early introduction than public servants. Public servants, on the other hand, are necessarily highly sensitive to adverse drug reactions, since when these occur they attract a good deal of public attention. Public opinion, by contrast, is little aware of the incremental improvements that may be made to health by the introduction of new drugs. This imbalance may induce undue caution in public servants who are criticized if drugs are released that have adverse effects but receive little recognition from the early introduction of effective new drugs.

Both the British and the French authorities make use of non-governmental advisors at other levels in addition to the final decision. In the United States the final decisions are taken by officials, but in the process extensive use is made of advisory committees of outside experts.

The Commission recommends that an expert committee supported by the staff of the Health Protection Branch should be established by statute to make final judgements on the issuance of Notices of Compliance for New Drug

Submissions. The Commission also recommends that the various steps in the process of review should make use of statutory advisory committees of outside experts.

In Canada outside experts are only used exceptionally to advise on a particularly knotty problem, such as may arise if there is disagreement amongst officials of the agency. But there are scientific questions of significance for costs and research activity, such as the appropriate length of time for tests of toxicology, on which expertise from outside government should be brought to bear in addition to that in the Health Protection Branch.

It is important that the fundamental review that is required and already partly undertaken within the Health Protection Branch to establish appropriate guidelines and procedures should be based on broad understanding and scientific consensus. To this end ***the Commission recommends that the Minister of Health and Welfare establish an advisory committee of experts from the Health Protection Branch, universities, hospitals, and industry (thus reflecting the many interests affected) to recommend appropriate regulations and guidelines for the evaluation and clearing of drugs for marketing.***

Notices of Compliance for Compulsorily Licensed Drugs

To produce and market a patented drug, generic firms must obtain a compulsory licence, approval for clinical investigation, and a Notice of Compliance for a New Drug Submission.

The generic drug contains the same active ingredient or ingredients as the patented drug. Having exhaustively studied the drug in the process of the clearance of the original product, the regulatory authorities need only be assured that the generic version of the new drug is sufficiently similar to the original drug in the way it is absorbed and treated by the body to be therapeutically equivalent. The products of the two firms are not necessarily identical, because the generic firm and the patentee may obtain the active ingredient from different manufacturers and because the excipients may not be the same. Provided that the generic manufacturer can demonstrate that its active ingredient is chemically identical to that of the patent holder, the regulatory authority only requires tests that determine the bio-equivalence of the new drug to the old. The degree of bio-equivalence does not need to be exact. Medical judgement is needed to decide on the permissible variation, which is fairly large for some drugs but quite limited for others. That judgement is exercised by the Health Protection Branch.

The two drugs may be adequately bio-equivalent without being identical, chiefly because the two drugs may have different inactive ingredients including colours, coatings, excipients, and fillers. Individuals may react adversely to ingredients other than the active ingredient in drugs. Such reactions are as likely to occur with ingredients in the branded product as in the generic

product. However, consumers should be protected against the unwitting absorption of a product to which they are known to react and all drug products should be sold to the final consumer with a complete list of the ingredients they contain.

A New Drug Submission requires the manufacturer to submit to the Health Protection Branch a complete report on the drug, including its chemical composition and the results of animal tests and of clinical trials. The generic firm does not engage in animal testing or in clinical trials beyond that of testing for bio-availability (i.e., the rate at which the medication is absorbed) and must in consequence rely on other sources in order to comply with that requirement. The patent for the product provides information on the composition of the product and usually indications as to how it can be produced. The innovating firm's Product Monograph, which accompanies the original Notice of Compliance, provides information on clinical and preclinical tests additional to the information that is published by researchers, which is usually only on the clinical tests.

If the generic firm could not obtain information necessary for the New Drug Submission from the Product Monograph of the patent-holding firm, from publications, or from clearance procedures in other jurisdictions, notably the United States, as it does now, it would be precluded from entering the market or obliged to carry out animal and clinical tests itself. Such tests are very expensive and would be a waste of resources, because they would duplicate information already existing and in the possession of both the regulatory authorities and the patent-holding firm. Inability to obtain this information would be a totally artificial barrier to authorization for the generic firm to sell a known product. If it is an objective of policy to impede the ability of generic firms to enter the market for a patented product, this should be done by direct regulation, not by imposing costs the incurring of which is wasteful.

The Commission recommends that no impediment be placed to the access to and use of Product Monographs, which should be treated as public documents.

A further reason for treating Product Monographs as public documents is that equivalent products should have the same monograph for the sake of clarity and safety.

Safety: Original Package Dispensing and Information Inserts

Patients often have insufficient knowledge of drugs and their effects. This is because of the high value of physicians' time which limits their communication with patients to oral explanation and advice. Oral communication can be ineffective when the subject matter is complex and novel. Patients may not absorb information sufficiently rapidly to understand it and may subsequently forget it. Patients are usually not provided with written information on the

medicines they are prescribed. This lack of written information to patients is largely owing to the anachronistic practice in Canada (in common with the United States, the United Kingdom, and a few other countries) by which manufacturers supply prescription medicines to pharmacists largely in bulk. Pharmacists then repackage and label the drugs for distribution at retail. This practice has its roots in the dispensing methods of the nineteenth century when pharmacists mixed their own medicines. Today pharmacists do not mix medicines, which is done at the plant, but are responsible for repackaging drugs and instructing patients. The written information provided to the patient in this process is usually fragmentary. In many cases it does not even include the generic name of the drug. It virtually never includes information on side effects, adverse reaction, combinations of drugs to avoid, and other vital matters that are in principle transmitted by physicians, but may be omitted or misunderstood.

Consumers in much of the rest of the world benefit from the dispensing of drugs in the manufacturers' original packages which contain printed inserts presenting instructions and information much fuller than are transmitted by other means. Obviously, many patients may not use that information, but it is available to those who wish it or need it. In its submission, The Allergy Information Association pointed out to the Commission the importance of providing the consumer with a full list of the excipients contained in a pharmaceutical product so as to avoid allergic reactions that can be predicted on the basis of that information. It is anomalous that packaging regulations for food in Canada require a listing of all the ingredients so as to protect the consumer against possible allergic reactions whereas pharmaceutical products are subject to no such requirement.

The present Canadian practice of supplying medicines in bulk is obsolete also from the standpoint of quality control. Modern manufacturing processes ensure extremely high levels of purity of compounds and proper sanitary or sterile manufacturing conditions. This quality can only be maintained if the product is packed appropriately so as to avoid excessive exposure to humidity or light and to other drugs, notably antibiotics, which may cause contamination. Dispensing in the original package avoids the danger of degradation on the way to the patient.

The other advantage is that the consumer of a product in an original package receives an insert which provides information about dosage, indications, warnings, expiry date, and other information to which, if he is of clear mind, he is entitled. A person has a right to know the potential effect of the medicines he takes. Furthermore, such information may become important when a patient changes physicians or contacts his physician at off hours and may be useful if he is a patient of a group practice. The product in an original package is easily identified and can be easily recalled if that becomes necessary. It also reduces possible errors in dispensing and illegitimate substitution.

A disadvantage of dispensing in original packages is that it increases the cost of the manufacture. This is clearly the case, but it would be more than counter-balanced by saving the valuable time of professional pharmacists. High-speed machinery is more efficient than the handicraft system at whichever level of distribution the packaging occurs.

The feasibility and advantages of original package dispensing are demonstrated by the universal distribution of non-prescription, over-the-counter drugs by pharmacies in this form. Over-the-counter drugs account for about one half of pharmaceutical sales.

The Canadian Medical Association, addressing the Commission at its Hearings, expressed views in general favourable to original package dispensing but cautioned of cases in which counter-indications indicated on package inserts might confuse or frighten vulnerable patients and reduce compliance. Clearly this situation ought to be provided for, and can be, by ensuring that a doctor could instruct a pharmacist to remove leaflets from packages destined for specific patients.

The Canadian Pharmaceutical Association informed the Commission that it encouraged its members to include informative inserts when they dispensed certain drugs. These inserts have been developed in cooperation with the Health Protection Branch and the Canadian Medical Association to be easily understood by laymen and appropriately informative. The number of leaflets included in prescriptions made up by pharmacists was increasing, but prescriptions including leaflets were still a regrettably low proportion of the total. This initiative reflects the Association's view that more information should be provided to customers. The leaflet program's partial success suggests that other measures are necessary.

Support for original package dispensing is growing in the few countries in which it does not now prevail. An example is the acceptance by the Council of the Pharmaceutical Society of Great Britain at the end of 1984 of a committee recommendation in favour of it and the support for the same objective by the Association of British Pharmaceutical Industries.

The Commission recommends that measures be taken to ensure that pharmaceutical products sold to consumers at retail in Canada should be dispensed in the manufacturer's original packages, and further, that complete product information be presented in a way that can be understood by laymen. Indications, administration, dosage, warnings with respect to adverse reactions, a full list of contents, and other relevant information should be included. Provision should be made that physicians could instruct pharmacists to withhold such information from designated patients.

Chapter 10

The Retail Pharmacy Market

Approximately 20 per cent by value of pharmaceutical products are sold to hospitals. The rest are distributed through pharmacies.

The conditions under which drugs are purchased in the retail market are strongly influenced and sometimes determined by provincial programs and policies respecting the prices of drugs, the interchangeability of one drug for another, and the responsibility of pharmacists for selecting low-cost drugs. The nature and application of these rules often depend on whether the drug purchases are paid for by the general public, most of which carries private drug insurance, or by the provincial governments themselves.

Provincial policies vary, but provinces have not sought to increase the amount of competition or to lower drug prices to consumers by measures that would make individual purchasers more sensitive to differences in prices.

Compulsory licensing of pharmaceutical products to import and manufacture under Section 41(4) of the Canadian Patent Act has put generic firms in a position to offer low prices for patented pharmaceutical products. The average price of compulsorily licensed drugs sold by both patent-holding and generic firms in Canada is approximately 54 per cent of the average U.S. price for the same drugs, whereas the prices of drugs without compulsory licences are 80 per cent of U.S. prices.

Sales of compulsorily licensed drugs by generic firms are affected by provincial policies concerning the retail market for pharmaceutical products as well as by the provisions of the Patent Act. In 1983, the share of the market for the 32 compulsorily licensed drugs supplied by both patent-holding and generic firms that was held by licensees was 22 per cent by value and 36 per cent by volume. These drugs accounted for 13.6 per cent of all sales of ethical pharmaceutical products, so that licensees' sales of compulsorily licensed drugs were 3 per cent of all drug sales. Generic firms also produced drugs not on compulsory licence. Their share of the entire market for pharmaceutical products was approximately 8 per cent.

Provincial governments set policies guiding the functioning of the retail markets within their jurisdictions. These apply to the part of the market for pharmaceutical products whose cost the province itself reimburses and to the private sector of that market in which customers may be reimbursed by third-party private insurance companies or pay at their own expense.

Table 10.1

Provincial Product Selection Laws: A Summary, 1983

Province	Date Product Selection Legislation Introduced	Permissive or Mandatory ^a	Rules for Selection ^b	Determination of Cost	Determination of Inter-changeability	Legal Protection for Pharmacist and physician
Alberta	1962	Permissive	None specified ^c	None specified	Pharmacist; no formulary	Not provided
British Columbia	1974	Permissive	Equal or lower priced than brand prescribed ^d	None specified	Pharmacist; no formulary	Not provided
Manitoba	1974	Permissive	Lowest price brand ^e	Formulary ^f	Formulary	No legal liability
New Brunswick	1975	Permissive	Equal to or less than the brand prescribed ^f	Pharmacist's usual and customary price ^g	Formulary	No legal liability
Newfoundland	1979	Permissive	Lowest price brand ^h	Formulary	Formulary	No legal liability
Nova Scotia	1983	Permissive	Equal to or less than the brand prescribed ^h	None specified	Formulary	Not provided
Ontario	1972	Permissive	Lower priced brand to that prescribed ^h	Lowest price brand in pharmacist's inventory ⁱ	Formulary	No legal liability
Prince Edward Island	No product selection legislation ^m					
Quebec	1974	Permissive	None specified ^j	None specified	Formulary ^j	Not provided
Saskatchewan	1971	Permissive	None specified ^k	None specified	Pharmacist (1971-74); liability formulary (1975 onwards)	No legal liability

Notes

^a All provinces do not allow product selection where the prescription is marked "no substitution" or in the case of Alberta "no equivalent" by the physician. In some instances the legislation specifies that the words "no substitution" be in the physician's handwriting. This reflects the provision of prescription pages by some drug firms with the words "no substitution" already printed across the prescription. In other words, the onus is on the physician to prevent selection.

^d Emphasis added in all footnotes to entries in this column.

^e "Where a prescription refers to a drug ... by a brand name [the pharmacist] ... *may* use a drug ... that is the generic or brand name equivalent of that named in the prescription. ..."

^f "... a pharmacist *may* use an interchangeable pharmaceutical product where its price to the purchaser is no more than the price of the prescribed drug."

^g "Every person who dispenses a prescription for a drug ... *shall* ... dispense an interchangeable pharmaceutical product other than the one prescribed ... [if it] is lower in cost than the drug prescribed." This is qualified by, "No person shall knowingly supply an interchangeable pharmaceutical product ... at a price in excess of the cost of the lowest priced interchangeable pharmaceutical product ... in the [formulary]." Hence the pharmacist, whether he product selects or not, cannot charge more than the lowest priced interchangeable pharmaceutical product in the formulary.

^h Until June 29, 1983 the legislation read as follows: "Every person who dispenses a prescription *may* ... dispense an interchangeable pharmaceutical product other than the one prescribed, provided [it] ... is lower in cost than the drug prescribed." This is qualified by, "No person shall knowingly supply an interchangeable pharmaceutical product ... at a price in excess of the lowest price interchangeable pharmaceutical product in his *inventory* ..." Hence, once the pharmacist has decided to product select, no matter which brand is dispensed, the lowest priced brand in the pharmacist's inventory determines the maximum price that can be charged. On June 30, 1983 a new Pharmacy Act came into force. The new product selection wording read as follows: "Every person who dispenses a prescription *may* ... select and dispense an interchangeable pharmaceutical product other than the one prescribed, provided that [it] ... is listed as interchangeable in the New Brunswick Formulary." This provision was supplemented by a regulation under the Act, which read, "A licensed pharmacist ... shall not sell an interchangeable pharmaceutical product ... at a total price which is higher than the pharmacy's usual and customary price for either the product prescribed or the product dispensed." The text of the table refers to the rules in the second half of 1983.

ⁱ "... [the pharmacist] *shall* dispense a substitute drug other than the drug specifically prescribed where ... the drug to be substituted is cheaper than the drug prescribed ... or if he does not have the lowest price drug, dispense another drug listed in the Formulary as a substitute for the prescribed drug, at the price of the lowest priced substitute in the Formulary. ..."

^j "Every person who dispenses a prescription *may* ... select and dispense an interchangeable pharmaceutical product other than the one prescribed ..."

^k Language same as that of New Brunswick prior to June 30, 1983. See footnote f, above.

^l "A pharmacist ... *may* substitute for the prescribed medication a medication whose generic name is the same ..."

^m "... the pharmacist about to dispense a drug pursuant to the prescription *may* select and dispense an interchangeable pharmaceutical product other than the one prescribed."

ⁿ As mentioned in the text, the Quebec formulary only lists drugs of acceptable quality. Apparently because the Quebec government delisted a substantial number of drugs from the formulary in the early 1980s, no references are made to the formulary in the actual Act, but nevertheless the formulary is widely used for the products it lists.

^o Legislation was proclaimed in January, 1984 but it has yet to take effect, because no interchangeable list has or is expected to be published in the near future.

Source: Paul K. Gorecki, "Compulsory Patent Licensing of Drugs in Canada: Have the Full Price Benefits Been Realized?," unpublished study, January 30, 1985.

Provincial governments reimburse approximately 43 per cent of pharmacy drug sales. Programs vary widely amongst provinces. In Saskatchewan, for instance, drug costs are publicly reimbursed to all residents except for an element of co-payment. In Ontario and Quebec, persons over the age of 65 and persons on welfare have their drugs paid for by the province. Though this group constitutes only about 14 per cent of the population in Ontario, its average number of prescriptions per annum per person is 19.2 as against 4.3 for the other groups in the province, which explains why 45 per cent of pharmacy drug sales are publicly reimbursed in Ontario. Private insurance programs cover approximately 45 per cent of the rest of these sales, the remaining 10 per cent being purchases of persons who are not reimbursed. That group constitutes about 15 per cent of the total population.

Lower prices of drugs owing to compulsory licensing have achieved savings for both consumers and taxpayers. The question remains as to whether all the potential savings from existing policies have been realized. Provincial policies are successful in realizing these savings according to the degree to which they lead to the substitution of lower-priced for higher-priced brands of the same drug. Such substitution is the result of official certification of the interchangeability of drugs, and of the rules that encourage or mandate substitution. Another variable determining the realization of potential savings is the extent to which the prices that are reimbursed by government are the prices that are actually paid for the drugs by pharmacists.

Substitution and Selection of Drugs

Table 10.1 summarizes the provincial laws affecting the selection of drugs applicable to all drug purchases, both those publicly reimbursed and others. All provinces except Prince Edward Island have product selection legislation which has the common element that physicians may prohibit the substitution of other brands for the brand they prescribe. In other respects, little uniformity prevails. Most provinces publish a formulary which specifies which drugs are interchangeable, but Alberta and British Columbia do not. (It is known that, at least in British Columbia, the Ontario formulary is often used by pharmacists to establish interchangeability, a judgement for which they are responsible.) In some provinces pharmacists and physicians who substitute one product for another are protected from legal liability for their action. In most provinces the price listed in the formulary is not mandatory for other than publicly reimbursed drugs. In most provinces, if pharmacists dispense a drug other than the one prescribed, they must choose a brand with a price no higher than that of the one prescribed.

The regulations determining substitution for drugs that are provincially reimbursed are more strict in most provinces than those that apply to other purchases. In British Columbia, Manitoba, and Saskatchewan 100 per cent of the population is covered by provincial reimbursement minus co-payment. Only in Saskatchewan is there mandatory product selection whereby a pharmacist

must dispense a particular brand of multiple-source high-volume drugs at a specified price unless the physician specifically prohibits substitution. For other drugs, reimbursement is at the actual cost of acquisition by the pharmacist. In other provinces product selection is permissive. Pharmacists may substitute at their discretion in Alberta, British Columbia, New Brunswick, and Nova Scotia. In Ontario, Newfoundland, and Manitoba they may also do so, but the price they must charge is the lowest in the formulary, or, in Quebec, generally the median price except for six high-volume drugs. These latter rules can be called mandatory price selection or maximum allowable cost. A summary of these policies for public reimbursement is shown in Tables 10.2 and 10.3.

In an attempt to determine the extent to which potential savings from compulsory licensing are realized, the Commission studied the provincial reimbursement programs using a sample of seven major drug products in all provinces but Alberta and Manitoba for which adequate data were not available. These drugs were indomethacin, flurazepam, naproxen, propranolol, methyldopa, cimetidine, and allopurinol.

A test was carried out to determine the effect of listing a product as interchangeable in a formulary on the proportion of the market held by generic firms holding compulsory licences. For this purpose it was necessary to compare provinces with similar rules for selection, but some differences in formulary lists. Table 10.4 compares Newfoundland and Saskatchewan, both of which have strict selection rules. For products listed as interchangeable in Saskatchewan, but not in Newfoundland, the proportion of licensees' sales in Saskatchewan was 59.2 per cent; it was only 9.7 per cent in Newfoundland. For products listed on the formulary as interchangeable in both provinces, the licensees' shares of the market were 57.2 per cent in Saskatchewan and 76 per cent in Newfoundland. Table 10.4 also provides data comparing Nova Scotia and New Brunswick which have permissive selection rules. The proportions of licensees' sales were low in both provinces, but the proportion was higher for the drugs listed as interchangeable in Nova Scotia but not in New Brunswick. For the sample of drugs interchangeable in both provinces, the proportions were similar for the two provinces at 5.8 and 5.1 per cent respectively. Thus, it is clear that formulary listing of drugs as being interchangeable is a major factor in encouraging substitution.

The differences in the licensee share of the market between Newfoundland and Saskatchewan on the one hand and New Brunswick and Nova Scotia on the other in Table 10.4 show that the nature of selection rules also has an effect on the amount of substitution.

Table 10.5 summarizes the selection rules for product and price. Table 10.6 reveals the proportion of the market held by licensees in the various provinces. These proportions result from the combined effects of listing and selection rules. The proportion in British Columbia is relatively low, doubtless because of the entirely permissive nature of substitution. Saskatchewan shows a surprisingly low market share for licensees given the mandatory nature of substitution in favour of drugs that are purchased in bulk under tender under its Standing Offer Contract (SOC) program. The reason for this limitation is

Table 10.2

The Coverage of Provincial Government Drug Reimbursement Programs: A Summary, 1983

Provinces	Percentage of Population Covered* (% of Total Drug Bill)*	Class of Population Covered and any Patient Payment*	Date Original Program Introduced and Extended to Present Coverage
Alberta	21 (n.a.)	welfare, nil; over 65, 20 per cent of the prescription; not covered under a private third-party scheme or either of above two categories, \$15.00 plus 20 per cent of the prescription cost in excess of this sum in a year	at least 1950s, present coverage since 1973
British Columbia	100 (45)	welfare and over 65, nil; others, \$175 plus 20 per cent in excess of this sum for any calendar year per individual or family unit	1974, extended to "others" in 1977
Manitoba	100 (n.a.)	welfare, nil; over 65, \$50 plus 20 per cent in excess of this sum for any calendar year per family unit; under 65, \$75 plus 20 per cent in excess of this sum for any calendar year per family unit	1950s, present coverage since 1975
New Brunswick	21 (n.a.)	welfare under 18, \$1.00 payment per prescription; welfare over 18, \$2.00 payment per prescription; over 65, \$3.00 per prescription to a maximum of \$30.00 per year; nursing home patients, nil	not known, present coverage since 1976
Newfoundland	22 (n.a.)	welfare, nil; over 65 and receiving Guaranteed Income Supplement, the dispensing fee	1960s, present coverage since early 1970s
Nova Scotia	13 (n.a.)	welfare; over 65; nil for both categories	not known, present coverage since 1976

Ontario	14 (45)	welfare; over 65; those under Family Benefit Act Extended Care Services and Homecare; nil for all categories	1974, present coverage since 1976
Prince Edward Island	11 (n.a.)	welfare; special disease states; nil for both categories	not known, present coverage since at least early 1970s
Quebec	19 (45)	welfare; over 65; nil for both groups	1972, present coverage since 1977
Saskatchewan	100 (100)	certain welfare recipients and special beneficiaries, nil; all others (including over 65) pay payment per prescription up to a maximum of \$3.75 to Nov., then \$3.95 in Dec.	1948, present coverage since 1975
Canada	33 (43)	—	—

* This refers to the total eligible population, not necessarily those receiving benefits. In Saskatchewan, for example, the total eligible population was 955,651 in 1982/83 but the number of beneficiaries was 661,151.

^b Refers to the proportion of the province's total drug bill, at the retail level (i.e., excluding hospitals) accounted for by the Provincial Drug Reimbursement Program. In several instances these are estimates and sometimes to per cent of prescriptions dispensed. Refers to 1983 or closest year.

^c Often referred to as co-payment. Note that not all classes of population covered by the province are included in the table, only the major ones. For example, Nova Scotia has a drug assistance plan for diabetes insipidus patients.

Note: A drug reimbursement program is defined as a scheme whereby government pays in whole or in part the drug costs of a certain category or categories of the population.

Source: Paul K. Gorecki, "Compulsory Patent Licensing of Drugs in Canada: Have the Full Price Benefits Been Realized?," unpublished study, January 30, 1985.

Table 10.3

Drug Pricing Under Provincial Government Drug Reimbursement Programs: Summary, 1983^a

Provinces	Drug Cost Definition for Reimbursement	Formulary (Date Introduced) ¹	Maximum Supply per Prescription	Product Selection
Alberta	Cost to wholesaler plus 25 per cent	None	34 days, with some exceptions up to 100 days	Permissive
British Columbia	Actual pharmacy cost ^b	None	100 days	Permissive
Manitoba	Drugs listed in formulary, price based on package size most commonly purchased by pharmacist; other drugs' price based on smallest package size available	Limited formulary for high selling multiple-source drugs (Jan. 1974)	None	Permissive (mandatory price selection) ^c
New Brunswick	Cost of smallest package size, usually 100s ^d	Limited formulary for high selling multiple-source drugs (Jan. 1977)	100 days	Permissive
Newfoundland	Cost of smallest package size, except for a small number of high selling multiple-source drugs where larger package sizes used	Limited formulary for high selling multiple-source drugs (May 1981)	None, but in practice 34 days or 120 doses whichever is the greater	Permissive (mandatory price selection) ^c
Nova Scotia	Cost of smallest package size, with some high volume drugs based on larger package sizes	Formulary (Jan. 1981)	34 days, but up to 100 days on instruction of physician	Permissive
Ontario	Cost to pharmacist of smaller package sizes (100's) except for a small number of high selling drugs where larger package size (1000's) used ^d	Formulary (Oct. 1970)	One month under normal circumstances, not to exceed 6 months in any event	Permissive (mandatory price selection) ^c
Prince Edward Island	Actual acquisition cost to provincial dispensary ^d	None (n.a.)	60 days	Permissive ^e

Quebec	Cost of most popular selling package size purchased by pharmacist ^f	Formulary (July 1972)	None	Permissive (mandatory price selection) ^g
Saskatchewan	Provincial government tender system for high selling drugs (Standing Offer Contracts); for other drugs pharmacists' customary replacement cost ^h	Formulary (Jan. 1975)	Six months ^h	Mandatory for Standing Offer Contract drugs and permissive elsewhere (mandatory price selection in both instances) ^h

^a Most of the provincial drug reimbursement programs have had the same rules for drug reimbursement to pharmacists since at least the mid-1970s to the present. In some instances, changes of some importance have taken place in the intervening period. For example, it was only in 1979 that Ontario moved to price high selling drugs based on larger package sizes, while Quebec moved to mandatory price selection in January 1982.

^b B.C. government looks at average true acquisition cost in any given area or city and demands to see invoices if store claims reimbursement above local average price. There are only a small number of wholesalers in B.C. and the prices they charge to the pharmacist are also monitored by the government.

^c See text for an explanation of this term.

^d Pharmacist's costs from wholesaler, unless data has proven 50 per cent of a manufacturer's sales of these drug products in Ontario are via direct channels, in which case latter source is used.

^e For Prince Edward Island the provincial government operates a central dispensary from which drugs are distributed to the eligible categories mentioned in Table 10.3 above. In doing so the dispensary does make use of lower-priced licensee drug products. In this sense product selection is permissive.

^f For a given drug Quebec will rank pharmacies in the province from high to low in terms of the number of (say) tablets dispensed over a six-month period under the Quebec reimbursement plan; select the median store and estimate its average monthly sales of the drug; assume that the non-plan to plan ratio of sales is (say) 3:1, then scale up average monthly sales by 3 to derive the amount of a drug typically purchased for *all* of the store's customers; then select the package size (100, 500, 1000 etc.) closest to this average monthly sales figure to derive package size upon which government will reimburse and place a price in the formulary. For a small number of high selling multiple-source drugs the formulary lists only one price for all brands of the given drug since July 1983. However, if the pharmacist purchases the drug for a lower price, then the province would reimburse at the lower price only. If there are two or fewer brands, median pricing does not apply and the province will pay for the brand dispensed as per the formulary price.

^g For non-SOC drugs manufacturers provide firm price quotations for a six-month period. Pharmacists must charge acquisition cost to a maximum of the price listed in the formulary for all drugs. Although the formulary price for low-volume products may be based on smaller package sizes, pharmacists who buy these products in larger package sizes, at lower prices, must submit and are paid actual acquisition cost. An allowance of 11 per cent for a wholesale mark-up is made in the published prices in the province's formulary on *all* drugs.

^h For most drugs the pharmacist is entitled to one dispensing fee for each 34-day supply of medication. A pharmacist is entitled to one dispensing fee for each 100-day supply for certain maintenance drugs (thyroid, digoxin, anti-convulsants, oral hypoglycemics) and one dispensing fee for each two-month supply of oral contraceptives.

ⁱ It might be noted that a formulary is sometimes introduced before product selection legislation. This reflects early attempts by some provinces to provide information to pharmacists and physicians in order to influence prescribing and dispensing habits. Product selection legislation then followed, as for example in Ontario.

^j Some drug firms supply direct to the pharmacist; others supply via a wholesaler, with a 20 per cent mark-up permitted by the wholesaler in the price he charges to the pharmacist.

Source: Paul K. Gorecki, "Compulsory Patent Licensing of Drugs in Canada: Have the Full Price Benefits Been Realized?," unpublished study, January 30, 1985.

Table 10.4

**The Importance of a Formulary Listing as Interchangeable in
Provinces with Differing Product and Price Selection Rules for
Seven Multiple-source Drugs, 1983**

Sample of Drugs	Average Licensee Market Share ^c	
Listed in Newfoundland Formulary in 1983 ^a as	Newfoundland	Saskatchewan
	9.7	
	Interchangeable	
	76.0	{ 59.2 57.2
Listed in New Brunswick Formulary in 1983 ^b as	New Brunswick	Nova Scotia
	3.2	
	Interchangeable	
	5.1	{ 13.9 5.8

^a All of the drugs were listed in Saskatchewan as interchangeable. The number in each category is listed in parenthesis. Data for Newfoundland refer to the six months ending September 30, 1983, and Saskatchewan to October-December 1983.

^b All of the drugs were listed in Nova Scotia as interchangeable. The number in each category is listed in parenthesis. Data for New Brunswick refer to September 28, 1983 to March 23, 1984 and for Nova Scotia, October-December 1983.

^c Measured in quantity (i.e., number of caps or tabs).

Source: Various provincial formularies and data supplied by the provincial drug plans in New Brunswick, Newfoundland, Nova Scotia, and Saskatchewan.

the exceptionally high proportion of prescriptions issued by physicians in Saskatchewan with the "no substitution" notation. This practice was estimated by the Saskatchewan Prescription Drug Plan to increase the cost of the total drug bill in Saskatchewan by \$4.4 million in 1983/84 or by about 10 per cent. The incidence of "no substitution" prescriptions is nearly 40 per cent in that province as against much lower proportions, probably less than 3 per cent, in other provinces. In Ontario, four-fifths of the public reimbursement market is held by licensees as a result of mandatory price selection. In New Brunswick and Nova Scotia, the substitution requirements are permissive and the proportion is low. The level in Newfoundland is explained by the fact that, though the selection criteria are strict, the program is recent and many drugs were not yet listed in 1983. The market share of licensees in Quebec is growing rapidly as a result of increasingly strict price and product selection criteria in 1982 and 1983.

To the extent the hospital market operates by tender, prices are low and licensees obtain substantial market shares. For one large hospital buying group examined by the Commission, licensees were awarded the contract to supply all seven drugs referred to above in 1983/84 and 1984/85.

Table 10.5

Price and Product Selection Rules Under Selected^a Provincial Drug Reimbursement Programs, 1983

Price Selection	Product Selection	
	Permissive	Mandatory
None	Pharmacist can select at own discretion: British Columbia, New Brunswick, and Nova Scotia	—
Mandatory	Must charge up to a maximum price, regardless of brand dispensed: Ontario and Newfoundland (maximum price = lowest); Quebec ^c (maximum price = median price)	Must dispense a particular brand at a particular price: ^b Saskatchewan

^aExcluded are Alberta (which would be classified with British Columbia, New Brunswick, and Nova Scotia) and Manitoba (which would be classified with Ontario and Newfoundland).

^bThis is the rule for Standing Offer Contract drugs. All seven multiple-source drugs in the sample are SOC.

^cFor: cimetidine, 300 mg tabs; naproxen, 250 mg tabs; and propranolol, 40 mg tabs. For July-December 1983 and all of 1984 Quebec set a single maximum price up to which it would reimburse, no matter which brand was dispensed. However, if the pharmacist purchased the drug for a lower price, then the province would reimburse at this lower price. For indomethacin 25 mg caps there are only two suppliers in Quebec and hence median pricing does not apply. The province will pay for the brand dispensed.

Source: Various provincial formularies.

The Cost of Acquisition and of Reimbursement

The third factor determining the extent to which the potential savings from compulsory licensing are realized by consumers and taxpayers in the publicly reimbursed market is the relationship of the price that is reimbursed by the province to the actual cost of the drug to the pharmacists. In all provinces, the payment for prescription drugs to the pharmacist consists of two parts. The first is the drug cost. In principle this is the price paid by the pharmacist to the wholesaler or manufacturer for the product. The second part is a flat-rate dispensing fee which is in payment for the pharmacist's professional services. The purpose of the dispensing fee system is to remove the incentive that would be given to pharmacists to dispense higher-priced drugs if their income were based on markup over cost.

In British Columbia, the pharmacist is reimbursed the cost of the drug at his actual acquisition price. Similarly, in Saskatchewan, the reimbursement price is the tender price accepted by the Saskatchewan government under its SOC system and the acquisition cost for drugs not included in those contracts. In other provinces, such as Ontario and Quebec, the reimbursed price is that

Table 10.6

**Average Licensee Market Share for Seven Licensed Drugs,^a
Selected Dosage Forms and Strengths, Various Provincial
Government Drug Reimbursement Markets, 1983^b**

Province and Period to Which Market Share Refers	Average Market Share of Licensees ^b (standard deviation)	
	Measured in Units of Output (i.e., quantity) ^c	Measured in Sales
British Columbia (1983)	30.58 (9.39)	19.89 (6.76)
Saskatchewan (Oct.-Dec. 1983)	58.01 (6.11)	36.42 (9.46)
Ontario (1983)	83.34 (n.a.)	77.40 (n.a.)
Quebec (1983 and Jan.-June, 1984)	54.71 (n.a.)	47.17 (n.a.)
New Brunswick (Sept. 28, 1983-March 23, 1984)	4.00 (3.17)	3.73 (3.08)
Nova Scotia (Oct.-Dec. 1983)	10.44 (6.20)	8.26 (4.91)
Newfoundland (April-Sept. 1983)	47.59 (35.81)	43.65 (34.29)

^a Indomethacin, flurazepam, naproxen, propranolol, methyl dopa, cimetidine, and allopurinol.

^b For all provinces except Ontario and Quebec, the provincial drug reimbursement programs provided individual market share data. However, for Ontario and Quebec averages were provided to the Commission which exactly matched the seven drugs. Hence some adjustments were made to derive the percentages for these provinces. It is believed they are probably accurate to within a couple of percentage points.

^c Usually number of caps or tabs. In some instances, prescriptions.

Source: The provincial drug reimbursement programs for British Columbia, Saskatchewan, Ontario, Quebec, New Brunswick, Nova Scotia, and Newfoundland.

shown on the formulary. This list price is periodically negotiated between manufacturers and provincial authorities. Provinces with formulary prices are aware that manufacturers compete with one another by obtaining relatively high list prices for their products on the formulary, but then selling to pharmacists at discounts from that price that are frequently substantial. As a consequence, in those provinces, pharmacists' incomes arise both from the dispensing fee and from the spread between the price at which they are reimbursed for the drug and the price that they actually pay. Under this system of formulary prices, manufacturers cannot attract business from pharmacists by charging low prices that would benefit taxpayers and consumers. They must create a spread between the formulary price and the lower price they actually charge; the benefit of the spread between the two prices goes to pharmacists, not consumers.

The Realization of Potential Savings

The three principal variables discussed in the previous two sections determine the licensees' share of the market and the extent to which the actual low prices of compulsorily licensed drugs result in savings to consumers and taxpayers. Table 10.7 presents the relevant information for the seven listed drugs in the seven provinces in the sample. In all instances the table refers to the provincial drug reimbursement sector of the market.

The maximum potential saving (POTSAV) is measured as the potential savings due to compulsory licensing compared to the total expenditure on the

Table 10.7

The Potential, Actual, and Still-to-be-Realized Savings Due to Compulsory Licensing and Associated Provincial Government Reimbursement Programs for Seven Multiple-source Drugs^a for Seven Provincial Drug Reimbursement Programs, 1983^b

Province	POTSAV ^c	ACTSAV ^c	UNSAV ^c
	Average ^d (Standard Deviation)		
British Columbia	0.6538 (0.094)	0.5447 (0.103)	0.4553 (0.103)
Saskatchewan	0.6538 (0.094)	0.5213 (0.062)	0.4787 (0.062)
Ontario	0.6538 (0.094)	0.4053 (0.144)	0.5947 (0.144)
Quebec	0.6538 (0.094)	0.4405 (0.236)	0.5595 (0.236)
New Brunswick	0.6538 (0.094)	0.0193 (0.031)	0.9807 (0.031)
Nova Scotia	0.6538 (0.094)	0.1854 (0.181)	0.8146 (0.181)
Newfoundland	0.6538 (0.094)	0.2262 (0.238)	0.7738 (0.238)

^a Indomethacin, flurazepam, naproxen, propranolol, methyldopa, cimetidine, and allopurinol.

^b See Table 10.6 for period to which index applies for a particular province.

^c These are defined in the text.

^d Unweighted average of the index across the seven drugs.

Source: Data provided by various provincial governments, licensees, and the Saskatchewan Formulary, various issues.

licensed drug had compulsory licensing not been introduced. The index will vary from 1 (no benefits from compulsory licensing) toward 0, as the licensee's price falls. The prices chosen as a benchmark for patentee prices to measure expenditure had compulsory licensing not existed were those where there was no licensee competition, namely in Saskatchewan where patentee prices are protected by the "no substitution" prescribing of some physicians. The licensee prices are the prices actually charged in a sample which included a very large proportion of all sales of compulsorily licensed drugs by generic firms.

Two indices were designed to measure the degree to which the dollar maximum potential savings were realized. ACTSAV is the proportion of potential dollar savings that have been actually realized in each province and varies from 1, where all the savings have been realized, to 0 where none of the savings have been realized. UNSAV is the residual and measures the unrealized potential savings.

Table 10.7 reveals that the highest proportion of the potential savings in 1983 were realized in British Columbia and Saskatchewan. Even so, they only realized approximately one-half of the potential. In British Columbia, this result was doubtless owing to the lack of mandatory substitution which in part offset the gains from reimbursement at actual acquisition cost. In Saskatchewan, the proportion was limited chiefly by "no substitution" prescribing. The Ontario proportion of 40 per cent despite licensee sales of about 80 per cent of total sales of compulsorily licensed drugs was doubtless owing to the excess of reimbursement prices over the prices actually charged to pharmacists. Despite a lower proportion of licensee sales in Quebec, the savings achieved were higher than in Ontario. The more permissive substitution requirements in New Brunswick and Nova Scotia and the relatively recent implementation of the program in Newfoundland explain the failure to realize a substantial portion of the potential savings in these provinces.

The potential savings in the private market in which reimbursement occurs through private third-party insurance plans or not at all is less than in the publicly reimbursed market. This is because of the voluntary nature of product and price selection and of substitution by pharmacists who have little incentive to do so. Indeed, in Ontario, the dispensing fee is a disincentive to substitution because the fee is less if the pharmacist substitutes a cheaper drug for a private purchaser than if he dispenses the brand prescribed. As a consequence, very little substitution occurs for private purchases, which account for over half the retail market. Manitoba and Newfoundland mandate price selection in the private market. In the other provinces, the price is usually the formulary price for the brand prescribed and dispensed. Their governments have instituted programs which lead to significantly lower prices for drugs they reimburse than for those paid by the general public.

The Effect of Price Regulation

Fiscal pressures on provincial governments will inevitably persist into the indefinite future and lead to a continuation of attempts to control the cost of

drugs to provincial treasuries and to some extent as well to individuals. Until now such measures have been regulatory and bureaucratic. They have achieved a considerable measure of success and realized nearly half the potential saving in costs arising from compulsory licensing. But control through increasing regulation has its dangers.

Regulation makes for uniformity in reimbursement prices and dispensing fees. These sources of income for retail firms are set by negotiation between provincial governments and the manufacturers on the one hand and pharmacists' associations on the other and only clumsily or inadvertently reflect the fact that different retail stores have differing profit potential because of location, volume, composition of sales, and management. Thus, in many provinces, both dispensing fees and, in principle, product prices paid and charged by pharmacies are the same for all stores.

The dispensing fees and prices are determined on the basis of some estimate of reasonable average costs and normal rates of return. They must be such as to cover the needs of low-volume, high-cost pharmacies. They therefore potentially give rise to profits that exceed the level necessary to provide those services for well-located or well-run stores.

The high profits may be dissipated by overcrowding of pharmacies in favourable locations or they may persist, but in neither case, in the absence of price competition, do they lead to lower prices for consumers and taxpayers. Nor do actual acquisition prices below the prices listed in the formulary get passed on to the consumer and taxpayer.

Regulations that raise the rate of return on capital invested in pharmacies also tend to persist. For instance, limits placed on the quantities that a pharmacist may supply on the basis of one prescription, as exist to varying degrees in most provinces, and which multiply the number of prescriptions and therefore the dispensing fees obtained by pharmacists, once applied are difficult to remove.

The rigidity of systems of administered prices, which give rise to high profits for some firms, is enhanced by the fact that such high profits become transformed into costs. The present capital value of a pharmacy is raised if it becomes exceptionally profitable. When a new owner purchases that firm, he must pay that raised capital value and does not himself make a high rate of return on his capital. Any measure to reform the system by lowering fees or reducing the margin he receives between actual and reimbursement prices is resisted especially vigorously, because it is regarded as an attack on a legitimate rate of return and tantamount to expropriation.

The same phenomenon of capitalizing the effect of a regulatory barrier to competition into the value of a business is familiar in other fields such as taxi licences or rights to sell agricultural products issued by marketing boards. Such regulations must be accompanied by barriers to interregional trade unless provincial programs are identical in their effects on prices.

An increase in price competition in the retail market for pharmaceutical products would tend to reduce the prices of drugs to consumers and taxpayers and halt or reverse the tendency of the retail market to rigid control and segmentation.

Provincial authorities are very much aware of the factors that influence drug prices to different groups of consumers in their complex programs. They adjust their regulatory practices in the light of their objectives and of the experience in other provinces. However, despite the variety of features between particular provincial programs in Canada, no province has sought to increase price competition in the retail sector by providing a greater role for consumers, although British Columbia has attempted to provide greater information to consumers by providing on the prescription receipt both the drug cost and dispensing fee. Consumers have little knowledge and in most provinces insufficient incentives to seek out low prices.

The Sensitivity of Consumers to Prices

In most cases doctors prescribe drugs by their brand name; in about 20 per cent of cases they prescribe them by their generic name. Except in Saskatchewan, a negligible number of doctors prohibit the substitution of the prescribed drug by pharmacists. In cases in which substitution is possible, the ability of the consumer to shop for the best price depends on his ability to identify substitutable products for the prescribed brand and to obtain knowledge of prices charged by different pharmacies for the same brands.

There are approximately 3,500 prescription drugs in Canada. However, the possibilities of substitution are most significant for compulsorily licensed multiple-source drugs of which 32 were sold by licensees in December 1983. (Another 14 had been compulsorily licensed earlier, but were no longer so, because the patent had expired.) These included 24 of the 50 largest selling drugs in Canada. Each drug has a complex chemical name, reflecting the chemical composition of the drug. The World Health Organization attributes a generic name to that drug. The generic name is derived from the chemical name, but is simpler. The patent-holding firms marketing that drug each give it a different brand name which can be easily remembered. Usually the brand names have little or no relationship to the generic name. Hence, every drug has a minimum of three names. Multiple-source drugs have even more names depending on the number of manufacturers. Generic manufacturers sometimes sell the commodity under its generic name or with a composite name that evokes both the generic name of the drug and the identity of the manufacturer. The multiplication of names for the same product makes informed purchasing decisions by consumers more difficult by reducing their ability to identify the same drug under different trade names. This product differentiation is all but artificial, an obstacle to choice and an impediment to price competition.

In order to facilitate informed choices between different brands of the same drug for consumers, the Commission recommends that all ethical drugs should be prominently labelled with their generic name, whatever other name may also appear on the label.

Part of the search for the lowest priced drugs could be carried out on behalf of the patient by the prescribing physician who is the consumer's agent. However, the physician is less concerned about the cost of drugs than the patient, because the physician does not pay for them himself. Secondly, the patients themselves, in choosing a physician, do not take greatly into account whether that physician prescribes economically for them or not. Patients buy a health care package from doctors who provide diagnosis, advice, treatment, and a prescription. The drug cost is only a portion of the cost of this multi-dimensional service. It does not greatly affect the demand for the entire service from a physician and in consequence physicians are not induced by this factor to search for cheaper drugs and prescribe economically. The responsibility for searching for cheaper drugs falls on the consumer and, where substitution is possible, on the pharmacist.

A further obstacle to the ability of consumers to shop for the lowest priced single-source or multiple-source drugs stems from difficulty in discovering prices. By law, prescription drugs may not be advertised to consumers in Canada as in many other countries, though they are heavily advertised to physicians and pharmacists. The rationale for such legislation is that the responsibility for prescribing rests with physicians and that these should not be exposed to remonstrances by consumers who, being inexpert, could be led by advertising to unrealistic expectations as to the efficacy of a drug. Whatever the merits of that reasoning, it is irrelevant to the question of advertising of price. The Commission sees no reason why the advertising of prices of drugs by manufacturers and by pharmacists should not be permitted. In Canada pharmacists may advertise their services, but they may not advertise drug prices. Under present arrangements, in most provinces, the extent of permitted price information is the posting of a list of drug prices in the pharmacy. This is often very cumbersome and ineffective in transmitting information to the general public. An example is the restrictions on advertising placed by Section 42 of the Health Disciplines Act of Ontario which requires that any posting of prices shall be of no less than 25 drugs with at least one from each of at least 15 classifications (out of 20) and shall not be displayed so that it can be read from the exterior of the pharmacy. Some pharmacies make available the provincial formulary. Most pharmacies will not give price information on the telephone.

For all these reasons, the cost of searching for the best price is very high for consumers and mostly not worth the effort. In the absence of such search by customers, pharmacists have no inducement to compete on the basis of price.

The Commission recommends that provincial governments should remove restrictions on the advertising of drug prices, dispensing fees, or the sum of both;

that pharmacists should be expressly permitted to provide information on drug prices over the telephone; and

that prescription receipts state both the drug cost and the dispensing fee.

A further aspect of encouraging price competition in the retail market is that consumers are unlikely to seek out cheaper brands of substitutable drugs or cheaper sources of the same drug unless they have a financial incentive to do so, such as paying a portion of the cost of the drugs they purchase.

Provincial drug reimbursement programs vary in the extent to which they reimburse drug costs. The majority of Canadians on welfare and over the age of 65 make no contribution to the cost of the drugs they purchase. This group comprises a substantial portion of the market, accounting for approximately 45 per cent of total drug costs in Ontario and Quebec, whose public reimbursement plans cover virtually no others, and probably a similar proportion in other provinces. The rest of the population pays some portion of the cost of the drugs they purchase whether they are covered by provincial or private insurance programs or not.

Consumers are given an incentive to search out and take advantage of low prices of drugs if their behaviour affects the payment they make themselves. Their contribution must rise as the cost of their total purchases rises. It is evident that this is not achieved by a flat deductible sum unless its level exceeds the total drug purchases of the consumer. A deductible sum has merit as an instrument to reduce the overall cost to the insurer from reimbursement of drug costs and to reduce administrative costs, but unless it is very large and designed to protect only the biggest drug users, it inhibits price competition in the market by reducing the incentives of consumers. A possible alternative is a co-payment which is set at a maximum with the pharmacist allowed to discount as in Saskatchewan.

The Commission recommends that provincial governments should ensure that public drug reimbursement programs require a significant contribution to each purchase by the consumer arranged in such a way that price competition is induced, and should encourage private drug insurance plans also to have this feature.

The variety of plans in different provinces in Canada is the result of the adaptation of policies to provincial needs in the pharmaceutical field. The variety also provides an opportunity by example and imitation to adapt programs in an informed way to governmental objectives. However, variety may bring costs. The administrative costs of selling drugs are increased by differences in provincial policies. Divergent provincial policies which cause manufacturers' prices to vary interprovincially lead to arbitrage and wastes in transportation and other costs through cross-hauling and similar inefficiencies. A degree of collaboration based on an exchange of information amongst provinces would in consequence be desirable. The federal government, which is itself a purchaser of substantial amounts of pharmaceutical products, can play a role in collecting data on the pharmaceutical industry and encouraging collaboration and the coordination of provincial policies.

Chapter 11

The Regional Distribution of the Pharmaceutical Industry in Canada

The pharmaceutical industry in Canada is concentrated virtually exclusively in the peripheries of Montreal and Toronto. In 1981, the Quebec share of employment in the Canadian pharmaceutical industry was 45 per cent, whereas the population of Quebec was 26 per cent of the total Canadian population. In Ontario the industry's share of employment was 52 per cent and Ontario's share of the Canadian population was 35 per cent. Only 3 per cent of the industry's employment was located in the rest of Canada, which contained 38 per cent of the population. Such a concentration of the industry is exceptionally high compared with other industries. This pattern of location is characteristic of the industry in other countries as well. In the United States, 30 per cent of the industry is located near New York City (42 per cent if Philadelphia is included in that conurbation) and another 27 per cent around Chicago.

Such concentration is no accident. Pharmaceutical firms are dependent on the purchase of services which are available in sufficient variety and sophistication only in large centres. The heavy dependency of the pharmaceutical industry on advertising makes it important to locate near major advertising agencies. Other services of importance to major firms are financial and scientific. Communication with medical centres and major hospitals is necessary to generate clinical data for the approval process for the marketing of drugs. Many of the pharmaceutical firms in Canada are affiliated with foreign firms, which makes location close to a major international airport an advantage. The very large sales force of the typical pharmaceutical firm also puts a premium on being in the centre of a transportation network. All these forces lead to location in major centres. However, transportation costs for the materials used in manufacturing final pharmaceutical products and the shipment of the finished product itself are a negligible part of the total cost of drugs. Hence, freight costs do not affect the location of firms.

Another factor causing concentration is the advantage of location not far from other firms in the same industry. Such an agglomeration provides a pool of skilled workers and executives from which firms can draw as they expand or alter their activity.

The pharmaceutical industry is one in which some principal types of activity can be separated physically. The manufacturing of the active

ingredient, which is chemical manufacturing, need not be close to or indeed in the same country as the manufacture of the final dosage form. Neither does the head office of a firm need to be close to the factories in which manufacturing occurs. Manufacturing of the final dosage form is a relatively simple enterprise which does not require close connection with the top management of the firm in Canada. The research and development that is carried out in Canada is chiefly of a clinical sort, which is often undertaken in conjunction with procedures leading to the clearance of new products for marketing and is in consequence best managed from head office. Basic research and development is typically related to the head office of the multinational firm and located abroad.

Table 11.1

Principal Statistics on Manufacturers of Pharmaceuticals and Medicines by Province: Selected Years, 1933-82

Year	Value of Shipments (\$000)	Value Added in Manuf. (\$000)	Total (\$000)	Total Employees	Total Wages & Salaries (\$000)
1982					
Quebec	626,179	401,366	479,343	6,808	165,188
Ontario	795,572	537,751	573,385	8,366	192,684
B.C.	13,310	4,544	4,682	237	5,446
	%	%	%	%	%
1982					
Quebec	42.993	42.224	45.045	43.344	43.720
Ontario	54.624	56.572	53.882	53.220	50.997
B.C.	0.194	0.478	0.440	1.509	0.014
1976					
Quebec	46.455	44.959	45.619	47.180	49.156
Ontario	51.239	53.614	52.832	50.457	48.564
B.C.	0.686	0.605	0.546	1.122	1.066
1969					
Quebec	45.938	44.100	43.695	45.132	48.400
Ontario	52.183	54.593	55.059	53.341	50.230
B.C.	—	—	—	—	—
1953					
Quebec	47.183	45.584	—	48.332	49.791
Ontario	50.422	52.094	—	48.812	48.113
B.C.	0.344	0.284	—	0.627	0.487
1933					
Quebec	29.096	28.949	—	31.398	32.225
Ontario	63.022	64.000	—	61.376	61.231
B.C.	0.469	0.585	—	1.609	1.480

Source: Statistics Canada, *Pharmaceuticals, Cleaning Compounds and Toilet Preparations* (Catalogue 46-223) and *Refined Petroleum and Coal Products* (Catalogue 46-209).

Table 11.1 reveals that virtually all the industry is located in Ontario and Quebec, which is to say in Toronto and Montreal. Whether the measure of regional distribution is the value of shipments, the value added, employment, or wages and salaries, it turns out that in 1982 the proportion of activity in Toronto varied from 51 to 55 per cent depending on the different measure and in Montreal from 43 to 45 per cent.

Table 11.1 also reveals the historical evolution of the pattern of regional distribution. In the 1930s, the industry was concentrated in Quebec and Ontario with nearly two-thirds of Canadian manufacturing being located in the latter province. Since the transformation of the industry after World War II with the development of science and the dominance of multinational corporations, the share of production in Montreal has grown relative to Toronto and has remained remarkably stable. The major interregional measures of economic activity in the industry have remained stable since the 1950s. Table 11.1 shows that the proportions of the industry in Montreal and Toronto described for 1982 were not greatly different from those in 1969.

Nevertheless, careful analysis permits the disentangling of certain relative changes that have occurred in the position of the industry in Montreal and Toronto. Table 11.2 presents somewhat more detailed census data for the industry for Quebec and Ontario for a number of years in ratio form. An examination of this information shows that the ratio of employment in Quebec relative to Ontario has declined from a peak in 1951 for both production employment and white-collar work. The movement in other indices of relative activity are not as smooth over the long term, but all have the characteristic of an increase in the Quebec share relative to Ontario from 1969 to 1976 and a decline thereafter.

The relative decline in Quebec since 1976 does not imply an absolute decline in employment or in the other measures. Indeed, these did not decline because the industry was growing, and at a faster rate than manufacturing as a whole. The shift in activity from Quebec to Ontario was minor, and it affected chiefly white-collar occupations and the type of manufacturing activity as between proprietary and ethical drugs. In 1977, the number of professional research and development personnel, which includes scientists, engineers, and senior administrators in research was 310 in Quebec and 110 in Ontario. More research was still carried on in Quebec than in Ontario in 1982 when there were still 310 research personnel in Quebec and 200 in Ontario.

Table 11.3 is a list of major firms that moved their head offices from Quebec to Ontario after 1976 or expanded their activities in Ontario relatively rapidly. This movement accompanied a divergence in the rate of growth of various business services between Montreal and Toronto from 1971 to 1981 as is shown in Table 11.4. These industries grew in both centres, but they grew more rapidly in Toronto and were part of a generalized westward movement of white-collar occupations, perhaps encouraged by relatively high rates of personal taxation in Quebec, which made it more difficult to recruit higher income employees there than in Toronto. Restrictions on the use of English in business and in schools may also have been a factor.

Table 11.2

**Quebec/Ontario Ratios for Various Indicators of Pharmaceutical
Industry Activity: Selected Years, 1945-82**

	1945	1951	1955	1962*	1969	1976	1982
Total Employment	0.8100	1.0330	0.9910	0.9620	0.8460	0.9350	0.8140
Product Employment	0.7120	0.8890	0.8014	0.6810	0.6040	0.8250	0.7570
Administration, Sales and R&D Employment	1.0150	1.5200	1.3540	1.1830	1.0700	1.0300	0.8570
Value Added in Manufacture	—	—	—	0.8730	0.8080	0.8390	0.7460
Total	—	—	—	0.8790	0.7940	0.8620	0.8360
Value of Shipments	0.7800	0.8199	0.9868	0.8610	0.8800	0.9070	0.7880
Wages and Salaries (Total)	0.8900	1.0100	1.0330	1.0410	0.9640	1.0120	0.8570
Number of Establishments	0.8160	0.9680	1.0110	0.9870	0.7450	0.6670	0.7270
Population	0.8800*	0.8821	—	0.4330*	0.7825*	0.7544	0.7465*

* Quebec includes New Brunswick and Nova Scotia.

* For 1941. *For 1961. *For 1971. *For 1981.

Source: Statistics Canada *Refined Petroleum and Coal Products* (Catalogue 46-209); *Pharmaceuticals, Cleaning Compounds and Toilet Preparations* (Catalogue 46-223); and Census.

Table 11.3

**List of Firms with Head Office in Quebec in 1976 Which Either
Left Quebec or Expanded in Ontario During 1976-83**

	1976 Address	1983-84 Address	Remarks
Abbott	Montreal	Montreal	Expansion at Brockville (1976) and Downsview (1978)
Allergan	Pointe-Claire, PQ	Willowdale, Ont.	
Ayerst	St-Laurent, PQ	St-Laurent, PQ	Laboratory moved to Rouses Point, N.Y. in 1983
Bristol-Myers	Candiac	Ottawa	
Ciba-Geigy	Montreal	Mississauga	
Cooper Lab.	Boisbriand	Mississauga	
Cyanamid-Lederle	Ville Mont-Royal	Willowdale	
Ex-Lax	Montreal	Cornwall	
Hoffmann-La Roche	Vaudreuil	Etobicoke	
Robins	Montreal	Mississauga	
S.K.F.	Senneville	Mississauga	
Revlon	Montreal	Mississauga	
Syntex	Montreal	Mississauga	

Note: The above list is not exhaustive and principally concerns firms which are members of PMAC.

Source: Statistics Canada, *Refined Petroleum and Coal Products* (Catalogue 46-209); *Profile* (PMAC, 1980 and 1983); and "84 Pharmaceutical Lineup" from *Drug Merchandising*, April 1984.

Table 11.4

**Business Service Industries Employment:
Montreal and Toronto, 1971 and 1981**

Industry	Montreal			Toronto		
	1971	1981	% Growth	1971	1981	% Growth
Finance and Real Estate	61,500	87,600	42.4	84,500	139,200	64.7
Computer and Information Services	1,115	3,865	246.6	1,540	11,740	662.3
Public Relations and Advertising	3,550	4,695	32.2	5,795	9,960	71.9
Scientific Consulting	8,315	14,910	79.3	9,585	17,220	79.7
Business Management Consulting	980	4,115	319.9	1,680	7,065	320.5

Source: Statistics Canada, *Industries by Sex: Census, Metropolitan Areas* (Catalogue 94-742) and special Statistics Canada compilations for 1981 provided by M. Polèse, I.N.R.S. Urbanisation - Montréal.

Table 11.5

Pharmaceutical Industry: Value Added per Production Employee, 1940-82

Year	Quebec	Ontario	Ratio Quebec/Ontario
1940-45	\$ 7,126	\$ 7,808	0.910
1946-50	10,024	8,973	1.120
1951-55	15,814	13,576	1.160
1956-60	24,101	22,328	1.080
1961		25,535	
1962	34,112	26,569	1.284
1963	40,996	28,437	1.442
1964	41,729	30,448	1.371
1965	46,065	31,551	1.460
1966	43,776	32,711	1.338
1967	46,094	33,608	1.372
1968	47,952	36,865	1.301
1969	54,381	40,636	1.338
1970	55,930	45,285	1.235
1971	61,608	45,578	1.350
1972	61,630	50,538	1.220
1973	62,637	52,652	1.190
1974	67,585	57,205	1.180
1975	69,169	58,573	1.180
1976	67,559	66,495	1.020
1977	83,095	67,713	1.230
1978	85,016	80,575	1.050
1979	98,224	96,315	1.020
1980	112,377	104,815	1.070
1981	133,186	123,146	1.080
1982	144,376	146,526	0.980

Source: Statistics Canada, *Refined Petroleum and Coal Products* (Catalogue 46-209) and *Pharmaceuticals, Cleaning Compounds and Toilet Preparations* (Catalogue 46-223).

It appears that a change may also have occurred in the type of manufacturing industry in the two regions. Table 11.5 shows changes in value added in manufacturing per production employee in the pharmaceutical industry for Quebec and Ontario during the 42 years following 1940. Following 1945 and until 1976, the value added per production employee in Quebec was significantly higher than in Ontario, reaching a peak in 1965, but declining thereafter. Since 1976, the ratio has been close to one, which indicates that the type of manufacturing that is now carried on in Toronto is similar to that in Montreal. This shift in production in Ontario towards higher value added per employee probably reflects an increase in production of ethical pharmaceutical products relative to proprietary goods.

A contribution to the slight shift in the locus of the industry's activities towards Toronto in the period since 1969 is the growth of production of generic drugs based on compulsory licensing to import. The generic industry was of insignificant size before the change in legislation in 1969 and has grown

rapidly since that time in both Quebec and Ontario. But the growth in Ontario has been faster. This is where two Canadian-owned firms, which are the biggest generic manufacturers, are located. Changes in total industry activity owing to the production of compulsorily licensed drugs can, however, easily be overestimated. Drugs produced by compulsory licences constitute less than 3 per cent of total drug production.

No census of industry data are available from Statistics Canada for 1983. The Commission itself made a survey of the principal manufacturers in Canada. These data are not directly comparable with those of Statistics Canada, but are consistent with them. They are presented in Table 11.6 which shows that approximately 90 per cent of the employment in the sample is located in Ontario and Quebec and that that proportion declined by 1.5 percentage points over the period from 1979 to 1983. The proportion located in Quebec fell from 44 per cent in 1979 to 42.1 per cent in 1982 and then took a three point drop to 39 per cent of the Canadian total in 1983. Statistics Canada data on production show a drop of over 1.5 points between 1981 and 1982, which is not reflected in its entirety in the Commission's survey. However, the general trends shown in the two surveys are not inconsistent. The drop in 1983 probably reflects chiefly the loss of 280 jobs when Ayerst closed its Montreal laboratory in 1983. The difference may have arisen owing to the timing in reporting.

Future trends in employment and output in Quebec relative to Ontario are difficult to foresee, but it is probable that the share of Montreal will show some recovery in future years as a result of investment programs either under way or announced for Montreal by Rhône-Poulenc, Mallinckrodt, Burroughs-Wellcome, Johnson and Johnson, and Ayerst.

Table 11.6

Relative Shares of Total Employment: Ontario and Quebec, 1979-83

Year	Ontario	Quebec	Ont. & Que.	Que./Ont.
1983	49.7	39.0	88.7	78.5
1982	47.3	42.1	89.4	89.0
1981	46.9	42.6	89.5	90.8
1980	46.9	43.1	90.0	91.9
1979	46.2	44.0	90.2	95.2

Source: Survey of the Commission of Inquiry on the Pharmaceutical Industry.

Chapter 12

Pharmaceutical Research in Canada

The pharmaceutical industry in Canada is intensive in research in comparison to other sectors of Canadian manufacturing industry (though not to the world-wide pharmaceutical industry). This relative research intensity is reflected in the fact that, in 1982, the pharmaceutical industry, with only .8 per cent of all employees in manufacturing, employed 3.5 per cent of that sector's scientists and other research and development personnel. The pharmaceutical industry expended 2.8 per cent of the funds spent on research in manufacturing. Furthermore, the scientific qualifications of the staff in the pharmaceutical industry are high.

Table 12.1 shows that the funds for intramural research and development in the Canadian pharmaceutical industry came predominantly from firms in Canada and their foreign affiliates. In 1982, these sources accounted for 79 per

Table 12.1

Sources of Funds for Intramural Research and Development in the Pharmaceutical Industry, Selected Years, 1975-82

Sources	1975 %	1977 %	1979 %	1981 %	1982 %
Canadian					
Performing firm	72	71	75	75	71
Federal government	12	11	9	9	10
Provincial govern- ment	1	3	2	2	2
Other	9	8	8	8	9
Subtotal	94	93	94	94	92
Foreign	6	7	6	6	8
Total	100	100	100	100	100

Source: Statistics Canada, *Industrial Research and Development Statistics* (Catalogue 88-201) and *Annual Review of Science Statistics* (Catalogue 13-212).

cent of the total expenditures; other private sources contributed a further 9 per cent. Government subsidies amounted to 12 per cent of the total spent. Government support to research in this industry was approximately the same as the average for all manufacturing which, in 1981, was 11 per cent. However, the contribution of government to research exceeds the direct funding identified above, because the Canadian government provides very substantial tax incentives for research by allowing taxpayers to deduct from income more than the sums expended for that purpose. These tax incentives are amongst the most generous in the world. Their adequacy in the judgement of the industry is reflected in the recommendation of the Pharmaceutical Manufacturers Association of Canada to the Commission that "the current system of grants and tax incentives for research be continued."

Forty-one of the 55 largest firms surveyed by the Commission had funded their entire research and development expenditures from internal sources and their foreign parent. This funding covered approximately 84 per cent of the total research of the 55 firms.

The level of research and development expenditures over the period from 1968 to 1981 has been quite stable both as a proportion of the sales of the pharmaceutical industry and in real terms. The submission of the Pharmaceutical Manufacturers Association of Canada provided provisional data indicating the maintenance of those expenditures into 1983.

The research of pharmaceutical firms can be categorized as basic, process, and clinical. Basic research includes the search to discover new biological processes, the synthesis of chemical compounds, and testing in animals. Process research comprises research for the purpose of reducing costs of drug production or of improving the quality of the product. Clinical research is to determine the safety and therapeutic effectiveness of drugs. The survey by the Commission indicates that, in 1983, approximately 15 per cent of research and development expenditures by pharmaceutical firms in Canada were devoted to basic research, a proportion that was slowly rising from 1979, and that approximately 15 per cent of the research was devoted to developing new processes, a proportion that was declining. The remaining expenditures were for clinical research which varied by firm and over time with the number of Preclinical New Drug Submissions made to the Health Protection Branch.

Five of the 55 firms in the surveyed group did the lion's share of basic and process research in Canada. These firms had a ratio of basic and process research and development expenditures to sales exceeding 4 per cent and did approximately 85 per cent of all such research in Canada. The eight firms with a ratio of such research to sales exceeding 2 per cent were responsible for approximately 90 per cent of the basic and process research expenditures of the surveyed firms. Basic research expenditures were less than .75 per cent of the sales of pharmaceutical products by the surveyed firms.

Canada is a negligible force in basic research in the world-wide pharmaceutical industry. Basic research is concentrated in the United States,

West Germany, Switzerland, the United Kingdom, France, and Japan. The headquarters of major international firms are chiefly located in those countries. The characteristic strategy of such firms is to carry out much of their basic research near their headquarters, though many also operate centres for basic research in locations with well-established research activity and experienced scientific manpower. Thus, U.S. firms, which dominate the Canadian market, do 85 per cent of their research in the United States, and most of the rest in the United Kingdom, West Germany, and France. European firms carry out a higher proportion of their research in foreign countries, and the favoured location for foreign research is in most cases the United States.

The location of significant research in the pharmaceutical industry is principally determined by the location of the parent firm's headquarters, which itself reflects historical evolution of specific skills and interests in that firm and the general scientific infrastructure of the country, but is also affected by the degree to which the host government is willing to aid pharmaceutical enterprises by heavy subsidies, tolerance of high prices, and support of relevant science in universities and institutes.

Canada does not now possess either the scientific manpower or the physical infrastructure that would make it a major world centre for basic pharmaceutical research. Nor, in the opinion of the Commission, would it be wise for governments to seek to create such an environment in competition with heavily supported long-established centres in other countries.

Canada does have comparative advantage in clinical research, however, because of a highly skilled medical establishment and hospitals with excellent facilities.

Some firms will undoubtedly continue to engage in basic research in Canada and others to find particular circumstances which will make it attractive to establish new centres and programs in Canada, but no development of basic research that would rival that existing in the major centres is likely to arise. Canada can expect a substantial increase in clinical research under appropriate circumstances such as those proposed by the Commission.

Are new opportunities for pharmaceutical research arising in addition to traditional large-scale undertakings? The Commission has been made aware of the growth of research in biotechnology and its possible application to the pharmaceutical industry.

Biotechnology comprises in general the application of biological organisms to manufacturing industry. These processes use bacteria, yeasts, and fungi to carry out biological reactions. Recent rapid advances in cell and molecular biology, notably in the manipulation of genes, aided by developments in process and control engineering and in fermentation technology, have led to the potential for completely new industrial processes.

The potential fields of application of biotechnology are very wide, including agriculture, the food, chemical, and energy industries, and the

pharmaceutical industry. Human insulin, antibiotics, vaccines, antiviral agents, and many other products are either new or can be produced more cheaply, in greater volume, and in purer form than was previously possible.

The prospects for world-wide progress in biotechnology are good, but it also seems that progress will not come as quickly or as easily as had been expected or hoped in earlier days of the new science. What progress will come will be the result of huge expenditures on research.

From the standpoint of industrial structure, biotechnology is principally to be distinguished in two respects from chemical processes for the discovery and production of pharmaceutical products. One is that the patentability of biotechnological products and processes is only currently being determined by decisions of the courts. Many of the products exist in nature and may not be patentable. The processes for making them may be more patentable. The other difference is that the theoretical basis for research is more explicit than has been the case up to now in the pharmaceutical industry, so that the cost of research leading to an invention might prove to be more readily established. However, the procedures for the development of products and the clinical trials that are necessary for marketing are not dissimilar for pharmaceutical products resulting from biotechnology and those of chemical origin.

The growth of research and the application of biotechnology has been most rapid and most extensive in the United States. The U.S. federal government has heavily supported research in biotechnology in universities and hospitals. Many small firms have been established, partly as a result of the relatively advanced state of scientific knowledge and partly because of the close interface between business and academic circles and of the entrepreneurship to be found in U.S. academic circles. Some of these firms have now reached very substantial size and employ as many as 300 PhDs while still occupied virtually exclusively in research. A number of large firms, including major pharmaceutical and chemical firms, have also established important research projects using biotechnology. Helped by government support, universities, small specialized firms, and diversified large firms together form a milieu of basic research that is able to exploit the high level of scientific knowledge and the highly skilled manpower that is available in that country. A lower but nevertheless impressive commitment of resources to biotechnological advance is to be found in Japan and some European countries.

In Canada, biotechnology has only a small and fragmented base at present. A number of small research-intensive firms across the country are seeking to develop new products and processes, many with substantial government aid. As these firms make discoveries applicable to human and animal medicine, it is to be expected that they will form linkages with established firms in the pharmaceutical industry, because such multinational firms have the skills and resources to carry out the testing required for clearance for marketing and the necessary promotion in the world market. So far, the principal examples of such arrangements are those between Connaught Laboratories and Novo Industri S.A. of Denmark and between Connaught

Laboratories and Squibb USA to produce and distribute pharmaceutical products, chiefly vaccines, in Canada and abroad.

Growth of the biotechnological industry in Canada is at an early stage compared to the United States where about \$3 billion has already been invested. A number of reasons may contribute to this relative backwardness. One is that the world's major centres of pure research (funded chiefly by governments and located in universities) are not in Canada. Yet those are the best locations for research-intensive firms which are either established by entrepreneurial academic staff or are within easy access to the latest scientific knowledge. Neither is Canada the location of the headquarters of large pharmaceutical firms which have a well-known preference for establishing their advanced research centres near their headquarters. Furthermore, the low level of pharmaceutical research that has been traditional in Canada means that there are few senior scientists and engineers with experience in management suited to research at the forefront of new multidisciplinary projects in pharmaceutical research. Canada does not appear to be an especially favoured site for biotechnological research applied to pharmaceuticals.

However, Canada does have substantial assets advantageous for biotechnological research especially in fields related to its abundant resources. Canada's tax laws are favourable to research and development spending compared to other jurisdictions and the level of direct financial support by the federal government to research programs in firms is generous by international standards. Canada has a good university system and good scientific personnel. Major research activities in agriculture, energy, mining, fisheries, and other fields where Canada is resource-rich are performed by firms, governments, and universities. Many firms in these fields are based in Canada where their managerial and research expertise is concentrated. Should these firms engage in biotechnological research, Canada would be the most likely location. Thus, though Canada does not appear to have advantages over some foreign sites for research in biotechnology applicable to pharmaceuticals, because of a lack of heavily funded university research in biology, genetics, and related fields, and because of traditional weakness in pharmaceutical research in industry, there is nevertheless good prospect that scientists in universities, small research-intensive firms, and the few pharmaceutical firms active in basic research will make discoveries with commercial prospects some of which might be in pharmaceuticals for human or veterinary use.

The Commission has been told by some observers that the Patent Act's provision for compulsory licensing to import pharmaceutical products is a disincentive to biotechnology and other research in Canada, because it conveys the impression that the Government of Canada does not welcome research. It may convey that impression. However, the present Patent Act does not have a substantial negative effect on the profitability of Canadian innovations in pharmaceuticals, because such research activities are undertaken to develop new products for sale on the world market and not simply in Canada. The present Patent Act, therefore, does not present a financial barrier to research

or to collaboration between small research-intensive firms and multinational pharmaceutical firms.

In the event that a Canadian innovation proved to be a big winner, it would be exposed to the possibility of compulsory licensing in Canada. However, should the changes in the Patent Act and its administration recommended in this Report be implemented, the new product would enjoy a period of exclusivity of a minimum of four years in Canada. Thereafter, the royalty payment received by the innovating firm on its Canadian sales, which would be based chiefly on its major research expenditures in Canada, would be high. The innovating firm would be adequately rewarded in this way by royalties that were a high proportion of the value of the Canadian sales of the licensed product.

In the Commission's opinion, no special provisions should be made to protect and encourage biotechnological research in Canada related to pharmaceutical products. Canada does not appear to have special advantages in chemical or biotechnological research applied to pharmaceuticals. In any event, the proposed patent and royalty arrangements would afford a suitable return should such research lead to a product that was sufficiently successful on the market to attract compulsory licensing.

The grants and tax incentives offered by Canadian governments to support research and development in Canada elicited little comment in either briefs or appearances before the Commission. It is possible to infer that firms find these measures adequate, as was indeed confirmed by the recommendation of the Pharmaceutical Manufacturers Association of Canada, found as well in some other briefs, that these measures not be changed.

While the Commission is satisfied with the amount of government support offered to research activities in the pharmaceutical industry, it is of the opinion that programs should be redesigned so as to better address the particular needs of small research-intensive firms. In the first place, such firms cannot benefit from tax incentives when, as is often the case, they have no profits, unlike large established profitable multinational firms. The second negative aspect is that grants are made for particular projects, rather than on the basis of the past performance of firms or their own research expenditures. This requires committees and government officials to evaluate projects, with consequent delays in funding, which are difficult for small firms to surmount; uncertainty, which makes planning difficult; and elaborate procedures, which small firms are administratively poorly equipped to meet.

The Commission believes that the administration of aid to research for the pharmaceutical industry should be simplified, perhaps by means of a simple subsidy that is a rising proportion of the ratio of a firm's own research expenditure to its sales so as to improve the access of small firms to such aid.

The Commission recommends that government departments review their procedures for granting financial support to research in the pharmaceutical

industry with a view to improving the access of small research-intensive firms to such support by making such procedures simpler, faster, more stable, and more predictable.

Chapter 13

International Trade, Transfer Prices and Tariffs

Between 1970 and 1983 the value of shipments of goods manufactured by the pharmaceutical industry in Canada increased from \$386 million to \$1,785 million or by four and one-half times. During the same period exports rose from \$35 million to \$144 million or by about four times and imports rose more than six-fold from \$81 million to \$510 million. The share of imports of the generic firms was about 5 per cent of total sales and of exports over 8 per cent.

The relatively rapid rise of imports needs some analysis. The rise might have been owing to a fall in the international value of the Canadian dollar, because transfer prices of active ingredients and final products are often set to cover costs and contribute to profits of the parent company which are denominated in the currency of the parent's country of residence. It might have been owing to a shift from imports of bulk active ingredients, which are manufactured into final dosage forms in Canada, to imports of finished products. This shift would imply a decrease in the proportion of Canadian consumption supplied by Canadian manufacturing. Lastly, the rise might have been owing to increases in transfer prices to raise intra-company payments into a lower tax jurisdiction owing to changes in the relative total tax burden between Canada and the parent's home country or to shifts of transactions to a tax haven.

For the purpose of analysis, the entire period was divided into two because of a change in statistical classification. In the earlier years from 1970 to 1978, the value of shipments of own manufacture in Canada rose by 135 per cent whereas the value of imports rose by 206 per cent. During those years the Canadian dollar depreciated against the currencies of the principal countries exporting pharmaceutical products to Canada by a weighted average of about 17.5 per cent. If this had not occurred, 1978 imports would have been valued at about \$210 million, not the actual \$248 million, for an increase of only 160 per cent. Depreciation was thus the principal cause of the increase in imports valued in Canadian dollars relative to domestic production.

From 1978 to 1983, the value of shipments of own manufacture in Canada rose by 96 per cent and the value of imports by 105 per cent. This difference was accompanied by a decline in the proportion of imports that were bulk ingredients as can be seen in Table 13.1. These rose by 65 per cent and thus by less than domestic manufacture. Imports of dosage forms rose by 137 per cent.

Table 13.1
Canadian Pharmaceutical Imports by Country of Origin,
1970, 1978, 1983 (\$ Million)

	1970	1978				1983			
	(1) Total	(2) Raw or Bulk Materials	(3) (2) as % of Total	(4) Dosage Form	(5) Total	(6) Raw or Bulk Materials	(7) (6) as % of Total	(8) Dosage Form	(9) Total
United States		39	.32	82	121	53	.24	174	227
United Kingdom		12	.37	21	34	8	.14	53	61
EEC		26	.62	116	42	28	.41	41	69
Switzerland		11	.62	17	60	45	.65	24	70
Japan		2	.27	1	3	4	.50	2	6
Other		20	.62	12	32	43	.57	33	76
Total	81	111	.45	138	248	182	.36	327	510

In 1978, bulk materials constituted 45 per cent of imports; in 1983 the proportion was 36 per cent. During these years, there was thus an increase in value added in manufacturing in Canada, where little active ingredients were produced. Over the entire period from 1970 to 1983, a small increase took place in the proportion of the growing Canadian market that was supplied by imports.

The third possible cause of change in import prices is changes in the basis on which intra-corporate transfer prices are set, which is discussed below.

Intra-corporate Transfer Prices

When international transactions are integrated within the operations of a single firm, the values attributed to these transactions are not determined by arm's-length prices. It then becomes a question of the extent to which these prices reflect true values. Eighty per cent of the value of production of the Canadian pharmaceutical industry is carried out by multinational firms, nearly all of which are heavy importers from affiliated firms abroad both of the active ingredients that are formulated in Canada and of finished products either packaged or in bulk which are then distributed in Canada. The prices set for these intra-corporate international transactions are called transfer prices.

Transfer prices, not being determined at arm's length in a competitive market, may be set by the firm carrying out the transactions with different objectives or criteria. In some cases the prices of active ingredients or of finished products may reflect only the cost of manufacturing. In that case they do not reflect the value of any patent that may be applicable or the costs of research, marketing, and central administration incurred by the multinational firms. These prices are similar to the ingredients purchased by generic producers from firms in countries that do not recognize patents. In most cases the transfer prices include, in addition to manufacturing costs, some allocated general costs such as a share of research and development and general administrative expenses that can be calculated on a variety of possible bases.

The way in which transfer prices are set would be of concern only for the firm were it not that prices also affect the share of different governments in the tax revenue created by the firm's activities. The level chosen for the multinational firm's transfer prices may be affected by the rational desire of the firm to minimize its total tax payments by setting prices so as to shift profits to low tax jurisdictions including tax havens.

The ability to shift profits internationally through the manipulation of transfer prices depends on a number of legal factors and on tax rates. The principal incentive to shift profits by transfer pricing is international differences in corporate income tax. The critical income tax rates are not only those applied by the central government of a country, but must be the sum of the effective marginal income tax rates of applicable federal, provincial, and municipal taxes in Canada compared to those in foreign jurisdictions. The

corporate income tax laws of countries differ in several respects. One difference is in the deductibility of certain expenses such as management fees, interest, or research and development allocations. This disparity creates an incentive to shift income to the country where those expenses are deductible. Another difference is the geographical domain over which the income is regarded as taxable by a particular government.

Most countries levy tax on the world-wide income of a company located in their jurisdiction and so include the profits of its subsidiaries abroad, but others do not. No country as yet has adopted a unitary tax system whereby the country in which a subsidiary is located taxes the income of the parent, though some states have done so in the United States. The Canadian government taxes the income of subsidiaries of firms resident in Canada only when the income is remitted as dividends. In contrast to some other countries, Canada does not tax the earnings of such subsidiaries when they are earned even when the subsidiaries are located in tax-haven jurisdictions. This permits the accumulation of earnings at low effective tax rates and the accrual of a benefit for the firm from the postponement. Withholding taxes, whereby governments tax the payments of interest and dividends from subsidiaries to foreign parent companies, are, in effect, a substitute for the personal income tax payable by residents on investments in domestic companies. They are also levied when the dividends or interest are remitted to the foreign parent at rates and terms that vary across countries. Countries also differ in the regime whereby they allow credits in the calculation of tax liabilities in respect to foreign taxes paid by their subsidiaries against corporate income and withholding tax liabilities arising in the repatriation of foreign earnings.

The taxes often second in significance after the corporate income tax are the customs and exise duties applicable to the transfer prices of the internationally traded goods. An increase in the transfer price of goods imported to Canada reduces Canadian corporate income tax liability and reduces profits, because it reduces Canadian income while foreign income is increased. But the increase in transfer price raises the import duties payable in Canada. In general, then, income taxes and customs duties create opposite incentives for the manipulation of transfer prices. The net effect depends on the difference in income taxes in the two countries and the level of customs duties. Duties, unlike foreign income tax paid, are not deducted from the parent firm's final tax bill as a tax credit.

Table 13.2 summarizes the features of corporate income tax rates in the provinces of Quebec, Ontario, and British Columbia where significant pharmaceutical production takes place. The combined federal and provincial corporate income tax rates of Quebec, Ontario, and British Columbia were 39.5 per cent, 44.5 per cent, and 47.5 per cent respectively in 1982. Table 13.3 summarizes the features of the corporate income tax laws of many countries including the United States, Switzerland, the United Kingdom, and Puerto Rico from which most of Canada's pharmaceutical imports originate. Imports of pharmaceutical products are shown in Table 13.4.

Table 13.2
Marginal Tax Rates on Manufacturing and Processing:
Canada, 1982

A. <u>Federal Tax</u>	
Basic Federal Rate	46
Abatement	10
Manufacturing and Processing Deduction	6
	<u>30</u>
Surtax (Reduction)	1.5
Net Federal Rate	31.5
B. <u>Inclusive of Provincial Tax</u>	
Quebec	39.5
Ontario	44.5
British Columbia	47.5

Figure 13.1 illustrates the relationship between foreign tax rates and possible levels of the Canadian tariff that would provide incentives to raise or lower the transfer price of imports into Canada for Canadian subsidiaries subject to taxation in three provinces. It is evident that the Canadian tariff, which currently averages about 10 per cent, reduces the incentive to shift profits out of Canada by transfer price manipulation and increases the incentive to shift them in.

A comparison of incentives to raise or lower transfer prices in Canada was estimated by comparing the taxes payable in Canada, including the sum of corporate income taxes and a 10 per cent import tariff duty, with the taxes leviable in foreign countries and special incentives offered there. The result is shown in Table 13.5. It indicates that, among the major supplying countries, net taxation is higher in the United States than in Canada; this fact would provide an incentive to lower transfer prices and raise profits in Canada. For Switzerland and Puerto Rico, the opposite is the case: net taxation is lower than in Canada, which would lead to raising transfer prices. A comparison of the tax burden with respect to the United Kingdom could not be made owing to regional differences in that country.

The Commission was concerned about whether or not these identified tax incentives had given rise either to increased transfer prices or to a shift in location of production. A test conducted by the Commission indicates that the import share of countries supplying significant amounts of pharmaceutical products to Canada and having a tax advantage over Canada increased from 20 per cent to 27 per cent between 1980 and 1983. These countries are the Bahamas, Hong Kong, Ireland, Italy, Puerto Rico, Spain, and Switzerland. This result does not distinguish between the growth in the value of imports owing to higher transfer prices and the growth owing to shifts in the location of production.

Table 13.3

Provisions of Corporate Income Tax Legislation Applicable to Large Manufacturers, 1983

Country	Base Rate			Taxes on Subsidiaries			State/Local/Province			Withholding		Foreign Taxes		Special Incentives
		D	U	Im	REP	Special	Rate	Credit	Ded.	Accrual	Canada	Deduct	Credit	
Australia	W	46	46	—	X	—	—	—	—	30	15	—	X	yes
Austria	W	27.5	55	—	X	—	14	—	X	20	15	—	X	
Bahamas	W	0	0	—	—	—	—	—	—	—	—	—	—	
Barbados	W	48	48	—	X	—	—	—	—	40	15	—	X	
Belgium	W	45	45	—	X	—	—	—	—	20	15	—	X	
Brazil	L	35	60	—	0	—	—	—	—	25	15	—	—	yes
Denmark	W	40	40	—	X	—	—	—	—	30	15	—	X	
Dom. Republic	L	41	41	—	0	—	—	—	—	18	18	—	—	
Finland	W	43	43	—	X	—	13 to 19	—	X	25	15	—	X	
France	L(W)	50	50	—	—	Tax Havens	—	—	—	25	15	—	—	
Germany (W.)	W	36	56	—	X	Tax Havens	11 to 18	—	X	25	15	—	X	yes
Hong Kong	L	16.5	16.5	—	0	—	—	—	—	0	0	—	—	
Ireland	W	50	70	—	X	—	—	—	—	0	0	—	X	
Italy	W	38.8	38.8	X	—	—	—	—	—	30	15	—	X	
Jamaica	W	45	45	—	X	—	—	—	—	37.5	32.5	—	X	
Japan	W	Varies	(High)	X	—	—	—	—	X	20	15	—	X	yes
Netherlands	W	48	48	—	treaty	—	—	—	—	25	15	—	by treaty	
Norway	W	51	51	—	X	—	—	—	—	25	15	—	X	
Portugal	W	40	52	—	X	—	—	—	—	18	15	—	X	
Puerto Rico	W	45	45	—	X	—	—	—	—	25	25	—	by treaty	
Singapore	W	40	40	—	X	—	—	—	—	0	0	—	X	yes
Spain	W	33	33	—	X	—	—	—	—	16	15	—	X	
Sweden	L	60	60.4	—	0	—	Included	—	—	30	15	—	—	
Switzerland	L	Varies	(Low)	—	0	—	—	—	—	35	15	—	—	
United Kingdom	W	52	52	—	X	—	—	—	—	0	0	—	X	
United States	W	46	46	—	X	—	0 to 12	—	—	30	15	—	X	

Abbreviations: X = applicable 0 = none levied W = world L = local Tax Havens = Income in Tax Haven Subsidiaries taxed as accrued.

Yes = exemption period 3-30 years in specified areas. D = Distributed profits U = Undistributed profits Im = Immediate REP = On Repatriation

Source: Price Waterhouse and Company, *Corporate Taxes, A Worldwide Survey (1913)* (New York: Price Waterhouse and Company, 1983).

Table 13.4
Pharmaceutical Imports, 1980 and 1983

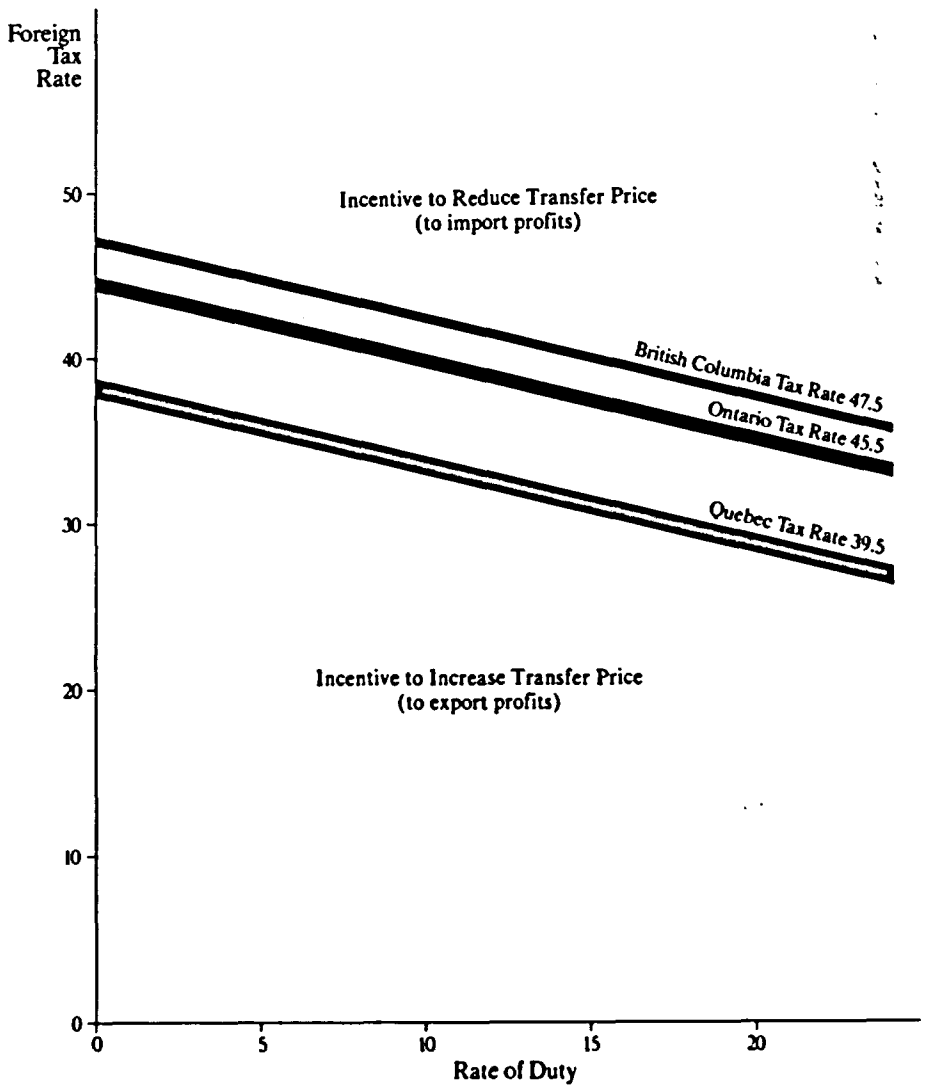
Country of Origin	Imports (\$000)		Per cent of Imports	
	1980	1983	1980	1983
Australia	1,910	3,055	0.5	0.6
Belgium-Luxembourg	4,966	3,317	1.4	0.7
Bahamas	1,661	2,576	0.5	0.5
Brazil	173	1,807	—	0.4
China (Peoples' Republic)	1,435	4,020	0.4	0.8
Denmark	5,904	3,202	1.6	0.7
France	9,792	6,737	2.7	1.4
Germany (W.)	16,981	24,860	4.7	5.2
Hong Kong	1,215	2,227	0.3	0.5
Ireland	3,131	7,293	0.9	1.5
Italy	8,858	9,537	2.5	2.0
Japan	8,511	6,958	2.4	1.5
Mexico	2,347	2,247	0.7	0.5
Netherlands	1,917	2,053	0.5	0.4
Norway	5,850	86	1.6	—
Puerto Rico	27,503	38,320	7.6	8.0
Sweden	6,334	8,435	1.8	1.8
Spain	842	3,223	0.2	0.7
Switzerland	23,916	60,416	6.6	12.7
United Kingdom	48,546	56,896	13.5	11.9
United States	172,500	223,832	47.9	46.9
Yugoslavia	1,086	570	0.3	0.1
Others, each less than \$ 1 million	6,374	5,809	1.8	1.2
Total	359,752	477,387		

Source: Statistics Canada, *Imports* (Catalogue 65-207), 1980, 1983.

Table 13.6 provides the result of a second test which compared the profits of the Canadian subsidiary with those of the parent firm for two groups of countries, one where the net tax incentives are to lower transfer prices to Canada so as to raise Canadian profits and lower foreign profits, and the other where the incentive is in the opposite direction, namely, to raise transfer prices so as to shift profits outward. Adequate data on Canadian subsidiaries and parent companies was available for 23 firms. For 19 firms the parent was located in high net tax jurisdictions and for 4 in low net tax jurisdictions. It turns out that the Canadian profits compared to the parent profits are significantly higher in the first case than in the second. This statistical result would be the consequence of random factors in less than one out of 50 cases.

The statistical evidence indicates that multinational drug companies are able to shift profits by using transfer prices and do so. This evidence is supplemented by the Commission's knowledge of particular cases in which transfer prices charged to Canadian subsidiaries have on occasion increased dramatically when the sourcing or the payment shifted to a low tax from a

Figure 13.1
Relationship Between Foreign Tax Rates and Canadian Tariff



The formula for the critical tax rates is:

$$\text{Foreign tax rate} = \text{Canadian tax rate} - (1 - \text{Canadian tax rate}) \text{ Canadian rate of duty}$$

higher tax jurisdiction. The total effect of such activities on profits in Canada and Canadian tax revenue could not be estimated. Nevertheless, because the Canadian tariff is an impediment to the outward shift in Canadian profits and tax revenue, it should be retained in the absence of good reasons to the contrary.

Table 13.5
Comparison of Taxes Payable in Canada and Other Countries

	Base	Effective Corporate Tax Rate	Incentive Tax Holidays	Incentive to:		Uncertain
				Lower Transfer Prices	Raise Transfer Prices	
Austria	W	27.5-55	No	X		
Australia	W	46	No	X		
Argentina	L	53	Yes		X	
Bahamas	W	0	n.m.f.		X	
Barbados	W	48	Yes		X	
Belgium/Luxembourg	W	45	No	X		
Bermuda	0	0	No		X	
Bulgaria		n.m.f.		X		
Brazil	L	35-60	No	X		
Chile	W	37			X	
China (P.R.)		n.m.f.		X		
Columbia	W	40	No			X
Czechoslovakia		n.m.f.		X		
Denmark	W	40	No		X	
Egypt	W	32	Yes		X	
Finland	W	43	No	X		
France	L	50	No	X		
Germany (W.)	W	36-56	No	X		
Haiti						X
Hong Kong	L	16.5	No		X	
Hungary		n.m.f.		X		
India	W	55-60	Yes		X	
Indonesia	W	35	No		X	
Ireland	W	50-70	Yes		X	
Israel				X		
Italy	W	38.8	No		X	
Jamaica	W	45	Yes		X	
Japan	W	50	No	X		
Korea (S.)	W	33	Yes		X	
Mexico	W	50	No	X		
Netherlands	W	48	No	X		
New Zealand	W	45	No	X		
Norway	W	51	No	X		
Panama	L	50	Yes		X	
Poland		n.m.f.		X		
Portugal	W	40-52	Yes		X	
Puerto Rico	W	45	Yes		X	
Romania		n.m.f.		X		
Singapore	W	40	Yes		X	
South Africa	L	46.2	No	X		
Spain	W	33	No		X	
Sweden	L	60.4	No	X		

Table 13.5 (continued)

Comparison of Taxes Payable in Canada and Other Countries

	Base	Effective Corporate Tax Rate	Incentive Tax Holidays	Incentive to:		Uncertain
				Lower Transfer Prices	Raise Transfer Prices	
Switzerland	L	Low	No		X	
Taiwan	W	35	Yes		X	
Trinidad-Tobago	W	45	Yes		X	
Turkey	W	40	Yes		X	
United Kingdom	W	52	Yes			X
Uruguay	L	30	No		X	
United States	W	46-53	No	X		
U.S.S.R.	W	n.m.f.		X		
Virgin Islands (U.S.)	L		Yes	X		
Yugoslavia		n.m.f.		X		

n.m.f. — No meaningful figure.

Note: Table 13.5 lists countries from which Canada imported significant volumes of pharmaceutical products or materials in 1980 and 1983. The table indicates the tax base, relevant tax rates, and the existence (or non-existence) of incentive tax holidays as reported in Price Waterhouse, *Corporate Taxes—A Worldwide Survey* (New York, 1980). In the last three columns, the direction of incentives to manipulate transfer price is shown. This is based on the tax rate; where incentives, tax holidays are available, it is assumed that the enterprise qualifies for such treatment. Such treatment accounts for the majority of situations where there is an incentive to raise transfer prices. Centrally directed economies in Eastern Europe and Asia are classified as having an incentive to lower transfer prices despite the lack of any meaningful tax rate, because of persistent shortages of hard currencies. A similar assessment has also been made in the case of Israel.

Table 13.6

Sample Statistics: Test of Parent/Subsidiary Profitability Ratios, 1982

	<i>n</i>	Mean	Standard Deviation*
Tax rates favour Reduction in Transfer Price: *	19	2.61	4.16
Tax rates favour Increase in Transfer Price: *	4	-.74	4.36
<i>S_D</i>	= 1.188 *		
<i>t</i> ratio	= 2.82 *		

* Estimated Population Standard Deviations, computed from sample data, where:

$$S = \frac{1}{n-1} [\sum (x_i - \bar{x})^2]$$

where

x_i = the i^{th} observation

\bar{x} = the sample mean

n = the number of observations in the sample [($n - 1$) = the number of degrees of freedom for the estimate]

S_D is the standard deviation of the difference between two sample means \bar{x}_1 and \bar{x}_2 . For samples of size n_1 and n_2 respectively, and sample standard deviations S_1 and S_2

$$S_D = \sqrt{\frac{n_1 + n_2}{n_1 n_2} \times \frac{n_1 S_1^2 + n_2 S_2^2}{n_1 + n_2 - 2}}$$

This statistic is distributed according to Student's "t" distribution with ($n_1 + n_2 - 2$) degrees of freedom.

*t is computed from the formula;

$$t = \frac{\bar{x}_1 - \bar{x}_2}{S_D}$$

The actual value of "t" is 2.52 at the 2 per cent significance level with 21 degrees of freedom. The odds *against* the hypothesis that the populations have the same mean are greater than 50 to 1, given the computed "t" value.

*Companies in the "Reduce Transfer Prices" sample include:

Company	Parent	Country
Organon	Akzo	Neth via U.S.
Ayerst	American Home Products	U.S.
Wyeth	American Home Products	U.S.
Astra	Astra	Sweden
Boehringer Ingelheim	Boehringer Ingelheim	West Germany
Beecham	Beecham	U.K.
Bristol-Myers	Bristol-Myers	U.S.
Cyanamid	Cyanamid	U.S.
Merrell	Dow Chemical	U.S.
Pharmacia	Fortia	Sweden
Hoechst	Hoechst	West Germany
Rorer	Rorer	U.S.
Roussel	Roussel	West Germany via France
Schering	Schering-Plough	U.S.
Smith Kline & French	SmithKline	U.S.
Squibb	Squibb	U.S.
Syntex	Syntex	U.S.
Burroughs Wellcome	Wellcome	U.K.
Eli Lilly	Eli Lilly	U.S.

*Companies in the "Increase Transfer Prices" sample include:

Company	Parent	Country
Ciba-Geigy	Ciba-Geigy	Switzerland
Fisons	Fisons	U.K.*
Hoffman-La Roche	Roche	Switzerland
Sandoz	Sandoz	Switzerland

*Fisons, a U.K. company, is included in the "Increase Transfer Prices" sample because of the proportion of its activities located in development areas offering special tax incentives in the U.K. and Ireland.

The Canadian Tariff

Tariffs have three principal effects. They raise the price of the imported product, of its domestically produced substitutes in the protected market, and encourage a shift in the location of production from foreign locations to the tariff-protected market. The higher prices decrease the amount of consumption. Tariffs are a source of government revenue because they are a tax on the imports that continue after the shift in the location of production.

The shift in location usually reduces the efficiency of world-wide production, because production would take place in the location with the lowest costs were it not for government intervention. If it has any effect at all, the tariff can be presumed to cause a shift of production from the least-cost world location to the protected market. Tariffs do raise prices to consumers and in all but the most exceptional cases reduce consumption below the amount that would take place in their absence. This reduces the effectiveness with which consumers are able to spend their income and their satisfaction from it by inducing them to buy less of the heavily taxed good than they would if its price reflected its costs of production. In so far as imports continue despite the tariff, it provides a source of revenue to the government levied on the consumers of the particular imported commodity, which may not be an equitable basis for taxation.

These distorting effects of tariffs are negligible in the case of imports of active ingredients for drugs into Canada, which amount to about two-thirds of total pharmaceutical imports. The shift in location of production that tariffs encourage has been slight in the case of active ingredients. The evidence is that very little active ingredient production takes place in Canada. Hence the Canadian tariff has not caused production of active ingredients in Canada that is inefficient by world standards.

The Canadian tariff on active ingredients undoubtedly has the effect of raising the costs of production of the final products in Canada and hence of raising their prices. But it is generally recognized that the responsiveness of quantity demanded of drugs to their prices is slight. The reasons are to be found in the low level of information consumers generally have about drugs and the fact that 90 per cent of Canadian drug consumption is by persons who either do not pay themselves for the drugs they consume or are reimbursed for most of their expenditures by governments or private insurers. Hence, the tariff has little effect in distorting consumers' choices.

Most drug purchases are paid for by taxes and insurance premiums. Most individuals pay the taxes that are the import duties on pharmaceutical products, not according to their consumption of drugs, but on more uniform bases of taxation or premiums. Hence, the fiscal inequity implicit in taxation based on what an individual chooses to consume is less for tariffs on pharmaceutical products than is generally the case for other products.

Much the same analysis applies to imports of finished products either in bulk or in packaged form. The duty paid on imports is chiefly paid on the basis

of insurance which applies to the great majority of Canadian consumers and has in consequence the effect similar to a sales tax. The increased price of the drug to consumers does not affect the amount consumed significantly, because of the many factors responsible for consumers' insensitivity.

The tariff does raise the cost of importing finished drugs in relation to local manufacture of final dosage forms and may result in more manufacturing in Canada than the efficient use of Canadian resources overall would call for. However, this consequence of tariff protection of pharmaceuticals is common to that of duties on imports of other manufactured goods into Canada. The Commission does not believe that the tariff on imports of finished pharmaceutical products should be addressed outside the context of the structure of tariffs on all goods and of general tariff negotiations with other countries.

However, another part of Canadian tariff policy demands attention. This is the Special Import Measures Act of 1984 which replaced the Anti-dumping Act of 1969. Generally speaking, dumping is the practice whereby an exporter sets a lower price on the goods he exports than he charges for sales in his home market. Most countries, Canada amongst them, seek to prevent the importation of dumped goods when they injure domestic producers by levying anti-dumping duties that offset the difference between the two prices. They tend to disregard benefits from importing cheap goods to consumers and to manufacturers using the imports as materials and the risk of retaliation by foreign governments against the products of their exporting industries.

Section 14 of the present Special Import Measures Act and Section 7 of the Anti-dumping Act provide that the Governor in Council may make regulations exempting any goods or class of goods from the application of the Act, thereby relieving imports of the possibility of anti-dumping measures. The only major exemption given under Section 7 of the old Act was for pharmaceutical products of a kind not made or produced in Canada. This exemption was dropped in 1984 when new Special Import Measures Regulations were adopted.

The prices of particular drugs vary widely amongst national markets owing to different governmental policies affecting the industry through price controls, subsidies, patent conditions, and other measures. The Canadian price level for drugs is lower than that of some countries and higher than that of others. It seems inequitable in these circumstances of a world drug market fragmented by differing national policies to inhibit exports to Canada from countries with high price levels by the use of anti-dumping duties. The costs of manufacturers in high-priced countries such as Germany and Switzerland are not necessarily high, yet their exports to Canada and the advantages to be derived from them by consumers are threatened by the possibility of anti-dumping action.

The Commission believes that pharmaceutical products should be exempted from the application of the Special Import Measures Act as they were from the application of the Anti-dumping Act that expired in 1984.

It is notable that the Canadian tariff, though mentioned in some briefs and in the Hearings before the Commission, appeared to be thought of little consequence by both representatives of the pharmaceutical industry and of consumers.

In summary, the Canadian tariff on imports of pharmaceutical products probably has less effect on location of production and certainly has less effect on the consumption of drugs than it has on most other products. The tariff has some effect on reducing the incentive given by the structure of taxation in Canada and abroad to transfer profits abroad through transfer pricing to the detriment of Canadian tax revenue. The Commission does not recommend changes in the rates of duty applicable to imports of pharmaceutical products outside general negotiations with foreign governments.

For their part, foreign tariffs against exports of Canadian pharmaceutical products undoubtedly have an inhibiting effect on Canadian manufacturing. This is notably true of the production of active ingredients. For most of these, substantial economies of large-scale production exist as is evidenced by the practice of multinational firms to concentrate production of active ingredients in very few plants to supply the world market. Unless some major offsetting cost advantage exists in a small country, facilities to produce active ingredients are best located inside tariff-free areas with a large share of world consumption, such as the United States area, which includes Puerto Rico, and the European Economic Community.

The Commission was informed at its Hearings that Canadian manufacturers of active ingredients do have a temporary advantage in the manufacture of compulsorily licensed active ingredients. This advantage arises because production could be established in Canada for the Canadian market and be ready to supply the needs of generic manufacturers of the final dosage forms for export abroad when patents on the product expired in foreign countries. This potential would be improved if foreign tariffs were lowered or removed. This factor should be a consideration in future international tariff negotiations.

Chapter 14

Conclusion

Examination and analysis of the pharmaceutical industry in Canada has led the Commission to believe that the thrusts of public policy specific to the pharmaceutical industry as they have developed over the years in Canada are sound. Principal among these policies are health regulations to ensure the safety and efficacy of drugs, compulsory licensing of imports to facilitate entry of new firms into the manufacture of finished products and to increase competition on the basis of price, and provincial rules for substitution and selection of drugs by pharmacists that cause consumers to reap at least part of the potential for lower prices created by compulsory licensing.

Despite the considerable achievements of these policies, the Commission recommends some major modifications and extensions. The process leading to authorization for marketing should become more rapid and more consultative. The terms on which compulsory licences are issued should ensure that the licensing firms pay their share of the research and development and promotion expenditures from which they benefit. Royalties should be distributed to the patent-holding firms in such a way as to encourage research in Canada. Provincial plans should provide consumers with greater knowledge about what drugs are substitutable, greater information on prices, and incentives to seek out cheaper drugs.

These measures would reduce delay in the introduction of new drugs, encourage research in Canada, and ensure that consumers could capture more of the potential benefits of existing policies.

This modified Canadian system for the pharmaceutical industry would make Canada a more attractive site for pharmaceutical production and research. The relative attraction of Canada for the industry compared to other countries will increase further in the foreseeable future because of the growing trend for governments of most industrially advanced countries to interfere directly and forcefully in the activities of the pharmaceutical industry. The purposes of these interventions are to restrict the number of drugs eligible for public reimbursement, thus decreasing profits for the industry and the ability of physicians to prescribe freely, to reduce the profits allowed to the industry, to impose strict controls on prices, to limit expenditures on advertising, and to substitute generic for branded products. Such programs, long in place in France, Italy, and Belgium, are spreading and are becoming more rigorous in countries traditionally regarded as providing especially favourable conditions

for patent-holding firms such as the United Kingdom and West Germany. Most of these restrictions are not applied in Canada.

The more favourable environment in Canada, together with the increase in demand for drugs owing to the aging Canadian population, will probably result in increased manufacturing of final products, and considerably increased clinical research, and perhaps a significant increase in the volume of basic research in the pharmaceutical industry. There are promising opportunities for research based on new technology in fields of special importance and traditional strength in Canada such as the application of biotechnology to animal husbandry. Canadians may develop specialties in which their research excels. But, in the Commission's opinion, Canada is not well placed to become a major world centre for pharmaceutical research or for the production of active chemical ingredients.

APPENDIX A

List of Submissions

The following is an alphabetical list of submissions filed with the Commission of Inquiry on the Pharmaceutical Industry.

Name	Brief No.
A.H. ROBINS CANADA INC. Mr. Harold M. Roman President A.H. Robins Canada Inc. 2360 Southfield Mississauga, Ontario L5N 3R6	104
ABBOTT LABORATORIES, LIMITED Mr. Martin McGlynn President & General Manager Abbott Laboratories, Limited 5400 Côte de Liesse Road Montréal, Québec H4P 1A5	88
ACT FOUNDATION OF CANADA Ms. S.E. Clarke Executive Director Act Foundation of Canada P.O. Box 15937, Station F Ottawa, Ontario K2C 3S8	101
ALBERTA PHARMACEUTICAL ASSOCIATION (THE) Mr. Larry J. Shipka Registrar-Treasurer Alberta Pharmaceutical Association (The) 10615-124 Street Edmonton, Alberta T5N 1S5	39
ALLERGAN INC. Mr. Gordon Politeski President Allergan Inc. 2255 Sheppard Ave. East Suite 414 West Willowdale, Ontario M2J 4Y3	69

Name	Brief No.
ALLERGY INFORMATION ASSOCIATION Ms. M. Susan Daglish Executive Director Allergy Information Association 7-25 Poynter Drive Weston, Ontario M9R 1K8	60
ANAQUEST E. Michael Koshowski National Manager Anaquest Division of BOC Inc. 1 Vulcan Street, Suite 201 Rexdale, Ontario M9W 1L3	99
ARCHAMBAULT, Professeur André Université de Montréal Faculté de Pharmacie Pavillon Principal S728 Montréal, Québec H3C 3J7	26
ASSOCIATION DES FACULTÉS DE PHARMACIE DU CANADA M. Jacques Gagné Président Association des Facultés de Pharmacie du Canada Université de Montréal C.P. 6128, Succursale "A" Montréal, Québec H3C 3J7	57
L'ASSOCIATION DES MÉDECINS DE LANGUE FRANÇAISE Dr Raymond Robillard Directeur général L'Association des médecins de langue française du Canada 510-1440 ouest, rue Ste-Catherine Montréal, Québec H3G 2P9	108
ASSOCIATION OF CANADIAN COMMUNITY PHARMACISTS Mr. D.A. Manore Executive Secretary Association of Canadian Community Pharmacists 321 Kerr Street Oakville, Ontario L6K 3B6	81
ASSOCIATION OF DEANS OF PHARMACY OF CANADA c/o Dr. John W. Steele Dean, Faculty of Pharmacy University of Manitoba Winnipeg, Manitoba R3T 2N2	55

Name	Brief No.
ASSOCIATION OF MEDICAL MEDIA (THE) Mr. Charles E. O'Hearn President Association of Medical Media (The) c/o The Medical Post 777 Bay Street Toronto, Ontario M5W 1A7	46
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