INTERNATIONAL PHARMACEUTICAL INDUSTRY STUDY

A report prepared for Industry Canada

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Maps produced by Queen's GIS Lab.

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INTERNATIONAL PHARMACEUTICAL INDUSTRY STUDY

EXECUTIVE SUMMARY

This study was conducted for Industry Canada in March, 1994. The purpose of the research was to present an overview of the current status of the pharmaceutical industry which will provide the basis for future work on the industry. The focus of this report is the nature and extent of regulation, corporate strategy, and research and development in the international industry.

Three qualifying statements are necessary. First, we use "international" because the study is not truly "global" in the sense that the developing world is not examined in any detail. We focus on the major markets and the leading corporate players in the industry. Second, due to the limited time frame and considerable breadth of this initial study, there is an emphasis on establishing a "snapshot" of the industry and identifying trends that we think will affect the industry in the 1990s. Finally, as many will testify, the pharmaceutical industry is in a state of flux as firms unravel regulatory controls and establish strategies to better effect competitive positions on a globalized scale. We have tried to capture the essence of this dynamism in this study.

The industry is comprised of a number of stakeholders. Governments, industry, consumers and gatekeepers interact with one another to provide effective drug treatment as part of society's commitment to health care. A pharmaceutical product flows through a continuum from the research phase to the end user - the consumer. The nature and extent of research, production and distribution of drugs, however, is a function of the marketplace and it is here that emotions run high as monetary value is attached to therapeutic benefits. Perhaps the most dominant player to date has been the brand-name manufacturer, although as we will suggest, the profitability of brand-name manufacturers is being threatened by a variety of pressures.

Several dominant issues are consistently affecting the industry in different national contexts. Governments are facing increasing pressure to contain healthcare costs, patent legislation is becoming harmonized in the industrialized economies and becoming more so in the developing countries, and most countries have introduced price and/or profit control mechanisms which place increasing threats to the profitability of the major companies.

Companies are responding to these issues in a variety of ways. Rationalization of production, a re-focusing of research on core areas of expertise, increasing use of collaborative relationships, increasing importance being placed on the generic drug sector, wholesaling and distribution and the over-the-counter (OTC) sectors, and a growing awareness that globalized markets are vital to recouping the high costs of R&D. Competition is fierce. In such a dynamic environment, how does a national industry maintain and enhance its competitiveness? It is hoped that this study provides a starting point for answering this question.

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A Typology of the World's Pharmaceutical Industries
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CHAPTER 1. INTRODUCTION TO THE PHARMACEUTICAL INDUSTRY

The 1980s have been characterized as a new "flexible" era of economic activity. Flexible technology in the production process, flexible labour practices and flexible organizational structures have contributed to the increasing complexity of industrial activity as firms develop new competitive positions in the global marketplace. There are many different theoretical interpretations of the changing industrial environment - for example, the flexible specialization school (Hirst and Zeitlin,1990; Piore and Sabel,1984), regulation approaches (Boyer,1989; Harvey,1989; Leborgne and Lipietz,1988), and techno-economic models which embrace long wave theories of economic cycles (Freeman and Perez,1988).

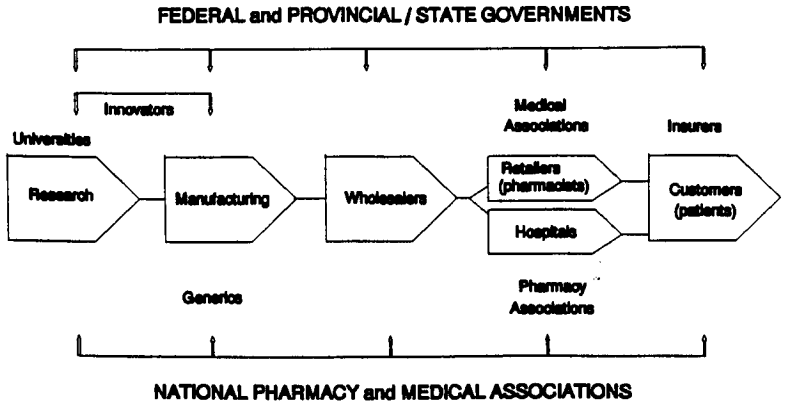
Irrespective of which theoretical approach is taken, however, the recurring message is that over the 1980s and 1990s something different is happening in the nature of production and consumption patterns in the industrialized world. Industries have been engaged in a process of restructuring as new technologies enter the working environment in all aspects. The pharmaceutical industry is no exception. As costs rise and profitability becomes less and less certain, dominant corporations are looking for new ways to maintain a strong presence in the global industry. Restructuring also offers opportunities for smaller firms to take advantage of market and product specialization and the new computer technologies now available. At the same time, nations are under increasing pressure to contain rising costs in health care, and the pharmaceutical industry is not immune to the changing political, economic and societal concerns.

The purpose of this report is to provide an overview of the international pharmaceutical industry as of early 1994. Three qualifying statements are necessary. First, we use "international" because the study is not truly "global" in the sense that the developing world is not examined in any detail. We focus on the major markets and the leading corporate players in the industry. Second, due to the limited time frame and considerable breadth of this initial study, there is an emphasis on establishing a "snapshot" of the industry and identifying trends that we think will affect the industry in the 1990s. Finally, as many will testify, the pharmaceutical industry is in a state of flux as firms unravel regulatory controls and establish strategies to better effect competitive positions on a globalized scale. We have tried to capture the essence of this dynamism in the chapters that follow.

The context

The "pharmaceutical industry" is comprised of a number of stakeholders, as illustrated in Figure 1.1. Governments, industry, consumers and gatekeepers interact with one another to provide effective drug treatment as part of society's commitment to health care. A pharmaceutical product flows through a continuum from basic research to the end user - the consumer. The nature and context of research, production and distribution of drugs, however, is a function of the marketplace and it is here that emotions run high as monetary value is ascribed to therapeutic benefits. Perhaps the most dominant player to date has been the brand-name manufacturer, although as we will suggest, the profitability of the brand-name manufacturer is being threatened by a variety of pressures.

Figure 1.1 Pharmaceutical Industry Stakeholders



Source: Gordon and Maule (1989).

It is also important to remember that although the industry is global it is concentrated and dominated by firms and countries in the industrialized world. This, as Tables 1.1 and 1.2 suggest, are where the major markets are located. In more visual form, the global consumption and production of pharmaceuticals is shown on the maps at the end of this chapter.

Table 1.1 Drug expenditures per head, selected countries

COUNTRY	EXPENDITURES PER HEAD (U.S. $)	COUNTRY	EXPENDITURES PER HEAD (U.S. $)
Japan	412	Brazil	16
Germany	222	Philippines	11
United States	191	Ghana	10
Canada	124	China	7
United Kingdom	97	Pakistan	7

COUNTRY	EXPENDITURES PER HEAD (U.S. $)	COUNTRY	EXPENDITURES PER HEAD (U.S. $)
Norway	89	Indonesia	5
Costa Rica	37	Kenya	4
Chile	30	India	3
Mexico	28	Bangladesh	2
Turkey	21	Mozambique	2
Morocco	17		

Source: **World Bank (1993:145)**

Table 1.2 World consumption of pharmaceutical products

REGIONAL GROUPS	SHARE IN WORLD POPULATION 1990	SHARE IN WORLD PHARMACEUTICAL CONSUMPTION 1975	1990	AVERAGE PER CAPITA CONSUMPTION OF PHARMACEUTICALS* 1975	1990
Eastern Europe & USSR	7.20	10.60	9.30	21.80	37.10
Developed market econ.	15.90	65.40	71.70	60.60	130.70
North America	5.40	20.50	23.00	58.60	123.90
EC	6.30	26.00	22.50	57.00	102.90
Other Europe	0.60	2.30	1.80	51.50	85.70
Japan	2.40	15.00	23.00	92.00	276.60
Others	1.20	1.60	1.40	24.40	35.60
Developing countries	76.90	23.90	18.90	5.70	7.10
Latin America & Caribbean	8.50	7.70	6.00	16.80	20.30
North Africa	2.80	1.00	0.90	7.40	9.00
Other Africa	9.00	2.00	1.00	4.70	3.30
South & East Asia	32.00	4.80	5.60	2.80	5.00
China	21.70	5.70	3.60	4.30	4.80
Others	2.90	2.70	1.80	18.20	18.00
World	100.00	100.00	17.20	28.90	

* = 1980 dollars

Source: Ballance et al (1992:30-31).

Similarly, production is concentrated in the industrial world with Japan increasing its level of production considerably over the past 15 years (table 1.3).

Table 1.3 World distribution and growth of production of pharmaceuticals, 1975-1990.

COUNTRY	PERCENTAGE SHARE IN WORLD TOTAL PRODUCTION 1975	1990	GROWTH RATE (%) 1975-1990
Eastern Europe & USSR	10.20	8.60	4.00
Developed market econ.	67.20	73.00	5.80
North America	20.40	22.70	5.90
EC	28.60	24.30	4.10
Other Europe	2.70	2.60	5.00
Japan	14.20	22.30	8.40
Others	1.30	1.10	4.10
Developing countries	22.60	18.40	3.80
Latin America & Caribbean	10.00	7.90	3.50
North Africa	0.50	0.40	3.60
Other Africa	0.80	0.40	0.90
South & East Asia	3.60	4.90	7.30
China	5.60	3.50	2.10
Others	2.10	1.30	1.80
World	100.00	100.00	5.20

Source: Ballance et al (1992:23).

The major markets continue to be the US, UK, Japan, Germany, Italy and France. Other countries, however, particularly the so-called newly industrialized countries, have shown considerable growth in the pharmaceutical market. South Korea and Brazil, for example, had growth rates of 15% and 19% respectively from 1992 to 1993 (table 1.4).

Table 1.4 Top ten pharmaceutical markets in 1993.

MARKET	% WORLD MARKET	% GROWTH
US (1)	29	6
Japan (2)	18	3
Germany (3)	9	5
France (5)	7	8
Italy (4)	6	5
UK (6)	3	13
Spain (7)	3	11
Canada (8)	2	9
Brazil (9)	2	19
South Korea (-)	2	15
Others	19	15

Figures in ( ) represent 1992 market position.

Source: Scrip Magazine (January,1994:32)

The corporate players

Although global in consumption and production, profit is concentrated in six countries. As the maps illustrate, the innovative national industries are based in the major industrialized countries. Some countries have innovative potential but need to instill an appropriate mix of regulation and incentives for the industry to develop. Essentially the industry is dominated by firms based in the US, Switzerland, Germany, Japan and the UK (table 1.5). All but 3 of the top 15 companies in 1993 had increases of over 10% in sales from the previous year. Some (Pfizer, Hoffman-La Roche and SmithKline and Beecham) had an increase of over 16% (Thorpe,1994).

Sales have become increasingly global, foreign ownership of national markets is increasing and linkages are being established globally to effect greater market share and enhance research capabilities. At the same time it needs to be recognized that pharmaceutical sales as a percentage of total sales differs from company to company. Redwood (1987) notes that of 110 top firms surveyed, about 47% had less than half of total sales in pharmaceuticals while 53% had more than half. Firms come from other major industries such as chemicals and health related products.

Table 1.5 Leading pharmaceutical companies and their sales

	1992		1980	
COMPANY	Rank	Sales ($)	Rank	Sales ($)
Merck & Co. (US)	1	8,214.50	2	2,200.00
Glaxo	2	7,986.40	16	1,000.00
BMS (US)	3	6,313.00	8	2,300.00 (a)
Hoechst (Ger)	4	6,042.10	3	2,000.00 (b)
Ciba (Sw)	5	5,192.00	4	1,800.00
SKB (UK)	6	5,100.50	17	1,800.00 (c)
Roche (Sw)	7	4,896.90	1	3,100.00
Sandoz (sw)	8	4,885.50	7	1,400.00
Bayer (Ger)	9	4,669.90	5	1,600.00
AHP US)	10	4,589.30	6	1,500.00
Pfizer (US)	11	4,557.90	10	1,300.00
Lilly (US)	12	4,536.50	12	1,200.00
J & J (US)	13	4,340.00	25	700.00
RPR (US)	14	4,095.90	14	1,000.00 (d)
Abbott (US)	15	4,025.00	21	800.00

(a) Combination of Bristol-Myers & Squibb
(b) Excluding Roussel.
(c) Combination of SmithKline & Beecham.
(d) Without Rorer.

Sales are in million of dollars (US.)

Source: Scrip Magazine (January,1994:34-35).

The catalyst, or driver, of profitability in the pharmaceutical industry is research. Estimates of the costs of R&D to bring a new product to the market range from US$100 million to $350 million. Between 1976 and 1990 the cost of launching a new drug rose from US$54 million to an estimated $230 million. In 1989 the 20 leading research companies allocated a total of US$15 billion to R&D (Drews,1993).

Central to the viability of a manufacturer is the maintenance of a healthy product pipeline. As Table 1.6 shows, the major corporations leading in the number of products being researched are Ciba-Geigy, Bristol-Myers Squibb, Merck and Eli Lilly. In addition to providing numbers of drugs (but not market potential of these), the table also illustrates the rise in R&D by Japanese firms over the 1980s when compared to their American and European competitors.

Table 1.6 Research and development rankings of the leading companies, 1980-1993.

Company	R&D 1993 In US $m	% R&D Sales 1993	Rank 1993 #drug	# R&D drugs	1990	# R&D drugs	1988	# R&D drugs	1986	# R&D drugs	1984	# R&D drugs	1982	# R&D drugs
Ciba	n/a	n/a	1	116	6	104	9	88	4	88	1	85	9	49
BMS	972	14.90	2	110	2	145	4	101	3	95	2	84	2	82
Merck	1,170	11.15	3	104	4	114	1	109	2	98	5	75	4	72
Eli Lilly	954	14.67	4	104	7	102	8	89	8	75	8	61	8	56
NIH	\	\	5	101	\	\	\	\	\	\	\	\	\	\
SKB	732	14.20	6	97	1	148	7	90	5	85	15	54	21	40
Roche	>1,240	23.56	7	87	5	110	6	90	9	75	3	83	1	100
Sandoz	>801	>16.2	8	86	22	60	13	71	17	59	12	57	11	47
Warner	380	18.00	9	85	13	75	11	75	6	80	13	56	19	41
J & J	1,200	8.5	10	84	8	97	2	108	10	73	7	68	7	56
AHP	663	7.98	11	79	9	91	18	57	14	63	6	73	5	66
Hoechst	n/a	n/a	12	78	10	90	10	83	1	104	4	80	3	73
Upjohn	566	18.80	13	76	17	68	15	61	13	64	14	55	6	64
RPR	561	14.05	14	74	3	136	3	103	12	65	9	60	13	43
Glaxo	1,093	18.00	15	67	34	44	14	51	43	27	59	19	44	19
Merrell	451	16.0	16	66	11	84	19	56	24	43	17	53	17	41
Fuji	357	14.80	17	64	12	83	12	72	22	50	28	34	29	32
Wellcome	482	15.90	18	61	23	59	22	52	7	77	19	53	28	32
Am.Cya	596	13.9	19	61	16	73	26	49	29	41	39	26	35	26
Yama.	360	n/a	20	61	20	65	36	43	36	32	51	22	40	21
Pfizer	888	14.30	21	60	18	66	27	49	21	51	26	38	22	38
Boehr	n/a	n/a	22	60	24	57	21	56	15	62	18	53	12	45
Chiron	\	n/a	23	58	75	23	65	25	51	24	56	20	\	\
Rous.	\	n/a	24	58	14	74	28	49	19	56	10	60	10	48
Sch.P	578	13.30	25	57	38	42	35	43	25	43	30	34	15	42
BTG	\	\	26	56	48	31	75	22	\	\	\	\	\	\
Abbott	881	10.48	27	56	26	55	43	37	47	26	42	25	41	21
Takeda	557	8.28	28	54	25	55	14	64	11	72	16	53	18	41
Monsa	620	7.80	29	53	37	43	32	46	20	55	\	\	\	\
EMerck	221	14.06	30	53	56	29	84	20	81	17	86	14	53	17
Sanofi	414	19.60	31	49	29	50	20	56	23	47	25	39	34	26
Elan	\	\	32	47	\	\	\	\	\	\	20	49	69	13
Sch.AG	\	\	33	47	27	53	16	58	16	59	21	49	26	34
Zeneca	429	15.49	34	45	\	\	\	\	\	\	\	\	\	\

Company	R&D 1993 In US $m	% R&D Sales 1993	Rank 1993 #drug	# R&D drugs	1990	# R&D drugs	1988	# R&D drugs	1986	# R&D drugs	1984	# R&D drugs	1982	# R&D drugs
Kodak	\	\	35	45	33	47	29	48	\	\	\	\	\	\
Genen.	299	65.00	36	43	28	50	37	41	37	31	47	22	77	12
Erba.	\	\	37	41	21	63	17	58	26	42	22	43	24	34
Kabi	\	\	38	40	73	24	70	24	89	15	75	16	85	11
Kyowa	\	\	39	40	32	47	41	38	44	27	29	34	27	33
Scios	\	\	40	39	\	\	\	\	\	\	\	\	\	\

Reference for Chart on "Research and Development ranking of Top Companies"
Abbreviations:

Ciba	Ciba-Geigy	Am.Cya	American Cyanamid
BMS	Bristol-Myers Squibb	Yama	Yamanouchi
Merck	Merck & Co.	Boehr	Boehringer Ingelheim
NIH	US NIH	Rous	Roussel Uclaf
SKB	SmithKline Beecham	Sch.P	Schering Plough
Roche	Hoffman La Roche	Monsa	Monsanto
Warner	Warner-Lambert	Sanofi	Elf Sanofi
J & J	Johnson & Johnson	Sch.Ag	Schering AG
AHP	American Home Products	Kodak	Eastman Kodak
Hoech	Hoechst	Genen	Genentech
RPR	Rhone-Poulenc Rorer	Erba	Erbamont
Merrell	Marion Merrell Dow	Kabi	Kabi Pharmacia
Fuji	Fujisawa	Kyowa	Kyowa Hakko
Well	Wellcome	Scios	Scios Nova

Notes Pertaining to Separate Years' Entries:

1990
- SmithKline Beecham was two separate companies until merge in '90.
- Bristol-Myers Squibb was two separate companies until merge in '90.
- Rhone-Poulenc was two separate companies until merge in '90.
- The figure for Merrell Dow is listed with Merrell. It does not include Marion which was not listed.

1988
- BMS = Bristol-Myers. Squibb was in position 38, with 40 R&D drugs.
- RPR = Rhone-Poulenc. Rorer was in position 62, with 26 R&D drugs.
- SKB = SmithKline. Beecham was in position 31, with 46 R&D drugs.
- Merrell = Merrell Dow. Marion not listed. The figure for Kodak includes products of Sterling Drug.

1986
- Merrell = Dow Chemical. Marion Labs was in position 98, with 13 R&D drugs
- BMS = Bristol-Myers. Squibb was in position 31, with 38 R&D drugs.
- SKB = SmithKline. Beecham was in position 18, with 57 R&D drugs.
- RPR = Rhone-Poulenc. Rorer was in position 58, with 24 R&D drugs. Kabi = Kabivitrum. Kabi a separate entity in 1988.

1984
- Merrell = Dow Chemical. Marion Labs was in position 87, with 14 R&D drugs.
- BMS = Bristol Myers. Squibb was in position 43, with 24 R&D drugs.
- SKB = SmithKline. Beecham was in position 11, with 57 R&D drugs.
- RPR = Rhone-Poulenc. Rorer was not listed. Kabi = Kabivitrum.

1982
- BMS = Bristol-Myers. Squibb was in position 30, with 30 R&D drugs.
- RPR = Rhone-Poulenc. Rorer was not listed.
- SKB = SmithKline. Beecham was in position 20, with 40 R&D drugs.
- Merrell = Dow Chemical. Marion Labs not listed. Kabi = KV Pharma.

Source: Scrip Magazine, Scrip, various issues and London Financial Times, March 23, 1994

Products

The major therapeutic categories for product development in 1993 were anti-cancer, other (338 compounds), anti-inflammatory (277), anti-asthma (255), anti-cancer, immunological (253), anti-viral,anti-HIV (231), recombinants,other (210), vaccine (202) and cardiovascular (201). The 231 anti-AIDS drugs in development represents a 15% increase on the number being developed in 1992 (Davis,1994a).

Four new chemical entities (NCEs) which have the potential to become blockbusters were introduced in 1993. "Blockbuster drugs" (those with over US$750 million in sales per annum) are very rare. There were only 14 of these between 1969 and 1990, 9 of which obtained sales of over US$1 billion (Redwood,1993a:13). These were developed by just 10 companies. The potential blockbusters in 1993 were Betaseron (Berlex's multiple sclerosis therapy), Cognex (Warner Lamberts Alzheimer's therapeutic), Taxol (Bristol-Myers Squibb's product for ovarian cancer), and FK-506 (Fujiasawa's immunosuppressant) (Davis,1994b).

Thirty-nine NCEs were introduced onto the market in 1993. Twelve of these were developed by Japanese firms, 11 by US companies and 4 each from companies based in Germany and Switzerland. Warner-Lambert and Johnson & Johnson each introduced 3, while Bristol-Myers Squibb and Ciba Geigy each introduced 2. Of these 39, 10 were for the anti-infective therapeutic category, 7 for central nervous system disorders, 5 were cardiovascular products and 5 were anti-cancer drugs. Table 1.7 outlines the expenditures on pharmaceutical products by region for the major therapeutic classes.

Table 1.7 Percent of Expenditures on Pharmaceutical Products by Region for Major Therapeutic Classes, 1988.

Therapeutic Class	Europe	North America	Africa/Asia/ Australasia	Latin America
Cardiovascular	22%	17%	13%	11%
Alimentary Tract and Metabolism	16	15	18	18
Anti-infectives	11	13	19	15
Central Nervous System	11	14	7	12
Respiratory System	9	9	6	11
Muscular-skeletal	6	6	8	7
Blood and blood-forming organs	6	4	8	2
Dermatologicals	5	6	3	7
Genito-urinary system	4	6	2	5
Other	10	10	15	11
Total	100%	100%	100%	100%

Note: may not add to 100 due to rounding. Source: Rapp and Rozek (1990:27).

The pharmaceutical industry in the 1990s

Several critical factors will affect the functioning of the industry in the 1990s. For the brand-name manufacturers there are potential threats to profitability:

- governments continue to contain health care spending
- firms recognize the need to adjust their product lines in keeping with changing markets
- generic drug competition is increasing
- growing levels of integration between wholesalers and retailers with generic drug producers
- consumer activism against certain drugs
- increasing costs of R&D.

There are, however, positive signs in the 1990s:

- the demographic profile of the industrialized world suggests an affluent, aging population (hence potential increasing demand for brand-name products)
- there is growing harmonization of patent protection and regulatory procedures
- still considerable research to be conducted on drug therapy for genetic disorders
- there is likely to be an increasing demand for drug products in newly industrializing countries.

The future of the Canadian pharmaceutical industry will be based on the inter-relationships of these critical factors.

The Canadian context

Canada has a relatively small percentage of the world's production and consumption of pharmaceuticals. Despite this, most of the major manufacturers have some form of operations in Canada (table 1.8 outlines the R&D-to-sales ratio for the major global firms in Canada). With recent changes to the patent legislation through Bill C-22 and Bill C-91 it is hoped that further R&D investment will flow into Canada even though it has been well documented that this will increase the costs of providing drug products to the Canadian population - a trade-off that has been the focus of heated debate and emotions amongst politicians, consumers and drug manufacturers.

Brand-name manufacturers have assured the Canadian government that they are, and will be, increasing the level of R&D in Canada and data from the Patented Medicines Prices Review Board tend to support this so far (table 1.9). But it is difficult to fully understand the role that Canada, as a location for R&D, plays in the global industry without answering some key questions regarding corporate strategy, appropriate regulatory mix and the nature of the "ideal" research environment. These are **BIG** questions that warrant further, more intensive investigation than the time for this current study permits.

Table 1.8 Ratio of R&D-to-sales of selected firms in Canada, 1988-1992.

COMPANY	RESEARCH & DEVELOPMENT - TO - SALES RATIO (%) 1992	1991	1990	1989	1988
Abbott	5.40	4.40	4.70	5.80	2.90
Boehringer Ingelheim	44.80	41.00	38.30	30.20	13.60
Bristol-Myers Squibb	12.00	9.80	9.10	***	11.50
Ciba-Geigy Canada	7.70	8.10	7.70	6.30	5.70
Eli Lilly Canada	9.80	8.20	6.50	6.30	5.20
Glaxo Canada	9.50	9.20	8.80	6.60	3.80
Hoechst Roussel Canada	9.00	*	4.50	5.90	4.60
Hoffman-LaRoche	14.50	14.10	12.80	9.40	7.80
Johnson & Johnson	10.40	11.50	12.40	9.30	8.60
Marion Merrell Dow	9.10	9.40	6.0**	5.80	4.60
Merck Frosst Canada	10.30	11.60	11.10	10.00	8.50
Pfizer Canada	9.00	11.10	8.60	7.60	6.00
Rhone-Poulenc Rorer	3.90	4.50	6.80	****	14.0@
Sandoz Canada	12.10	12.10	11.60	10.20	10.20
Schering Canada	7.30	9.10	8.80	7.90	5.80
SmithKline Beecham	11.40	9.40	8.70	#	6.40
Upjohn Canada	7.80	7.30	6.40	5.60	4.00
Warner-Lambert Canada (Parke Davis)	12.00	11.10	11.50##	10.60	11.60

Source: Patented Medicines Prices Review Board, annual reports.

Legend to Table of Ratios of Expenditures to Sales Revenue

* Hoechst Canada and Roussel Canada merged in 1992. The R&D Sales ratios for Hoechst Canada and Roussel Canada in 1991 were 6.0% and 7.0% respectively.

** Merrell Dow Pharmaceutiacls Canada and Nordie Lab. merged in 1991 to form Marion Merrell Dow Cnada. Nordie Lab. was not a patentee in 1990.

Warner-Lambert Canada includes Otsuka Pharmaceuticals Co. in 1990.

*** Bristol-Myers merged with Squibb Canada in 1990. The 1989 ratios for Bristol-Myers and Squibb Canada were 13.6% and 4.8% respectively.

**** Rhone-Poulene Pharma and Rorer Canada merged in 1990. Rhone-Poulene was not a patentee in 1989. The R&D sales ratio for Rorer Canada was 10.9% in 1989.

SmithKlein and French Canada and Beecham Lab. filed separate R&D reports for the 1989 reporting period. The 1989 R&D sales ratios for the two companies were 6.4% and 12.7% respectively.

@ This figure is for Rorer Canada.

Table 1.9 PMAC member's R&D spending by type of research ($ millions).

Type	1992	1991	1990	1989	1988	Total
Basic	113.9	94.2	78.4	53.5	30.3	370.3
Clinical	281.2	261.0	210.0	175.1	128.3	1055.6
Capital	24.1	21.2	17.1	16.2	7.1	85.7
Total	419.2	376.4	305.5	244.8	165.7	1511.6

Source: PMAC (1993:16).

It is hoped that this report provides the foundations for a larger study which looks at many of the issues raised in greater detail. The following chapter presents an overview of the current regulatory environment internationally and also in 11 national markets. This sets the framework for examining the corporate strategies of the major brand-name manufacturers and the issues that are influencing their decision-making process. Chapter Four then focuses more directly on the nature of R&D, and this is followed by a short concluding chapter which re-visits the major observations raised in the preceding sections. While we feel the study provides a comprehensive overview of the industry there are clearly many issues which require closer inspection to understand how Canada "fits" into the dynamic industrial environment.

A Typology of the World's Pharmaceutical Industries

Source: Ballance et al, 1992

Percent Share of World Pharmaceutical Production, 1990

Source: Ballance et al, 1992

Percent Share of World Pharmaceutical Consumption, 1990

Source: Ballance et al, 1992

CHAPTER 2. REGULATORY MECHANISMS IN THE INDUSTRY

2.1 INTRODUCTION

This chapter examines how regulatory mechanisms are currently impacting on the pharmaceutical industry in the following countries: Australia, Denmark, France, Germany, Italy, Japan, Netherlands, South Korea, Sweden, United Kingdom and the United States. In total, these countries represented over 66% of the world's total consumption of pharmaceuticals in 1990 and 65% of total production (table 2.1). In addition to profiling each of these countries the chapter examines the effects of the European Community, NAFTA (North American Free Trade Agreement) and the GATT on regulatory mechanisms in the industry.

Table 2.1 Percentage of world consumption and production of pharmaceuticals in 1990, selected countries.

Country	Consumption	Production
Australia	0.67	0.51
Canada	1.49	1.34
Denmark	0.22	0.45
France	5.69	6.34
Germany	6.08	6.50
Italy	3.92	3.69
Japan	23.3	22.30
Netherlands	0.70	0.64
South Korea	0.97	1.00
Sweden	0.51	0.75
United Kingdom	2.52	3.14
United States	21.55	21.31

Source: Ballance, Pogany and Forster (1992:226-233).

Virtually all industrial countries provide patents on products and processes for a period of 20 years. Since the mid 1970s there has been a gradual shift towards a harmonized system of patent protection throughout the industrialized countries. Until very recently there were several countries in the industrialized world that gave no product patents.

Patents are typically for 20 years but because of regulatory requirements effective life is about 8 years. Redwood (1992) notes that effective patent life for the top 100 drugs in the US was decreasing from the 1970s to 1988, and that the patented products are seldom profitable until long into their patent term. Pressure has thus been placed on governments to extend the effective patent life of products. About 70% of R&D in drugs by US firms abroad is in western Europe, but the share in other strongly patent protected countries such as Japan and Australia is growing. Pressure is also being put on newly industrialized countries such as Brazil and India to develop patent protection regulation (Rapp and Rozek,1990).

There are differing views on patent protection. The brand-name research based industry and governments where the industry is strong are supporters of stronger patent protection while a wide range of health providers, and other parts of the "government body" stress the need to curb the costs of health care. The other opponents of patent protection are the developing countries which simply can not afford the cost of pharmaceuticals in health care. Patent protection has become a national and international football which the stronger, more resource-endowed players can play with to their advantage.

Patents provide market exclusivity for a limited time only. Despite this, patented products still find competition in their respective therapeutic markets. The narrow definition of market exclusivity should not be confused with monopoly power. There are often close substitutes (for example, Tagamet and Zantac in the anti-ulcers therapeutic category and Intron-A and Roeferon in the interferon products), although they may not be assumed equally safe and effective for every patient (Rapp and Rozek,1990).

Using regression analysis Rapp and Rozek (1990) show that the level of economic development correlates closely with the level of patent protection. Pharmaceutical R&D is shown to be conducted in the countries where intellectual property is protected. Where patent protection has been increased the level of R&D has also increased.

In addition to patent protection, price controls and "good manufacturing practices" (GMP) represent additional forms of regulation affecting the industry. GMPs are guidelines for quality assurance in the pharmaceutical industry and focus on the manufacturing, processing and packaging of drug products to ensure products are safe. The manufacturing process must be monitored and facilities proven safe and conforming to certain standards. The World Health Organization has developed guidelines which most countries conform to, although some industrial countries have even tighter regulations for GMP (see chapter three).

By far the most dominant intervention affecting the industry in many countries, however, is the use of price control mechanisms. Pricing policy is having a direct effect on the level of investment, employment and rate of return where it has been put in place. The UK firm, Burroughs-Wellcome, for example, opened a plant in southern France and was content to run it at half capacity to gain price advantages for its products through French government policy. Similarly, in response to the Limited List in the UK in 1984 and other reform suggestions US multinationals moved operations to France. G.D Searle (part of Monsanto) closed its main R&D and manufacturing centre in the south of England. French government incentives were also important in Eli Lilly reversing a decision and building a new high tech plant in France instead of the UK (Howells, 1990).

Governments have the ability to influence the size of profits and distribution in the market through price controls. To some observers, ".....society must resolve the trade-off between the degree of regulation and ease of therapeutic competition. This decision is likely to have greater influence on pharmaceutical prices than the strength of patent protection"(Rapp and Rozek, 1990:33). There are a variety of models of price regulation in industrialized countries - pricing freedom, product-by-product price control, partial pricing freedom, reference prices and profit control.

Table 2.2 outlines the regulatory environment of the 11 countries surveyed in this report. As the table shows, most countries now provide considerable patent protection but the nature and extent price controls vary. Recent changes to national markets brought about mainly through health care reforms has meant that many national industries are in a state of flux. What follows in the country profiles, therefore, is a snapshot and interpretation of the industries which will likely change in the near future.

Table 2.2 Profile of Regulation in Selected Countries.

Country	Patent Term (a)	Extra Patent Protection	Orphan Drug Approval	Number of Regulating Bodies	Sub-national Regulations	Manufacturing Guidelines	Public sector % of drug expenditure (f)	comparison of % growth rates of health care and drug expend. (g)	Price Controls
Australia	16-20 years	4 years	No	One	Yes	WHO	50%	DE > HC	Limited
Denmark	20 years	6 years	Yes (EC)	One	No	PIC (b), WHO	43%	HC > DE	Limited
France	20 years	5 years	Yes	Six	No	WHO	61%	DE > HC	Substantial (c)
Germany	20 years	5 years	No	One	Yes	WHO	69%	DE > HC	Limited
Italy	20 years	5 years	Yes	One	No	WHO	66%	DE > HC	Substantial
Japan	15-20 years	5 years	Yes	na	na	WHO	81%	HC > DE	Limited
Netherlands	20 years	5 years	na	na	na	Local	67%	DE > HC	Limited
South Korea	15 years	na	na	na	na	GMP	na	na	Substantial
Sweden	20 years	5 years	No	One	No	PIC, WHO	na	DE > HC	Substantial
United Kingdom	20 years	5 years	Yes	na	No	Local, PIC, WHO	78%	HC > DE	Limited (d)
United States	17 years (e)	5 years	Yes	Two (major)	Yes	FDA Regulation	11%	HC > DE	Limited

Notes:
a) refers to from date of application;
b) European Free Trade Association pharmaceutical inspection convention;
c) excessive profits can lead to price modifications;
d) if profit margins are above or below a certain % margin prices are modified;
e) from date of grant;
f) 1990 data, source -Redwood (1993a:35);
g) percentage growth rates of health care and pharmaceuticals between 1980-1990, Source - Redwood (1993a:51)

Source : Based on correspondence with Industry Associations and Government organizations, and Ballance, Pogany and Forster (1992:142-145).

- Stronger intellectual property protection was recently negotiated as part of the Uruguay Round of GATT (General Agreement on Tariffs and Trade).

- Harmonization of patent protection is a central objective of the industrial countries in which the pharmaceutical industry is based.

- Patent term restoration has now been put in place in the United States (1984), Japan (1988), France (1990), Italy (1991) and the rest of the European Community (1993).

- As harmonization of the patent term develops there will be increasing importance placed on the mechanisms for price controls in pharmaceutical producing countries.

Discussion:

Intellectual Property Protection, that is, the ability to retain exclusive marketing ownership for the originators or inventors, covers patents, copyrights, trademarks, trade secrets and proprietary technical data. The most obvious advantage of patent protection is that it encourages researchers and companies to take risks in developing new products. The Pharmaceutical Manufacturers Association in the United States, for example, claims that about 90% of the prescription drug products in the US may not have been made had it not been for the market exclusivity of patent protection (PMA, Ind Brief,16th Jan,1993:2).

The US, Japan and the EC now restore up to 5 of the 8-10 years of effective life that is lost in the patenting process. The US provides a maximum effective patent life for 14 years while the EC provides 15. France, Italy and Japan now provide more protection - in part, Redwood (1992) claims, because their industry's competitiveness has fallen behind other industrial countries due to the lower level of patent protection.

Negotiations have taken place on TRIPS (trade-related intellectual property protection) as part of the Uruguay Round of GATT. The objective of these negotiations was to develop stronger IPP than that in use through the Paris Convention of the World Intellectual Property Organization. GATTs former Director General, Arthur Dunkel, issued his own proposal which was subsequently adopted. This included 20 years of patent protection for pharmaceuticals, strict limitations on compulsory licensing, and strict enforcement of intellectual property rights

With the TRIPS text confirmed and the successful completion of the Uruguay Round of GATT, the decision of the G7 summit in Tokyo (1993) to cut tariffs (including pharmaceuticals and medical equipment) will go ahead. The OECD estimates that the tariff cuts will result in savings of US$8 billion a year for the chemical and pharmaceutical industries and up to US$20 million a year for major pharmaceutical companies (Scrip,24th/28th,1993:19) (Dower,1994).

Despite general approval for the length of patent protection the proposal has been criticized for the following reasons;

- It does not provide an immediate time frame for action.

- It allows countries that do not have patent laws 10 years to enact them.

- To many developing countries it is the "developed world's" intervention in a sovereign nation's rights to suit their own purposes.

- Patent laws created through the proposal do not have to cover products already patented in another country but not yet marketed in that country (commonly called "pipeline protection").

This latter point could enable the so-called "pirate developing countries" such as Brazil and India (which are also large markets), to continue production of products patented in the rest of the world (PMA, Ind Brief,16th Jan,1993:3; PMA, News Release, 22nd Feb,1994).

Questions:

- With harmonized patent protection being developed how can Canada take advantage of a more level playing field to attract pharmaceutical investment?

- As newly industrialized countries develop greater levels of protection will drug producing companies find these countries increasingly attractive locations for investment and manufacturing?

- What strategies could Canadian-owned companies adopt to take advantage of new, potentially large markets in the industrializing countries?

- What could be the negative effects for the Canadian industry of greater patent protection in the newly industrialized countries?

2.3 EUROPEAN COMMUNITY

- The European community member states have adopted several health reform, drug pricing and cost-containment measures that have impacted upon the industry (see country profiles - section 2.6).

- The European Commission has adopted the use of a Supplementary Protection Certificate to provide patent term restoration.

- Many firms have restructured and re-organized their operations in Europe as a result of the changing regulatory environment (see Chapter Three - Corporate Strategy).

- More generally most firms are rationalizing their European operations in light of the ensuing common market.

- Several mechanisms are being put in place to develop a harmonized, single market.

Discussion

Five key factors are seen to influence the changing market structure in Europe (Smith,1992:24):

- creation of a single European community and attempts at harmonization
- reduction in trade barriers
- possible participation in the markets by non-EC members
- the emerging Eastern European market and healthcare environment
- increasing efforts to control national health care budgets.

Although the industry sees itself amidst R&D and profitability issues, the key to government regulation are the concerns of the public and the crises in health care funding and management. Government policy, therefore, is a mixture of recognizing the needs and desires of the public (consumer), industry and government.

The European Commission has an apparent 'sympathy' with the research-based industry (Hancher,1992). Currently most European countries offer 20 year patent protection from the date the patent is filed. Manufacturers argue, however, that they cannot take advantage of the exclusivity a patent offers until the product is marketed, and that delays in the regulatory process sometimes run up to 7-9 years. "Effective" patent protection is therefore much shorter and puts European firms at a competitive disadvantage vis-a-vis American and Japanese firms where patent term restoration is in place. France recognized this and put supplementary patent protection in place in 1991.

The European Commission's supplementary protection certificate (SPC) ensued from the concern regarding effective competition with global competitors. Article 8 of the SPC proposal gives protection from the date at which the product gained its first marketing authorization in a member state. The SPC has an incentive effect in that firms will want to introduce a product as quickly as possible throughout member states to take full advantage later of the SPC. Duration of the total effective protection given through the patent and SPC is set at 16 years, with the duration of the SPC no longer than 10 years. The regulation applies to all products protected by a patent that have not received final safety approval. Protection is available for all products authorized after January 1, 1984 for which the patents expire after July 1992.

The SPC will delay the arrival of generic products on the market, in contrast to the patent term restoration of the 1984 Waxman-Hatch Act in the US. Even without SPC, however, manufacturers could still assume some rights through trademarks and copyrighting to protect their product. There are very divergent rules on this across the EC member states (Hancher, 1992).

To date, pharmaceutical regulation within the EC has been mainly national and slow. To create a single market for pharmaceuticals, the EC is setting up 2 new Community authorization procedures. Many in the industry are confused as to how these will work and how they will be implemented in January 1995 (Harvey,1993:9). The new proposals are seen to undermine national autonomy and met with opposition from the member governments before being adopted.

The *Multistate* was first introduced in 1975 to develop mutual recognition of national marketing authorizations - but it has been limited and the outcomes not uniform even though they have been based on the same criteria (quality, safety and efficacy). The *Committee for Proprietary Medicinal Products (CPMP)* was set up to coordinate multistate procedures (set up in 1987).

The two new mechanisms are the *European Medicines Evaluation Agency (EMEA)* (a technical secretariat) and a revised, reinforced CPMP (which will coordinate the scientific evaluation of medicinal products). The EMEA will merge the 12 existing drug regulatory bodies of the EC into one and should reduce costs for companies who in the past have had to get separate approval from each of the member countries. The EMEA will be decentralized with experts across Europe being linked via computer networks. There should be a faster, cheaper, more efficient approval system in place which, it is hoped, will encourage further R&D by European firms who have been falling behind Japanese and American firms in the number of new drugs being developed.

During a 3-year transitional period applicants can submit parallel applications to member states up until an authorization is granted. The pharmaceutical industry is concerned about how the assessments will be conducted, whether politics will override scientific/medical concerns, and how they will be implemented at the national level. Industry will have to cover the cost of applications (Harvey,1993:9). A negative arbitration from the CPMP will mean the "delaunch" of a product - 1-2 states can no longer take a national view as can happen in today's current multistate procedure (Macarthur,1994:12).

Another issue that companies will face with EC 'harmonization' is the 5-year phasing-in period to bring labels and leaflets of existing products up to Community standards under the patient information directive. Marketing strategies will become increasingly pan-European. Companies will need a "European mindset" as national approaches are replaced by standardization (Macarthur,1994:13).

The future enlargement of the EC to include Austria, Sweden, Finland and Norway can be more easily accommodated in the drug industry than others because of existing ties among regulatory bodies. DG111 (the Commission directorate responsible for pharmaceuticals policy) drafted along with the EFPIA (European Federation of Pharmaceutical Industry Associations) a document on Industrial Policy - the aim being to "stem the tide of cost-containment procedures" and encourage deregulation. Another objective was to help national industry associations put their cases to authorities at the local and national level. The restoration of the patent term through the SPC helps this industrial policy but there have been fewer SPCs than expected so far (Macarthur,1994:13).

The European Generics Association (EGA) argues that additional legislation is needed to establish better conditions for the development of generic drugs. The ECs new SPC will delay the development of generic products by up to 5 years which, the EGA say, will delay cost savings to consumers and national health budgets. The EGA wants generic firms to be able to make all preparations for a product during the operational life of a patent and supplementary protection period. This is allowed in the US but not in Europe. The EGA would also like a reduction in the time required for the authorization and registration of generic drugs. The current situation also allows US companies to market a generic product from 'day one' of a patents' expiration (World Pharmaceuticals Report,July 15,1993:9).

The effects on the locational structure of the industry in Europe because of Europe 1992 is likely to be a decline in clerical activities (with gradual removal of national registration), and little effect on marketing and R&D. There could, however, be the relocating of secondary production facilities (rationalization into fewer production facilities - into the likes of Germany and the UK at the expense of France, Italy, Greece, Spain and Portugal). Yet there is also a move to lower-cost countries such as Italy, Portugal, Spain and Greece, so there are conflicting tendencies. The UK is seen to benefit the most from Europe 1992 (Howells,1990). Falling trade barriers between European countries will mean greater potential to rationalize production and subsidiaries' operations because of less need for local medical and regulation expertise/presence, local manufacturing and aspects of marketing. In essence, more effective scale economies.

The European Commission has tried for harmonization but has been rebuked by the national governments in Europe. The Commission has urged member states to shift attention from direct price controls on drugs towards measures more specific to reimbursement as it would like to see a convergence in pricing to ensure the effective functioning of the single market. The Commission also recognizes the need for the industry to generate sufficient returns to R&D for investment to continue (Scrip,1st October,1993:2). It maintains there should also be a role for generic producers but that must be with the appropriate safeguards, quality checks and so on.

The European Commission is developing à pharmaceutical database (ECPHIN) in collaboration with member states to promote information about drugs, including price. Member states are already exchanging information and hope ECPHIN is ready for other interested parties by 1996.

Patents are vital to the development of a strong biotechnology industry. European Union industry ministers have approved legislation that will harmonize biotechnology patents across the 12 member states. National rules will have to be consistent with a European directive by 1997. This legislation emerged, in part, because of the concern that highly trained scientific personnel may leave the Community, and the competitive advantage that American firms currently have with more effective patent protection (Scrip,22nd June,1993:4; World Pharmaceuticals Report,11th Jan,1994:5).

By far the most critical issue facing the industry at present in Europe is the nature and extent of cost-containment measures put in place by national governments and this has led to some scepticism as to the level of EC unity. In 1993 healthcare reform in Germany and Italy, for example, led to drug sales falling 10% and 3%, although sales in France grew by 7% (Schofield,1994:8). As one commentator stated regarding the attempts to harmonize pricing and reimbursement decisions *"only an inspirational soothsayer would prophecy with blind certainty that the second half of the 1990s will see system unity"* (Scrip Magazine,May,1992:20). To some analysts, drug pricing and reimbursement systems in Europe have been diverging, not converging.

Several countries in Europe in 1993 either cut the number of products available under national health services or made people pay more for their drugs (Schofield,1994:8). Italy, for example, took 700 products of its reimbursement list (Prontuario) and promised a higher prescription charge for 1994. The Prontuario itself was scheduled to be removed at the beginning of 1994. The French cut reimbursement by 5%. In Germany, new reimbursements were adopted while the Dutch government, following reports that cost-control measures were not working, sought to impose even tougher measures such as reducing reference prices further.

Reference pricing has also come under closer scrutiny. A reference price is a single price for a cluster of drugs. Companies can charge at a higher price but only the reference price will be reimbursed to the consumer. The patient/consumer will have to pay the difference. Germany, Netherlands and Sweden have reference pricing systems based on price clustering of multi-sourced products that are deemed therapeutically comparable.

Reference price systems are "hated" by the industry in Europe. The most arguable element of a reference price system is the clustering of supposed interchangeable drugs. Reference prices also reduce the level of generic competition as generic prices are adjusted to the reference price level. Redwood (1993a:41) observes that net savings are, so far, disappointing in Netherlands and negligible in Germany.

A number of national associations have presented their own proposals to ward off tougher measures by their governments. Concerns about the extensions of the reference price system led the Dutch industry association to consider price cuts. The French government proposed a new pricing system based mainly on negotiations between companies and the drug pricing committee involving sales targets. The french industry association - SNIP, gave the proposals a "qualified" welcome.

Health care reforms have placed considerable pressure on all the elements of the chain which brings drugs to patients. It is unwise to artificially separate the interrelationships between patients/consumers, physicians, distributors, manufacturers and governments as the behaviour of each element impacts upon the others. For example:

- physicians may preserve the right to freedom of practice but in Europe with so many physicians unemployed are they competing for patients who like high prescribers? (Scrip Magazine,May,1992:21)
- with the German health care reforms in 1993 physicians began to prescribe generics and cheaper equivalents to stay within their budget. This put pressure on companies - many of whom laid off staff citing reduced sales of up to 50% (Schofield,1994:8).
- co-payments are also dangerous politically, so governments must proceed with caution (eg, threatened hunger strike in Spain in 1991 by the *"Democratic Union of Pensioners"* when the govt. threatened co-payments for seniors).
- in France in 1993 there was continual pressure on physicians to curb their prescribing patterns.

In a recent discussion of regulation Heinz Redwood comments that "health care can afford pricing freedom if the system is tuned simultaneously to moderate consumption without discouraging innovation" (Redwood,1993a:5). He adds that "Structural changes in the consumption pattern of price-controlled drugs contribute to an increase in drug expenditure, because R&D is re-oriented to develop non-innovative new products with contemporary price tags to replace older drugs with low, controlled prices" (Redwood,1993a:5).

Such behaviour cannot be controlled by further regulation as firms will respond to changes in the market structure as they please. Redwood feels that once countries adopt price controls they become addicted to them and are forever tampering with their structure and increasing the level of regulation.

Price regulation and cost-containment policies in Europe have been regarded as undermining innovation while not necessarily containing health care costs. All signs indicate that cost containment activities will continue in Europe in 1994 and companies will experience declining sales as a result (this is already observed in Germany and Italy). Although there may be some room for generic producers to gain market share the downward trend of brand-name products makes generic products less profitable. Moreover, the use of SPC's will prevent generic products from coming on to the market earlier and the combination of these 2 factors has made North American investment appear much more attractive.

A survey by a consulting group in Europe of health care industry representatives revealed that 82% expected an increase in the use of "approved lists", 72% expected that attempts to control costs will come through increased co-payments for prescription drugs, and an increase in generic drug use was expected by 76% of respondents. The effect on innovation, the consulting group concluded, could be disastrous, but the fact that most of the countries want a strong industrial base means some compromise would likely be worked out (Scrip,2nd July,1993:4).

Questions

- What is the appropriate mix of government policy required to encourage R&D while at the same time keep the costs of health care down?
- What will be the effects of Europe's price controls and cost containment on the Canadian pharmaceutical industry?
- Could Canada become a potential area for new investment by European firms - both brand-name manufacturers and generic drug producers?

2.4 THE NORTH AMERICAN FREE TRADE AGREEMENT (NAFTA)

- NAFTA has led to the creation of a single 360 million customer market.
- NAFTA has increased the profitability potential of brand-name manufacturers.
- NAFTA provides opportunities for generic producers to gain increasing shares of the Mexican market.

Mexico is the 11th largest chemicals and pharmaceuticals market in the world (estimated at US$2.1 billion). About 99% of all drugs consumed in Mexico are produced locally (Scrip, 12th Nov,1993:18). Mexico had a highly protected drug industry but with the opening of the economy, NAFTA, GATT negotiations, new patent laws and changes to its state purchasing system, it has become a large potential market. Increasing dominance of multinationals from Europe and the US is expected as is a rise in the number of mergers and acquisitions. Mexico's patent law took effect in June 1991. Mexico invests just 0.3% of GDP on research compared to over 3.0% in most developed economies (Torbett,1993:9).

NAFTA has provided American and Canadian pharmaceutical manufacturers enormous opportunity to develop a strong market presence in Mexico. American firms were able to gain increasing levels of patent protection from both Canada (Bill C-91) and Mexico through the agreement.

NAFTA:

- strengthens intellectual property protection through affording protection to pipeline products
- provides 20-year protection from the date of filing for both product and process patents (or 17 years from the date of grant)
- allows for patent term restoration to compensate for regulatory delays
- compulsory licensing applications to be considered on an individual basis - applicant must first make effort to obtain approval from the patent holder on commercial terms
- pipeline protection is also granted for products with a valid patent elsewhere as of July 1991 for the unexpired term of the patent in another NAFTA country so long as the product has not been marketed in that country (PMA,Ind Brief,17th Jan,1994:3), (Scrip 2nd Nov,1993:16), (Scrip,12th Nov,1993:18).

Currently Mexico levies 20% tariffs on pharmaceuticals but NAFTA will phase out tariffs. American and Canadian drug products will be able to compete for Mexican government procurement - currently the Mexican government discriminates in favour of domestic companies (PMA, Ind Brief, 17th Jan,1994:3) (Scrip,2nd Nov,1993:16) (Scrip,12th Nov,1993:18). American and Canadian investments will be given the same treatment in Mexico as domestic investments. There is one important provision in the agreement, however, - a clause which reserves the right for the Mexican government not to purchase essential drugs outside Mexico until 2002. The Public sector accounts for about 30-40% of the US$2000 million sales in Mexico annually (Torbett,1993:9).

It is generally agreed that the GATT TRIPS would be a step back from what was accomplished in the NAFTA agreement - because of the problems noted earlier in section 2.2. Also, NAFTA provides some degree of patent protection in biotechnology whereas TRIPS does not (Scrip,2nd Nov 1993:16).

Questions

- Will Mexican government procurement favour generic or brand-name producers?
- Will Mexican government procurement continue to favour Mexican producers or are there opportunities for Canadian and American producers to capture an expanding market?
- To what extent do Canadian pharmaceutical manufacturers function in Mexico and are there plans for future Mexican investment?
- How will the opening of the Mexican market impact on the Canadian domestic industry?

2.5 COUNTRY PROFILES

This section reviews the current status of the pharmaceutical industry in each of the 11 countries listed earlier with regard to the role that government regulation is playing. The dominant theme in virtually all the countries is the changing nature and level of price control. The Appendix provides additional descriptive information on the countries.

The recurring theme that impacts upon the activities of firms in the industry is that reimbursement systems and reference pricing also place pressure on consumers (when choosing what to take as medication) and physicians (who are now under cost containment pressures while still trying to ensure quality care is provided). As governments also become more unwilling to reimburse the public for their medications manufacturers must look for other ways to maintain profitability. As we will see in the following chapter this has resulted in greater coordination and integration of activities throughout the "value chain".

It is beyond the scope and time frame of this study to fully document the effects of these regulatory adjustments to the operational environment of the pharmaceutical industry. In many respects the assumed effects of the regulatory transformations such as reduced profitability, job losses, changing locational patterns of manufacturing and R&D, and the rationalization of operations will become more apparent over time as the pressures stemming from rising health care costs are only now beginning to be addressed by governments in the past 5 years.

Any examination at this point can only be partial and incomplete, and will be quickly outdated as the industry is in a very heightened state of flux. This current period of industrial restructuring also offers threats and opportunities for national industries as governments themselves compete for the investment potential of R&D. Firm-specific examples of the impacts are provided in the following chapter on corporate strategy.

2.5.1 Australia

Australia's pharmaceutical industry's sales of prescription drugs were US$643 million in 1991 (Scrip, 12th October,1993:15). Drug prices in Australia have traditionally been very low - 75-80% of drugs available in Australia cost 50-55% of the world average prices (Scrip,17th September,1993:17). The *Pharmaceuticals Benefits Scheme* sets national prices for pharmaceutical products. At the end of 1992 as part of cost containment measures the government moved to require economic as well as clinical evaluation of drugs on the Pharmaceutical Benefits Scheme. New drug approval guidelines now enable firms to submit more timely applications for registration based on EC documentation (Scrip,28th Sept,1993:18).

The main government player in the industry is the Department of Health, Housing and Community Services. The department is responsible for the Therapeutic Goods Administration (TGA) which oversees the evaluation and approval of applications to conduct clinical trials and manufacture and market drugs. The department also administers and controls the Pharmaceutical Benefits Scheme which is responsible for policy, budget and monitoring functions covering the range of drugs eligible on the Scheme (Parry and Creyke,1991).

A central industrial strategy for the pharmaceutical industry is the *Pharmaceutical Industry Development Plan* which began in 1987. The key to the plan is what is known as the Factor F scheme which links R&D in Australia with the determination of prices. Under the scheme companies can receive price increases for their products if they have invested in Australia (Thwaites,1989). The scheme, observers say, has changed the psychology of the Australian industry and the country is now seen as an attractive site for development (World Pharmaceuticals Reports, 1st July,1993:9).

Companies that want to enter the scheme must meet 2 criteria: "to increase the value-added in Australia on pharmaceutical production by 50% over 3 years and boost R&D spending at 3% of turnover" (Scrip,4th May,1993:25). Both must be accomplished within 5 years of entering the scheme. Pharmaceutical price increases up to a maximum of 25% will then be calculated based on the value of increased activity by each company.

Since it was set up, manufacturing exports have increased from AU$166 million to $500 million. Exports are expected to grow to Aus $3.5 billion by 1999 making Australia the 5th largest exporter of pharmaceutical products in the world ((World Pharmaceuticals Report,1st July,1993:10;11th July,1993:10). R&D funding has increased from AU$7 million in the mid-80s to $70 million in 1992. This figure is expected to rise to AU$403 million by 1999. Merck is to invest AU$75 million in a plant and Australia will be one of only 3 sites to produce Merck's BPH treatment finasteride. Astra has also decided to manufacture a number of products in Australia that have not been manufactured outside Sweden before (Scrip,6th July,1993:19).

Factor F has influenced the Australian industry in a number of different ways. Parry and Creyke (1991) for example observe that:

- without the scheme major plants would have been closed
- it has helped local subsidiaries convince their parent company to locate production in Australia
- it has underlined the government's commitment to the industry
- it has helped locally-owned firms to focus their own R&D initiatives
- has stimulated alliances between international and local firms
- has contributed to firms upgrading R&D in Australia.

The industry was critical of the Australian government in 1993 when the government decided not to increase level of funding for the Factor F development plan. Factor F and the streamlining of drug approval procedures have increased investment confidence in Australia and many firms are now establishing regional sourcing centres and making the most of Australia's scientific institutions. There are estimates that Factor F funding has cost the government about AU$200 million in its first five years. In 1992 the government announced further funding totalling AU$821.5 million until 1999. Meanwhile the APMA has commissioned a study of the impact of Factor F to help persuade the government to increase its funding. R&D to sales has increased from 2.9% in 1987 to 6.5% in 1990. If the government hopes to get to other norms of countries of 16-20% then it will likely have to increase funding of Factor F.

In most cases products being put forward for marketing approval have far longer delays in Australia than in other industrialized country markets. Firms also complain of delays in gaining PBS listings. Concern has been voiced that the combination of delays and the administration of the TGA is one of the key obstacles to the development of the industry in Australia (Parry and Creyke,1991).

In October 1993 it was revealed that the federal government was considering allowing generic substitution. Under the National Health Act pharmacists must provide what is said on prescription unless they have the permission of the physician to substitute. Generic substitution would probably only apply to those products that have been already determined as interchangeable through the Maximum Pricing Policy (about 160 products) and only if endorsed by the physician (Scrip,26th Oct,1993:16).

2.5.2 Denmark

Consumption of human pharmaceuticals in 1991 was US$1.3 billion - an increase of 8.2% over 1990. Imported drugs were 56% of the total compared to 50% in 1980. The increase is due to the shift toward newer, more expensive drugs. Per capita consumption, however, is considerably lower than the average for other industrial countries (Scrip,9th Sept,1993:4).

Seventy-five percent of consumption is through pharmacies, with the remainder in hospitals. Government health insurance finances 56% of drug expenditures. A generic substitution scheme was introduced in 1991 but physicians made little use of this in its early phase. The largest therapeutic classes are the central nervous system, cardiovascular and respiratory groups of drugs.

Until recently Denmark had pricing freedom similar to that in the United States. In Denmark prices could be increased as long as authorities were notified, and firms did not have to get permission. Both the US and Denmark have high drug prices but relatively low drug consumption.

In June 1993, a new Danish reference price system came into force. Health insurance will now pay up to a ceiling price for multi-source products where there are several of these available. The ceiling price will be the average of the 2 lowest prices. Since its introduction products have either had their prices reduced or have come closer to the reference price level (Scrip,10th Aug,1993:7). Denmark's Competition Council said it was on the lookout for coordinated price fixing between firms following the introduction of the reference price scheme (Schofield,1994:10). More recently the Danish pharmaceutical associations (MEFA and MEDIF) and the Health Ministry agreed on a price freeze for reimbursed pharmaceuticals until April 1 1995 (Scrip,14th Jan,1994:4).

2.5.3 France

France is the world's 4th largest pharmaceutical exporter with its main market being Germany (which receives about 12% of French exports). Exports in 1992 were $US 3.4 billion (Scrip,11th June,1993:6) to give a 1992 trade surplus of US1.4 billion (Scrip,17th Sept,1993:3). France now exports 24.6% of its production, compared with 19.2% in 1980. Imports now account for 17% of the market compared with 4.6% in 1980.

Since the 1970s there has been increasing concentration in French market - 507 companies in 1970 to 363 in 1990 with foreign producers increasing their market share in France from 4.6% in 1980 to 17% in 1992 (Scrip,2nd Feb,1993:2) (World Pharmaceuticals Report,20th Sept,1993:5). Foreign groups now account for nearly 55% of the French market by investments, 48% of employment and 49% of sales (Scrip,17th Sept,1993:3). Large French companies such as Rhone-Poulenc Rorer and Sanofi are finding it difficult to match the market penetration of foreign companies (Scrip,2nd Feb,1993:2).

Per capita consumption in France is high and prices low compared to rest of Europe. Between 1980 and 1992 the consumption of pharmaceuticals increased by an average of 8% per year. French officials want to reduce consumption so pressure is being placed on the industry. The drug prices of manufacturers have not been increased across the board since 1988 but they have been cut as the French government has attempted to contain costs. In 1991, for example, products received an across the board cut of 2.5%. Some products were cut by more than this while others faced cuts when their licence came up for renewal after two-and-a-half years on the market (Caston and Carre,1993). As compensation for these cuts, during 1992 and 1993 the government allowed a number of companies to raise their prices on certain products.

The focus on curbing the health care budget has drawn attention to the prescribing practices of physicians. Two new measures were introduced to reduce the pressure manufacturers were placing on the prescribers; the non-deductible tax payable by companies on all types of promotional spending was increased from 7% to 9%, and physicians were prohibited from any form of financial ties with drug companies unless they followed very strict guidelines.

Another recent regulatory control put in place has been the formation of the *Medicines Agency*. One of the roles of this agency is to monitor the financial aspects of innovative drugs, and this will include asking for cost evaluations of new products as part of the application process.

The recent practice of allowing drugs originated in France to be marketed without proper clinical trials has damaged the image of the domestic industry and discouraged foreign investment (Gombeaud,1993:8). And whenever a foreign drug product is seen as a threat to the domestic industry the company is "invited" to share the market with a local company. This practice undermines foreign investment and local R&D.

France dropped plans to introduce a fixed patient charge in 1993, and opted instead for a cut in reimbursement levels (i.e. the patient will still be paying more). The French pricing system does not allow for annual increases to be kept in line with inflation and discourages price competition and the development of a generic market (Scrip, 2nd Feb,1993:2).

The industry is advocating a contractual pricing system based on an umbrella agreement with the government, and this would be supplemented by individual agreements by companies on annual sales targets. This would include a commitment by industry to reduce promotional expenditure, improve the quality of information to physicians and investment in the therapeutic and economic evaluation of drugs. Individual contracts would include a commitment to annual ceilings on volume sales of new products in exchange for better prices for product launch. This was formally submitted to the industry association by the French government in December 1993 and subsequently agreed upon (Scrip,30th July,1993:2, Scrip,7th Dec,1993:2, Scrip,7th/11th Jan,1994:7). Foreign manufacturers feel this will strengthen state control of the industry and favour the domestic companies.

2.5.4 Germany

In January 1988 Germany had the 3rd highest pharmaceutical price level among EC countries but by 1993 they ranked 6th. German prices used to be 20-50% higher than the average for Europe but there now appears to be a downward spiral in prices due mainly to the reference pricing component of the Healthcare Reform Act and the lower prices that were available in East Germany (Smith,1992:24).

Germany was the first country in Europe to introduce fixed payments. Germany's reference price system was introduced in 1989. The statutory health insurance groups (the KrankenKassen, of which there are over 1000) had spent 15.9% of total expenditure on pharmaceuticals in 1987, while manufacturers' prices had risen by 14.5% between 1982 and 1987 (Wilkes,1992:16). A reference pricing was seen as a mechanism to curb costs. The German government also felt prices were unfavourably higher in West Germany than other European countries (60% more than European average).

Prior to the reference price system being implemented a *Price Comparison List* had been introduced in an effort to curb physicians' prescribing. It did not have the large scale effect it was hoped to achieve but it did increase the awareness of generic products and contributed to the growth of that sector over the 1980s.

The objective of the German government was to control expenditure on drugs without directly controlling their price. The basic principle of the reference price system is that if any group of drugs are in competition with one another a fixed payment level (Festbetrag) is established. It is below the level of the most expensive product but above the price of the cheapest. If a physician prescribes a product more expensive than the reference price the patient has to pay the difference. But when it is at the same price or below the reference there is no co-payment (Wilkes,1992:16). Co-payment does not control costs itself, but through other regulations the physician is required by law to inform the patient whether or not co-payment will be involved with the prescription. When a product is not covered in the fixed payment system there is a patient co-payment. Currently about 35% of eligible drugs have been put on the reference price system but estimates place the future figure at around 60% (Scrip,16th March,1993:8). There is a clear link between the behaviour of the consumer and the profitability of the manufacturer.

There are three categories of drugs listed for fixed payment; stage 1 multi-source drugs (i.e. containing the same active ingredients), stage 2 me-too products, and stage 3 which covers drugs that are "pharmacologically and therapeutically equivalent" (Wilkes,1992:17).

The pharmaceutical industry can influence decisions about the way products are grouped together and the final value of the fixed product - it has opportunities at different times to comment on the decisions being made by the physicians and Krankenkassen which make up the national board. On average fixed payments are 20% lower than the most expensive product in the group, although some are 40-50% lower. When companies did try to keep their prices above the reference price they quickly lost their market share. Some companies had good reasons (for example, the German price had been used as a reference for pricing in other countries so companies had to think of the potential difference in sales in other markets). For some firms sales have fallen by over 30% and this has severely affected the profitability of the German operations.

New regulatory measures were introduced at the beginning of 1993 to control the costs of healthcare. For the pharmaceutical industry this included a price cut of 5% for prescription drugs not covered by reference prices in 1993 and 1994, and the development of a "positive list" as of 1996. One of the main elements of the reforms is that if the pharmaceutical budget is overspent physicians and the industry will be responsible for paying the bill.

Although reference pricing does not promote the use of generic drugs the recent budget cuts and cost guidelines and auditing of physicians prescribing and services may encourage their use. One estimate has put the reduction in pharmacy sales in the first 2 months since the beginning of 1993 in Germany at 15-30% (Scrip,23rd Feb,1993:2). Wholesalers are now having to grant discounts to pharmacists of 10-12% as pharmacy profits are put under pressure with physicians prescribing more generic products. The pressure to maintain profitability has lead to some manufacturers considering carrying out their own distribution. Bayer has already started to supply about 6,000 of the 20,000 pharmacies (Scrip,5th Oct,1993:9).

Manufacturers reduced their prices in order to keep their market share. As a result firms have been forced to look at ways to increase productivity and cut costs. Hoecsht, for example, stated that the health reform measures could cost it up to DM 100 million in lost sales in 1993, while Schering estimates DM 30-40 million. Bayer claims that it lost DM 35 million in the first 2 months of 1993 (Scrip,6th April,1993:7).

About 60% of pharmaceutical companies in Germany are making staff reductions. Boehringer Mannheim, for example, is reducing its workforce of 8,000 by 1,200. In the first 3 months of 1993 turnover was down 30-50% in half of the firms surveyed by the industry's association. Sales losses in January 1993 included the following: Boehringer Mannheim 31.8%, Bristol-Myers-Squibb 29.9%, Merck, Sharp and Dohme 29.9%, Smith-Kline-Beecham 29.8%, and Glaxo 28.6%. In contrast several generic firms sales rose. By the end of 1993, spending on drugs were estimated to be down by 10% from the spending level in 1992. Overall, there was a 13.4% decline in German drug sales in the first 3 months of 1993 attributed to the health care reforms (Scrip,25th Sept,1993:8).

2.5.5 Italy

Per capita consumption in Italy is high and prices are low when compared to the rest of Europe. The Ruoppolo Commission was set up in 1987 to develop a new method of price control while trying to encourage R&D. Italy had moved towards encouraging drug R&D by granting prices near the European average (Scrip Magazine,1992:20). The Italian government removed 700 products off the reimbursement list in 1992 (the Prontuario). These were products primarily similar to OTC products but the government suspected savings would be less than hoped for as physicians would probably change prescribing to use drugs still on the Prontuario (Scrip,16th Oct,1992:2).

The Italian government has attempted to reduce consumption through a series of recent measures (Smith,1992:25). The government looked indecisive during 1993 as it produced a range of cost-containment proposals. These were seen as unpopular, unfair, and unworkable. One plan to link drug provision to income was attacked by the public and politicians, and subsequently dropped. In early 1993 price cuts were placed on reimbursed pharmaceutical products. About 67% of lost revenue would be assumed by the industry. This put further pressure on an industry that was already having problems through health care reforms (Scrip,16th/20th April,1993:3). The Italian drug budget for 1994 was then slashed to 30% less than the level of pharmaceutical spending in 1992 (i.e. about US$6,250 million).

A new price monitoring system was due to come into effect in January, 1994 which would allow companies to get their products in line with the EC average for each product containing the same active ingredient (Scrip 24th Sept,1993:2). Alignment on the EC price average, however, is only immediate for drugs selling above the average. Other prices will be moved to the average over the next 5 years. The system was to come into effect as of March 1994 although this date was postponed for another 60 days (Scrip,7th/11th Jan,1994:2). At that time there will also be the introduction of price monitoring instead of price controls - but then price will still be based on EC average (World Pharmaceuticals Report, 11th Jan,1994:8).

The industry faced further pressures with the proposal to reduce drug prices by 5% for 1994. Italian drug prices are already about 20% below EC average (Scrip,2nd Oct,1993:3). The Italian pharmaceutical industry association, the Farmindustria claimed 20,000 jobs could be lost in the industry if the proposals went through (7,000 of these in research). The proposed 5% cut in prices was officially dropped at the end of 1993 (Scrip 17th Dec,1993:3).

About half of the Prontuario is to be de-listed from the 1994 list. There are also plans to have either 100% reimbursement, 50% co-payment or 100% payment by individuals (Scrip 14th Dec,1993:2), The Industry has forecast a 20% cut in employment levels if the de-listings are made. A number of multinationals said they expected to lose 30-40% of their Italian sales in 1994 because of the delistings. Among those hardest hit are Rhone-Poulenc Rorer, Boehringer Mannheim and Sandoz with 54.1%, 49.9% and 42.4% of their product lines being delisted. (Scrip,14th Jan,1994:2). Industry officials worldwide have been amazed at Italy's new drug classification system, especially as internationally recognized drugs have been left off the list (World Pharmaceuticals Report,11th Jan,1994:8).

The Italian industry is known for its lack of international competitiveness due mainly to the nature of its evolution. It emerged out of small pharmacies as opposed to huge chemical company concerns. This was shown in the 1970s when the introduction of pharmaceutical patents revealed structural weaknesses, and these were compounded by cost containment policies of the government (Scrip,13th Nov,1992:7).

There are about 300 human-use pharmaceutical companies in Italy (Scrip, 9th Oct,1993:3). Farmindustria notes there was a 4.1% reduction in pharmaceutical production in 1992 with 60% of Italian companies experiencing a decline in sales (Scrip,3rd/7th Sept,1993:7).

The Italian pharmaceutical industry spent Cdn$306 million on R&D in 1990 - an increase of about 20% over 1989. This accounted for 8.7% of total sales (Patented Medicine Prices Review Board,1993). The Italian Ministry of Scientific Research drafted a new national drugs research plan under which a total of US$87 million would be allocated by the state for research in innovative pharmaceuticals. This, critics claim, is a drop in the bucket compared to what is required. Firms and academic institutes would be able to apply for the funding.

Presently there is a very poor R&D environment in Italy mainly due to the lack of private and public funds, lack of university/industry collaboration, limited venture capital and a lack of "meaningful tax incentives". Few Italian companies are prepared for innovative research - most have relied on licensing-in and me-too products. One of the few firms with a research pipeline is Farmitalia which has recently been acquired by Procardia (Scrip,25th May,1993:8).

The pharmaceutical industry has never been a priority for the Italian government and there has been increasing domination of the industry by foreign capital (for example, the sale of Montedison's pharmaceutical arm - Erbamont/Farmitalia Carlo Erba to Procardia received widespread criticism around Italy. Erbamont was to merge with the Procardia subsidiary, Kabi Pharmacia. In total, 28 Italian companies have been acquired by foreign firms since 1983 (Scrip,2nd April,1993:5).

2.5.6 Japan

Twenty-five years ago, patents were only available for processes. In the mid 1970s a product patent system was enacted and in the late 1980s patent term restoration was introduced. Until 1967 no preclinical studies were required, and only basic clinical studies mandated. Without a patent law (first one in 1976) Japanese firms could make copycat versions of drugs without the original proprietary firms' approval. Although a patent process law was in place it just meant that the Japanese firm could develop a different process and come up with the same drug. In this way the Japan industry was able to exploit the research of American and European firms (Neimeth,1991). Some analysts believe Japan's drug market could rise to US$70 billion by the year 2000 because of rising incomes, an aging population, more physicians and more drugs being approved (Maurer,1992-93:24).

Like other industrial economies the challenge in Japan is to contain the costs of healthcare. While many other countries have focused on the use of generic products, Japan provides fast track status and high prices to innovative drugs. In the 1990s restructuring has occurred in the reimbursement price mechanism, medical fee formulas and market price mechanisms. Government imposed price reductions are more transparent and moderate and less frequent.

The Japanese drug market is worth about US$35 billion. Foreign companies are now establishing fully integrated operations in Japan and the foreign share of the Japanese market has steadily increased over the past few years. During 1980s many collaborative ventures folded or were taken over by foreign partners who began to build up research units and added production capacity.

Research has been focused on "small step innovation" (modifications of existing drugs). In part, this has been demanded by risk aversion executives (Maurer,1993b:33). Only about 100 of the 978 manufacturers in Japan have a discovery research capability, and only 140 have more than 300 employees. The top 10 companies hold 35% of the market and all are Japanese-owned

(just 4 foreign affiliate companies are in the top 20 firms). Major Japanese firms have increased their commitment to research, but to support this increase the sales base must be broadened. It is anticipated that Japanese sales will increase off-shore - mainly in the US and Europe.

Two factors are central to the changing regulatory environment in Japan - deregulation and the promotion of R&D. There have been revisions to the Pharmaceutical Affairs Law (enacted April,1993) and another related Law (Adverse Drug Reaction Suffering Relief and Research Promotion Fund Law (ADR Fund)). This latter law states that the promotion of R&D is fundamental (Maurer,1993a:42) (Scrip,16th Mar,1993:18).

One focus of R&D promotion is the new Orphan Drug Law which was adopted as of 1st October 1993. Orphan status is based on 2 criteria: the target population must be 50,000 or less, and a serious medical need or superior usefulness of the new drug must be evident. Subsidies for research will be granted and a 6% tax credit for R&D expenses will be made available. The new drug will be given priority review along with other drugs as deemed necessary. The post-marketing re-examination period is also to be extended from 6 to 10 years - guaranteeing effective market exclusivity since approval of "me-too" drugs is not allowed in a re-examination period.

Within the first 3 months of the Orphan Drug Bill being enacted 87 firms made applications for 256 different approvals. To streamline the process consultation and advice is given through the development of a drug (e.g. in clinical trials) as opposed to waiting until the final review process (Maurer,1993a:42). The Orphan Drug Scheme has been welcomed by the industry as a positive step towards R&D growth and has also been supported by the American PMA (Haydock,1994:23). The Japanese authorities hope to build databases on rare diseases that can be accessed by modem by physicians and patients who need information about orphan drugs (World Pharmaceuticals Report,26th Aug,1993:11).

From October 1994 the ADR Fund will grant financial subsidies and guidance to companies intending to develop, or who are working on, products seen to be orphan drugs (Scrip 16th March,1993:19). Applications for orphan drug designation will be received once a year (Scrip 20th Aug,1993:20). All orphan drugs qualify for an extended re-examination period (exclusivity after first approval).

A pre-grant opposition system which allows rival companies to raise objections to a proposed patent before it is granted has been in place in Japan. There had been concern expressed by the US government and industry that Japan's patent practices prevented US companies from doing business in Japan. Under the *US-Japan Structural Impediments Initiative* the Japanese government agreed to reduce patent pendency time and to increase the number of examiners.

Japan is streamlining its approval process. To improve efficiency the government is adopting a paperless system approach to license applications (ie, greater use of electronic systems) (Maurer,1993a:43). There are relatively fast review times for drugs in Japan. The average review time is approximately 18 months - about 1 year faster than US FDA

(Maurer,1992-93:38). There has been an average of 37 approvals per year between 1982-91 compared to the FDA whose average was 23 approvals over the same period.

Post-marketing surveillance is being overhauled. By early 1994 all ethical drugs, including generics are to comply with Good Post-Marketing Surveillance Procedures (GPMSP), irrespective of the patent status of a new drug. Longer life cycles should result and so increase the period of return for firms (Maurer,1993a:43). GPMSP in Japan are considered to be long overdue. GPMSP will increase costs of doing business but in long run they will have a positive effect because they will extend market exclusivity from 6 to 10 years.

Less than half of all drugs produced in Japan are on the national health insurance reimbursement tariff (the yakka), although that still totals over 14,500 products. Japan's national health insurance system has operated in the black for many years. Drugs represent 28% of the medical bill and this has also been a constant figure for many years. There are no restrictive drug lists. The government caps drug prices under which buyers (hospitals, physicians, etc) and sellers (manufacturers who are caught between reducing the level of discounting while trying to raise volume) are free to negotiate. Insurance groups want reimbursement prices to be lowered to reflect actual market price. But even the adoption of a flat fee reimbursement system in over 500 facilities for elderly and chronically ill had only a slight negative impact on drug consumption, although there were predictions of increasing use of generics (Haydock,1994:23).

In Japan generics are not favoured in regulatory policy and there is a cultural bias against them. Although new drugs are listed on the reimbursement tariff every 3 months generic products are listed only once every 2 years. Culturally, the bias is toward new, not old and generics are regarded as old technology (Maurer,1993b:33). Despite this the low cost enables suppliers to offer large discounts to medical institutions and some forecasts put sales of generic drugs doubling to US$16 billion by the year 2000 (Scrip,19th Jan,1993:14).

The downward price of drugs has meant that over the years profitability for Japanese firms has been relatively low compared to European and American firms. In 1992 8.1% price cuts caused several leading companies to have stagnating sales and operating profits. This has continued over the past few years. The next official reimbursement price revision is due in April 1994 and an average cut of 7% is predicted (Haydock,1994:23). Typically, the product life cycle for drugs in Japan has sales increasing in the first 2 years, flatten off for 3 years and then decline. Adopters use the drug in the first 2 years, reimbursement price revisions cut growth, and then newer competitive products enter the market and the volume of sales decline. The manufacturer has limited time to make good profit margins (Maurer,1993b:33).

Finally, changes to the distribution practices under Anti-Monopoly Act in Japan could slow Japanese corporate growth and will open up the market to increasing levels of foreign competition and increase pressure on companies to lower prices further (Scrip,23rd Feb,1993:13).

2.5.7 Netherlands

Pharmaceutical consumption is lower in the Netherlands than the rest of Europe. Manufacturer's sales in the Netherlands in 1991 were US$1,623 million - up by 7.8% over 1990. Growth for generics and parallel imports were much higher at 23.9% and 36.2%. R&D was up by 14.3% from 1990 in 1991 and this represented about 18% of the industry's overall drug sales (Scrip,26th Aug,1992:6). The Dutch government relies on parallel importing and generics to keep costs down. In 1991 the growth of these was 25% (i.e. 7% of total drug bill) (Scrip,12th Jan,1993:3).

Since 1991, however, with the introduction of a new reimbursement system, the GVS, sales growth has slowed down. If a patient pays a price above the GVS group level of reimbursement the patient pays the difference. There have been suggestions that the pharmaceutical industry may have increased the price on non GVS drugs to offset the impact of the GVS.

In 1993 the Dutch government stated that the GVS price system was not sufficient to control drug costs and so is now targeting newer products and hoping to bring these into GVS clusters. In addition, the government was looking to reduce the margin provided to wholesalers and also to lowering the pharmacists fee. In response to these suggestions, R&D firms, generic drug producers, pharmacists and wholesalers presented an alternative plan which would involve a 3.5% price cut at the pharmacy level for brand name products, a 4.5% cut for parallel imports, and a 6% cut for generic products (the lost profitability would be absorbed down through the distribution chain) (Scrip 18th June,1993:5).

A complete restructuring of the Dutch healthcare system is expected in the near future and this will have implications for the pharmaceutical industry, particularly as recent measures were unable to result in a structural reduction in costs. One of the measures already employed has been the closure of one section of the drug reimbursement system (annexe 6). This means that there will be no reimbursement for new products unless they represent new classes and are for conditions for which there are no current therapies (Scrip,5th Oct,1993:2).

2.5.8 South Korea

In 1991 South Korea signed an *Intellectual Property Agreement* (IPA) with the European Community. Under this agreement South Korea will provide patent protection for up to 350 pharmaceuticals and agrochemicals (Scrip,30th April,1993:21). To qualify for protection products must have been patented in an EC member state but not marketed in a member state or South Korea between Jan 1,1980 and July 1st,1987. Glaxo has 19 on the list, Farmitalia 18, Janssen 15, Hoechst 13 and Sanofi 13 (Scrip,19th Aug,1992:15).

South Korea requested that 10 products be dropped from the list because they are already being developed by domestic firms. The EC rejected this but an agreement was finally reached at end of 1993. Following some concessions given on both sides the final list contains 193 products (Scrip,14th Sept,1993:15, Scrip,7th Dec,1993:19). It is generally felt that the intellectual property agreement will restrict growth in turnover by domestic firms as now they will have to pay royalties on certain products (Scrip,9th Sept,1992:21).

The history of the IPA can be traced back to 1987 when South Korea introduced patent legislation. This included retroactive protection to products patented in the US between January 1980 and July 1987. These products were to receive protection for 10 years. The European Community and Japan strongly objected to this, citing the GATT. Meetings were held with the EC and Japan and seemingly similar protection was agreed to (Scrip,7th Dec,1993:19).

In 1992 there were 706 pharmaceutical firms in South Korea manufacturing 42,065 products (Scrip 19th Aug,1992:15). There are 8 Chaebol-affiliated pharmaceutical companies in South Korea while another 10 have announced plans to enter pharmaceuticals (Scrip,12th Feb,1993:20). The R&D sales ratio of the top 100 companies in the Korean industry in 1992 was 3.15% - down from 3.3% the previous year. In comparison, the average for the industry worldwide was between 10-20% (Scrip,9th Sept,1992:21; 12th Oct,1993:17). Forty-five percent of Korean company employees are in sales and marketing compared to just 10-15% of the multinational subsidiaries based in Korea (Scrip,9th Feb,1993:16). The continued production of me-too drugs by the large companies is seen to be threatening the livelihood of the smaller companies.

Good manufacturing practice conformance (GMP) for these firms is to be required by mid-1994 and for raw materials, by 1995. This has led to a new production capacity surplus and consequent development of me-too drugs as firms do not have the resources to modernise their manufacturing facilities. Many South Korean drug companies are having difficulties trying to reach conformance standards for GMP by the due date of May 1994 . Some are taking excessive loans to get GMP status and some are going bankrupt as a result (Scrip,12th Jan,1993:17; 18th June,1993:22; 10th Aug,1993:18).

South Korea had a pharmaceutical trade deficit of US$379.3 million in 1992 despite exports rising by about 10%. Markets targeted for exporting include China, North Korea, and South America (Scrip, 21st May,1993:23). It is estimated that South Korea should be a net exporter of drugs by 2002 assuming that exports will grow by 20% and imports by 10%. South Korea has eased restrictions on foreign investment in collaborative agreements. Investors may now have a controlling share of a domestic firm. Of the 39 collaborative ventures in Korea at the end of May 1992, foreign companies had controlling shares in 19 (Scrip,14th Aug,1992:17).

2.5.9 Sweden

Total pharmaceutical sales in Sweden in 1991 were US$1.2 billion - up 15% on 1991. Leading companies were Astra, Kabi, Glaxo, Merck, and Novo Nordisk. The leading therapeutic product areas are anti-ulcers, corticosteriods, other hormones, and ace-inhibitors (Scrip, 27th April,1993:7).

A new reimbursement model was introduced in Sweden in 1992. Patients must now pay a fixed amount per item rather than per prescription form. They must now pay $22 for the first product on a prescription and "x" amount (much less) for additional products. A number of OTC drugs were removed from the reimbursement list as part of government package designed to reduce drug bill by around US$146 million.

The package of reforms which were introduced in 1992 included a reference price system that took effect in January,1993 (Scrip,15th July,1992:2). Sweden is the first nordic country to introduce a reference price system. Drugs regarded as interchangeable now have a reference price 10% higher than the cheapest product (Scrip,14th Dec,1993:6).

Many companies, but especially the foreign multinationals, decided to take their products off the reimbursement system and instead raise their prices (Schofield,1994:10). In the first half of 1993 following the introduction of reference prices the value sales of reference price products fell by 27% while those with non-reference prices rose by 12% (Scrip,7th/11th Jan,1994:11).

The sales value of innovative products on the reference price system fell by 42.2% when compared with sales in the first half of 1992, while sales value for generic products with reference prices rose by 2.7%. In total, products with reference prices had their share of total human pharmaceutical sales fall from 14% to 10% (Scrip,7th/11th Jan,1994:11). Both foreign and domestic industry associations have complained about the reference price system.

Supplementary protection certificates for pharmaceutical patents are also being adopted by Sweden. To cover the "gap" when the SPC regulation took effect in the EC and when it is regulation in EFTA countries, manufacturers can apply for SPCs for products coming off patent during this period. (Scrip 26th Oct,1993:6).

2.5.10 United Kingdom

The GDP of the UK drug industry grew by 6% in 1992. About 330 national and international manufacturers operate in the UK (about 6% of world production). The UK is the 4th largest exporter of drugs in the world (around 12% of trade annually). About 76% of UK exports went to other OECD countries compared with 59% in 1975 (the rise due mainly to increasing penetration in Europe) (Scrip,23rd Oct,1993:8). A high percentage of these exports come from UK subsidiaries of foreign firms using the UK as an export base. It is estimated that about 8% of total R&D expenditures in drugs in the UK is made by subsidiaries of foreign firms.

By 1992 the UK's drug industry's R&D had grown to a record £1,451 million a year, which was over double that spent in 1982. As a proportion of turnover the figure grew from 12% in 1982 to 17% in 1992. Now drug R&D represents almost 20% of all R&D in UK compared to just 10% in 1982. The UK is the fifth largest investor in R&D in the world, accounting for about 18% in Europe and 8% of the world total (Scrip,3rd Dec,1993:7).

Drug expenditure in the UK is about 10% of the NHS (Scrip,23rd March,1993:4). The average cost of a prescription in the UK between 1980 and 1990 increased by 87% (after inflation). This was due mainly to the cost of new drugs, especially cardiovascular and gastro-intestinal products.

The distinguishing regulatory mechanism of the United Kingdom's pharmaceutical industry is the Pharmaceutical Price Regulation Scheme (PPRS). The PPRS serves 3 roles: controls spending on drugs by the NHS, promotes a profitable industry and encourages UK based research. It does not directly control price but rather controls overall profitability measured by the return on capital for firms. The limit is between 17% and 21% and varies from company to company. Selling and promotion expenditure is capped on a company by company basis by means of a formula aimed at limiting expenditure to 9% of sales overall. The PPRS is only one of several cost control measures in the UK. Others include the extension of a selective list, introduction of prescribing controls, parallel trade and the rise in use of generic products (Watts,1993:30-31).

The PPRS involves direct negotiations between firms and government. It attempts to both contain costs and encourage R&D, and requires firms to notify authorities of the introductory price for new products. Origins of the agreement go back to 1957 with the Voluntary Price Regulation Scheme.

A new PPRS was agreed upon in August 1993. It includes an across the board 2.5% price decrease (which will last for 3 years). The agreement includes the following: the "grey" area - whereby firms were able to retain profits up to 50% above their target return has been stopped and replaced by a "margin of tolerance" of 25% in either direction. Companies exceeding their profit targets (plus margin) are required to repay the excess. Companies can only apply for a price increase if they forecast their profit margin is lower than their estimated rate of return by more than 25% (Watts,1993:30-31, Scrip,17th Aug,1993:2).

The ABPI reluctantly accepted the revised PPRS (which also includes harder criteria for allowing price increases), but the American PMA stated the revised scheme was "a serious threat" to the operations and research activity of the industry in the UK (Schofield,1994:10).

In 1992 the government announced that the Limited List concept (introduced in 1985) would be extended to 10 additional clinical categories in a bid to reduce the health budget. This sent shockwaves through the industry with many representatives claiming it could undermine the industry. It was also announced without consultation with the industry (World Pharmaceuticals Report, 6th Oct,1993:7-8). Also, in October it was announced that 62 drugs would no longer be available on the List, and this came into force in November 1993 (World Pharmaceuticals Report,3rd Nov,1993:7).

Drugs introduced into the UK in the past 5 years account for 69% of growth in the cost of drugs dispensed by UK pharmacies. An incentive scheme for GPs who prescribe economically has been introduced - the idea being that these GPs would be able to retain part of the savings to put into spending on improvements on other services such as; incentive payments to individual practices and money to improve other services and equipment. To help support the cost-cutting measures a new pharmacoeconomics research centre (PERC) has been set up in Dundee, Scotland to do economic evaluations of medicines - the first of its kind in the UK (Scrip,19th March,1993:4).

Profit levels in the UK have always been high compared to the size of the market. This has been due to the high penetration of new products, above-average overall prices and favourable corporate tax rates. But prices are now under pressure through the PPRS and also parallel imports. In early 1994 the British government was considering plans for pharmacists to substitute generic drugs even if physicians prescribed a brand-name product. Following concerns from several different groups, however, the government decided to abandon this scheme. Nevertheless, physicians are increasingly encouraged to consider cost-benefit trade-offs when they prescribe and there are limits on the level of pharmaceutical promotion (Smith,1992:25). As one analyst observed "the UK pharmaceutical industry is now entering a period of lower success rates and lengthening times of return from few successful innovations, while R&D costs escalate and more regulatory and cost-containment controls are imposed by the government" (Scrip, 3rd Dec,1993:7).

2.5.11 United States

The US drug industry is forecast to grow by 5% in 1993 - primarily through "blockbuster" drugs and a growing demand from the elderly for new chronic care medicines. In 1992 exports rose by about 18% to almost US$6.8 billion and imports grew by almost 14% to about US$5.5 billion. As of the end of 1992, total employment in the industry was about 195,000. The US market is expected to expand over the next 5 years but will be under increasing pressure to control prices (Scrip,26th Jan,1993:16).

A General Accounting Office (GAO) study reports that US pharmaceutical manufacturers charge on average 32% more to US wholesalers than they charge Canadian wholesalers (with 81% of the products priced higher than in Canada). The GAO concluded that the price difference was due to the action by governments in Canada to curb federal and provincial drug prices (Scrip,30th Oct,1992:6).

Recent US legislation affecting the drug industry could cost research-based manufacturers about $14.5 billion over the next 5 years - according to a study by Price Waterhouse. The legislation includes: 1990 Medicaid rebate law, extension of similar discounts to the Departments of Defense and Veteran Affairs, the Prescription Drug User Fee Act of 1992, the revenue raising provisions of the 1993 Omnibus budget bill including cuts in Section 936 tax credits, a rise in the corporate income tax rate, and an end to the ban on medicaid formularies (Scrip 29th Oct,1993:21). So although some analysts may advocate the pricing freedom of the US market, in reality there are many other mechanisms being put in place which could impact on the profitability of the industry (see the response to these in chapter three).

Intellectual property protection (IPP) has been central to US international trade policy. As part of "special 301" (under section 301 of the US Trade Act of 1974), the US can consider measures of retaliation against other countries not having adequate IPP. The US has continued bilateral initiatives to put pressure on several countries to develop stronger patent protection. Patent protection is slowly taking place in the developing world (in Argentina, for example, a patent protection law was introduced in 1991). Brazil also moved in this direction in 1991 but the legislation has not been moved forward. Other countries where patent protection laws have been introduced in the past few years include Chile, China, Indonesia and Korea. Other countries, such as Hungary, Colombia, Turkey and India do not have patent protection for pharmaceutical products and could face further US government initiatives to improve their IPP (PMA, Ind Brief,16th Jan,1993:3).

Lack of IPP is a continuing impediment to further expansion globally by US firms especially in some of the major markets (for example, India, Brazil, Argentina, Venezuela, Turkey and Thailand). Also, other problems confront American firms such as discriminatory pricing, compulsory joint venture requirements with local firms and high import duties. American companies lose up to US$5 billion every year in sales to "patent pirates" (PMA, Ind Brief,16th Jan,1993:1).

The most significant change to the market life of a drug product in the 1980s was the rise of generic competition. An examination of the market in the 1970s by Statman (1982) showed that brand-name drugs maintained a high level of the market share after generics were introduced. The 1984 Drug Price Competition and Patent Restoration Act shortened and simplified the regulatory process for generic drugs by allowing firms to submit abbreviated new drug applications (ANDA). Grabowski and Vernon (1992) focused on 18 'significant' drugs whose generic competition occurred after 1983. They found on average that the products faced 25 generic competitors and lost half their market share within 2 years.

The Waxman/Hatch Act of 1984 accelerated FDA approval of generic drugs by creating the abbreviated new drug application (ANDA). This law struck a balance between the need to increase availability of low-cost medicines and the desire to compensate brand-name manufacturers for R&D. In other words, the solution was a short term patent restoration offer to the industry in exchange for agreement on a streamlined ANDA. The result has been an increase in the role of generic drug producers while brand name manufacturers have been able to get patent extensions - of about 2 years which many say offset delays from FDA regulation times. Once a manufacturer applies for extending a drug patent the Patent and Trademark Office seeks understanding from the FDA of the actual review time and bases its decisions on this (Tobias,1992-93:6-7) (see section 3.3 of Chapter Three).

Kaitin and Trimble (1987), however, show that effective life is increased by about one and a half years. Grabowski (1991) observes that manufacturers now operate in an environment where they must recoup their R&D expenses in the first 10-12 years of the patent life. The share of prescriptions for generic products in the US is expected to exceed 50% by 1995 and to increase further by the year 2000 when more than 200 drugs (with sales of $22 billion in 1991) will have come off patent protection (Scrip,9th/13th April,1993:18).

Drug formularies are expected to become the norm as the Clinton health care reforms evolve. Some analysts fear that this will result in less demand for innovative drug research. There are also suggestions that brand-name manufacturers pay a rebate of 17% on drugs supplied to medicare patients while no rebate is required of unbranded generics. Another proposal is the creation of a new Advisory Council on Breakthrough Drugs which would "examine the reasonableness of launch prices of breakthrough drugs". There is also a provision for prior approval for physicians prescribing certain drugs. This would also act like a formulary (Schwartz,1994:20). The PMA estimates the Clinton Bill would reduce revenues of the brand name (or innovative manufacturers) by 11.2%.

There will also be an important role for managed care - which, in different ways, influences 50% of drug volume. Managed care organizations are also becoming more aggressive about cutting drug prices (many of whom use formularies and have a Drug Utilization Review program) and corporate strategies are beginning to take into account the emerging managed care markets.

Through a variety of pressures the industry is having to make some critical decisions regarding pricing. As Schwartz comments: *"The PMA has abandoned all its past allegiance to free pricing and is now hoping, at best, for government acceptance of a pricing formula in which pharmaceuticals may only increase by roughly the consumer price index each year"* (Schwartz,1993:10). Indeed, in 1993 the PMA sought through a large block of companies to agree to keep drug price increases tied to the annual rate of inflation. It sought an anti-trust waiver but did not get it. Instead the PMA had to ask firms for voluntary restraints.

Many pharmaceutical companies have been taking advantage of huge tax concessions for operating plants in Puerto Rico. Recent legislation, however, has reduced that level of tax concession. The US Senate Finance Committee investigated use of section 936 of the internal revenue code and limited the tax credit for pharmaceutical companies although it did agree to lessen the original amount it was going to curb (World Pharmaceuticals Report, 1st July 1993:8).

So although government regulatory mechanisms in the US have avoided price controls it is inevitable that pharmaceutical companies will face increasing demands to lower the prices of their products. Recognizing this, brand-name manufacturers have developed an array of strategies ranging from alliance formation with generic producers, development of OTC expertise, collaboration with small research intensive companies, alliances with university and other research institutions and the re-focusing on what the companies perceive to be their "core" activities.

CHAPTER 3. CORPORATE STRATEGY

3.1 INTRODUCTION TO THE NATURE OF CURRENT COMPETITIVENESS

The previous chapter outlined some of the current regulatory changes occurring in the major markets of the global pharmaceutical industry today. With the growing level of patent harmonization in the industrialized world, the nature of price and profit control mechanisms in place in different countries takes on increasing importance to the corporate strategies of pharmaceutical firms. Nation states attempt to balance cost containment and health care reform with appropriate industrial policy to ensure the continuation and/or enhancement of research and development. These "contextual changes" provide both threats and opportunities for pharmaceutical firms.

This chapter focuses on the following broad themes which are integral to the competitiveness of pharmaceutical firms today:

- business orientation of the major brand name manufacturers
- business orientation of the major generic drug manufacturers
- anticipated growth areas
- the role of new technology and management practices.

Pricing practices are increasingly important, product development is becoming more focused and firms more specialized in their research activity, technological sophistication is critical to product and process development, and research, production and distribution patterns are becoming increasingly diversified. At the market end of the production spectrum there is a move away from 'detailing' the physician to 'educating' the patient, physician, pharmacist and drug purchaser. The backdrop to these changes is that costs are increasing throughout the pharmaceutical business.

The transformations affect both the external industrial environment and the internal structure of pharmaceutical firms. The brand-name manufacturers are now searching for other elements of the pharmaceutical delivery continuum to maintain their profitability. The following sections look into these issues in greater detail.

3.2 BUSINESS ORIENTATION OF THE MAJOR BRAND NAME MANUFACTURERS

- Cost containment policies of governments have had a considerable impact on the strategies of pharmaceutical companies.

- The stock market response to cost containment policies and healthcare reforms: *"advise that companies such as Merck. Glaxo, SmithKline Beecham and Pfizer be taken off recommended "buys" list"* (Scrip,23rd Feb,1993:2) Revenue growth for the industry as a whole declined from 17.7% in 1990 to 11.1% (estimate) for 1993. Standard and Poor's Drug Index of pharmaceutical stocks lost 22% of its value in 1992 and declined by an annual rate of 25% in the first half of 1993 compared to gains of 4% and 7%

respectively for the whole share market. The 13 pharmaceutical companies tracked by S&P lost $90 billion in market value over the 18 months ending June, 1993 (Scrip 29th Oct,1993:21).

- Some companies have shifted focus from pricing to higher sales volume as the key to maintain earnings (for example, Merck and Pfizer) (Tobias, 1992/1993:6).
- Companies are looking at integration **in various forms** along the "value chain" to maintain earnings.

- Generic products, over-the-counter (OTC) drugs, and wholesaling and distribution networks are being pursued by the brand-name manufacturers.

- Collaborative integration is central to many corporate strategies.

- New regional markets offer opportunities for expansion.

There are a variety of strategies that the brand-name manufacturers are developing. There are expansions into new geographical markets, new niche product markets, and other stages of the value chain. In addition, the internal structure of firms is changing in light of new technologies and "new" management practices.

The changes are taking place within an industry that is becoming increasingly global as firms develop greater market presence in different geographical markets and research is conducted in an increasingly de-centralized manner. Japanese firms, for example, are developing a greater market presence in both North America and Europe while at the same time further developing their research capabilities.

New "strategic plans" are being developed. It is a period in which firms are re-assessing their capabilities. At SmithKline & Beecham the marketing and R&D departments spent 18 months developing a plan that outlines the traditional strengths/weaknesses, threats/opportunities for their global operations. Eli Lilly has dropped its distinction between US and non-US operations and has stated it will push decision-making downwards in the organization (Scrip,27th Nov,1992:7).

Generic products are receiving increasing attention. Rhone-Poulenc Rorer (RPR), for example, is establishing a US generics division - Arcola Laboratories. This forms part of RPRs "lifecycle extension strategies" (i.e. through the generic market). Similar generic divisions have also been set up by Merck (West Point Pharma), Zeneca (IPR) and Syntex (Hamilton Pharma). In the UK Rhone-Poulenc entered the generic market in the 1980s through buying APS, while Rorer already had a generic subsidiary - Berk (Scrip,10th Aug,1993:9).

Rationalization of production has become increasingly common. Yet while many of the brand-name manufacturers have announced job cuts and plant closures other firms have been announcing expansions (for example, the US biotechnology-based company Amgen announced plans to hire over 1,000 employees over the next year (Scrip,24th,Sept,1993:9). Although lay-offs and "rationalizing" tendencies are dominating corporate strategy firms have also been expanding into different territory in search of further profit. Some firms choose not to rationalize their activities. In Europe, for example, instead of rationalizing production Glaxo is shifting resources to meet regional need. (Scrip,11th Sept,1992:11). Many companies are extremely well-off financially. It is not all gloom and doom in the pharmaceutical industry.

Not all companies pursue the same strategies. Some refuse to get involved with the generic industry, others choose to re-focus their therapeutic lines and product markets, and some choose certain geographical markets for expansion over others. In this latter case, the industrial policies of specific countries help shape corporate strategy. In Australia, for example, the Factor F incentive scheme has attracted investment from several overseas companies.

3M Pharmaceuticals entered Australia's Factor F incentive scheme and plans to invest US$ 14.5 million over the next 7 years - mainly on projects that will upgrade GMP (Australia is one of 3Ms 3 manufacturing locations worldwide, the others being the US and UK (Scrip,25th May,1993:12). Similarly, Glaxo opened a US$7 million development laboratory in Melbourne which focuses on anti-asthmatics, analgesics and cystic fibrosis therapies. The Chief Executive of Glaxo Group Research stated the incentive scheme showed *"how well the industry and government can work in partnership to the benefit of the economy, and, most importantly, the patient"* (Scrip,16th Oct,1992:11).

3.2.1 Observations of Corporate Strategy

- Despite many reports in the pharmaceutical business literature which state that firms plan to get products to the market quicker none say how this is going to be done.

- Glaxo's 4-point focus for 1993 was: 1) maximize sales of established products in world markets, 2) penetrate global markets rapidly and effectively, 3) bring new and innovative products to the market, and 4) invest in developing markets. With 4% of the world's pharmaceutical market, Glaxo continues to develop its "integrated international network of manufacturing sites", with new projects in the UK, France, Canada, Australia, Indonesia, Saudi Arabia, Argentina and Turkey (Scrip,12th Oct,1993:6).

- Merck's focus for 1993 was strategic marketing initiatives, a focus on the managed care sector, streamlined manufacturing, cost control programs, productivity improvement, and organizational changes (Scrip,2nd April,1993:7).

- The long-term strategy of Swedish company Pharmacia in Japan is to maintain partnerships with local companies while positioning to develop a more independent marketing position in core areas (such as oncology, opthamalics and diagnostics).

Pharmacia claim that you can not get to physicians effectively without some form of collaboration (Scrip,22nd Oct,1993:11).

- Hoffman-La Roche's country-by-country marketing is regarded as bad management by analysts who maintain that products must be focused globally. Roche claims it is turning things around with research centres focused on specific programs and with a global focus (Scrip,27th Aug,1993:12).

- Over the past few years Schering Plough has focused its business on 7 markets: Canada, France, Germany, Italy, Japan, UK and Spain (almost two-thirds of revenue compared to 50% in 1987). It is now expanding in eastern Europe and China and also creating a special marketing unit for the managed care industry in the US (Scrip,2nd April,1993:12).

- Bayer is entering the US generics market and is building a new R&D facility in Japan in Kansai Science Center near Kyoto. This R&D facility completes its R&D triad - Wuppertal (Gmny), and West Haven (US). Bayer's strategy is to locate R&D in market potential areas and where there are high scientific standards (Scrip,16th March,1993:14; 3rd Dec,1993:8).

- Part of Eli Lilly's strategy is to increase its global presence, speed up its R&D activities (by 50%), and overhaul its cost structure. This is because of its mature portfolio, downward pressures on prices and few major product launches expected in the next 2 years. Increasing the global nature of the industry is critical to EL. Over the past few years it has increased its overseas sales force by 113% but it is still minor when compared to other firms. ELs non-US sales force, for example, is about 2,300, whereas Merck's is 4,800 and BMS's is over 6,500 (Scrip,30th July,1993:14).

- Hoechst is developing a 4-point corporate strategy: cooperation, coordination, concentration and cost-reduction (Scrip,29th Oct,1993:10).

- In the 1990s Sandoz will seek to 'fine-tune' its group structure. Flexibility will be sought through decentralization. It will seek a logical agglomeration of its core interests.

- With the increasing proportion of the population being elderly, Abbott is focusing attention on hypertension, rheumatoid arthritis, antibiotics, antacids and new ulcer therapies.

3.2.2 Globalization

- The globalization of markets and research is dominating many brand-name manufacturers business strategies.

- Japanese firms are increasingly focused on global operations.

- European firms are moving into the much larger and more lucrative and hospitable American market.

- American and European firms are expanding operations in Japan.

Examples of globalization strategies:

- Eli Lilly has increased its presence in the Pacific Rim, eastern Europe and Latin America and is looking at collaborative ties with firms in Japan, Germany, China, Australia, Hungary, Turkey and Greece (Scrip,30th July,1993:14).

- In response to reforms in Germany HLR says it is now increasing its efforts to reduce the time it takes to bring products to the market, and to increase the use of its global manufacturing network (Scrip,22nd June,1993:14).

- In October 1993 Sandoz opened its R&D facility in Tsukuba Science City, Japan, thus providing a research facility in each of the triad markets. This is part of Sandoz's global strategy to be able to bring new products to the market simultaneously in each of the three major markets and being able to produce and market according to the local context (Scrip,5th Oct,1993:11).

- Examples of Yamanouchi's (Japan) global strategy include: being listed on the Paris stock exchange, the building of a research institute in the UK (and plans to build similar research centres worldwide), a production facility in Ireland, acquisition of a US healthcare and household products company and the creation of a European base with the acquisition of Gist-Brocades' pharmaceutical division (Scrip,15th July,1992:10; Scrip,11th Sept,1992:15).

- The R&D operations of firms based in the United Kingdom have become increasingly global (see table on the following page).

Table 3.1 Globalization of R&D activity by the top four UK Pharmaceutical Companies, 1978-1988.

Top 4 Companies *	number of employees, 1978	%	number of employees, 1988	%
UK Based	5,049	86.4	10,297	72.1
Overseas	798	13.6	3,975	27.0
Total	5,847		14,272	

* Glaxo, Beecham (now SmithKline Beecham), ICI Pharmaceuticals, Wellcome.

Source: Howells (1990:30).

Sophisticated communications, design and transportation technologies have contributed to the growing dispersion, or de-concentration, of pharmaceutical activity. There is no longer a necessity to have various stages of the production process located close to one another. What is more important is access to skilled researchers and new and expanding markets.

3.2.3 Product Mandates

Companies are now developing explicit product mandates for their operations at the regional and global level. Decisions on product mandates are based on a variety of location-specific factors of different countries:

- skill level of the scientific community
- commitment to R&D by the local, regional, state/provincial governments
- extent of the specific disease for which products are being developed
- extent to which specific branch plants have advanced manufacturing and/or research expertise
- ability of local operations to utilize other resources which specific locations may possess (for example, national research institutes).

To a branch plant operation, product mandates provide security, enhanced status and the infusion of capital for expansion within the global operations of the major manufacturers. Many companies have national mandates within Canada but some also have regional and world mandates. Boehringer-Ingelheim's Canadian operations, for example, now has regional mandates for the Caribbean, Merck-Frosst has regional mandates (North America and Europe) and global mandates, and Sandoz has global mandates for neo-citran and Lescoll (a cholesterol lowering drug). Other companies are in the process of re-visiting their product mandate strategies.

There may be different reasons for why certain operations receive product mandates. At Merck, for example, a global product mandate for 'Proscar' was awarded to a UK plant. The decision was likely based on the availability of the necessary technical skills and the location being where there is the greatest incidence of 'symptomatic benign prostrate enlargement', which is treated with Proscar. Of a total potential patient population of 38 million almost 20 million are in Europe. With Sandoz's Lescoll, the global mandate was given to the Whitby, Ontario plant which was able to demonstrate its superior capability with process design.

Companies such as Merck, which perceives Canada as providing a high calibre of technical personnel, will weigh this national location for R&D against its other R&D facilities around the world (ie, UK, Japan, US (2), Spain and France). Global product mandates also increase the level of internal competition within global corporate structures. There is a need to examine this element of corporate organization in much more detail. More (nd), provides a starting point for this in the context of pharmaceutical subsidiaries operating in Canada but more intensive analysis of the decision-making process at corporate headquarters is required - particulalry if we are to fully understand how the Canadian industrial environment compares to other subsidiaries of a company's global structure.

3.2.4 Rationalization

"Rationalizations are merely a structural adaptation to long term technological and economic challenges. Restructuring is not a retrenchment, but the new lean reality that will be required to generate advantages in the new global marketplace with global mandates".

- Rationalization has occurred primarily in Europe and North America.
- Involves mainly manufacturing workers, administration, sales and marketing staff.
- Cost containment measures in Germany and Italy are responsible for many European lay-offs.
- Cuts are being instituted in product areas which are "not performing" or unprofitable.
- Downsizing and disinvestment in one country has often led to relocation and investment in another.

Discussion:

As with other industries, pharmaceutical companies appear to be advocating the "lean production" approach to their operations. Recent drug company announcements of impending lay-offs in the industry have totalled about 7,000 jobs (Pfizer - 3,000 worldwide, American Cyanamid - 2,500 over the next 3 years, and Upjohn - 1,500 by the end of 1994). Associated with these cuts will be a reduction in excess capacity (World Pharmaceuticals Report,3rd Nov 1993:9).

There has been considerable restructuring activity in Europe over the past few years. There are numerous examples - some of which relate to the reforms in Italy and Germany, and others which suggest a transition in keeping with the rationalization associated with European integration:

- In 1992 Bristol-Myers Squibb (BMS) announced plans to lay-off 2,200 workers (about 6% of its worldwide workforce) because of pressure on prices. In 1994 BMS announced a further restructuring involving about 5,000 employees worldwide, 3,000 of whom are in the pharmaceutical industry. In Europe the current 4 region structure will be replaced. This gets rid of a layer of management with business units now reporting directly to a central European headquarter. BMS blamed the cost-containment measures in Germany and Italy among other things for its sales decline in the 2nd quarter of 1993 (Scrip,6th Nov,1992:9; 30th July,1993:12; 7th/11th Jan,1994:12).

- SKB expressed difficulties with Germany and Italy following its sales falling by 9% and 18% respectively and laid off 100 sales staff in Germany (Scrip,27th July,1993:9).

- BASF is laying off 10-15% of its pharmaceutical industry staff (the Knoll group - recently named BASF pharma, which in Germany employs about 3,785 staff). The job losses are part of a broader restructuring of Knoll which includes the centralization of Knoll's core markets (Germany, Italy and the US) under single management structures (Scrip,16th July,1993:9; 3rd Dec,1993:13).

- Boehringer Mannheim is moving its therapeutics headquarters from Germany to the US because of Germany's changing pharmaceutical industry environment. BM's pharmaceutical sales declined by 23% in the first 5 months of 1993 in Germany because of the recent reforms. BM made 300 redundant in 1992. The CEO of the parent company Corange also made recommendations that about 1,800 of the 9,600 workforce in Germany be laid off, although the R&D facilities would be not be restructured. The move to the US is also an attempt to gain better access to the world's biggest market and to key technologies such as gene therapy (Scrip,2nd July,1993:7; Scrip,19th Oct,1993:7).

- With sales also down in Italy and Germany, Hoechst commissioned a report which states that 300 jobs could be trimmed from its German pharmaceutical workforce of 1,400. Eighty percent of Hoechst's product lines are affected by fixed payments following the reforms (Scrip,29th Oct,1993:10).

- Bayer has been hit by the German reforms. With turnover down 20-40% in the first 2 months of 1993 the company is looking at rationalization measures (Scrip,26th March,1993:7).

- With continuing lower sales in Italy and Germany (and the US) Rhone-Poulenc Rorer stated that it would have to "streamline" its operations (Scrip,29th Oct,1993:18).

- Rationalization by MNCs in Europe is having an impact on the less developed areas of Europe (In Portugal, for example, SKB, Wyeth and Schering have each closed plants) (Scrip,20th May,1992:6).

A similar situation exists in the United States and Canada, although in Canada, several large investments have been made by brand-name manufacturers as part of their commitment to Bill C-22. The US industry has announced over 10,000 positions lost in the past year. Examples of downsizing and disinvestment in the US include:

- Merck has announced a restructuring program involving the reduction of its workforce by 2,100 employees at a cost of US$450 million. It also plans to restructure/rationalize its manufacturing facilities at a cost of US$325 million, which will reduce the workforce further. Merck claims these plans will reduce annual employment costs by over US$150 million (Scrip,30th July,1993:9).

- Eli Lilly will be cutting costs. Through attrition, voluntary retirement and "very selective hiring" up to 2,000 jobs will be cut worldwide by mid-1994. An additional 2,000 positions are expected to be eliminated in subsequent years. It is downsizing its administrative centres in London and Vienna although it also plans to expand in Europe and other regions in the world (Scrip,19th Oct,1993:6).

- J&J plan to eliminate 3,000 jobs in 1993 through early retirement programs and "other cost cutting initiatives". There are some reports that J&J will cut back in Europe where many firms have excess capacity (Scrip,20th Aug,1993:6).

- Pfizer is to reduce its workforce by 3,000 over next few years. Pfizer says this is part of its attempt to streamline operations and focus on its core business. Since 1988 Pfizer has closed or divested 14 operations which were unrelated to health care or under-performing (Scrip,27th April,1993:13; 26th Oct,1993:10).

- Upjohn's restructuring includes a workforce reduction of about 1,500, and the elimination of excess capacity in 14 plants worldwide. It has already reduced its workforce by 2,000 from its 1989 total of 21,000 (Scrip,26th Oct,1993:10).

- Cyanamid is reducing its staff by 2,500 - mainly in its medical business (Scrip,26th Oct,1993:10).

- Syntex cut its workforce by 800 in the first part of 1993 and plans to cut another 1400 by the end of fiscal 1995 through the closure of manufacturing plants and cuts in administration and marketing. It is winding down facilities in the US, UK and France and consolidating in Canada, Mexico, Puerto Rico, Spain and South Korea. Its restructuring is expected to save about US$180 million annually (Scrip,4th/8th June,1993:13).

- Wyeth-Ayerst's 2 Canadian operations - Ayerst, McKenna, Harrison in Montreal and Wyeth in Windsor merged and this meant the closure of the Windsor facility and consolidation in Montreal. It did, however, build new operations in Toronto (Scrip,4th May,1993:7).

- Ciba-Geigy cut its workforce of 5,550 in the US by 10% in 1993 as part of a cost reduction program. Ciba cut 1,000 jobs in 1992, as well as 2,100 in 1991 - future cuts will be in areas deemed as not being high growth (Scrip,15th Jan,1993:12;6th April,1993:11).

- Searle faces major job losses following its parent, Monsanto's, cost cutting exercise. An estimated 2,250 jobs have, or will be, cut at Searle (nd).

This information can be summarized in the following table.

Table 3.2 Examples of recent empoyment effects of rationalization strategies by brand-name manufacturers

Company	Region	Rationalization strategy
Bristol-Myers Squibb	worldwide	5,000 employees involved in restructuring (1994)
Eli Lilly	worldwide	2,000 jobs to be cut by mid 1994, additional 2,000 in subsequent years (1993)
Syntex	worldwide	800 jobs cut, further 1,400 to be cut by 1995 (1993)
SmithKline & Beecham	Germany	100 sales staff laid off (1993)
BASF (Knoll group)	worldwide	10-15% of pharmaceutical staff (1993)
Ciba-Geigy	U.S	550 jobs cut (1993)
Merck	worldwide	at least 2,100 employees to be laid off (1993)
Johnson & Johnson	worldwide	3,000 jobs to be cut (1993)
Boehringer Mannheim	Germany	recommendations that 1,800 be laid off (1993)
Hoechst	Germany	recommendations that 300 be laid off (1993)
Pfizer	worldwide	3,000 jobs to be cut (1993)
Upjohn	worldwide	2,000 jobs cut and a further 1,500 jobs to be cut (1993)
Cyanamid	worldwide	2,500 jobs to be cut (1993)
SKB, Wyeth and Schering	Portugal	plant closures by each company (1992)
Ciba-Geigy	U.S	1,000 jobs cut (1992)

Company	Region	Rationalization strategy
Bristol-Myers Squibb	worldwide	2,200 lay-offs (1992)
Boehringer Mannheim	Germany	300 employees laid off (1992)Searle
Ciba-Geigy	worldwide	2,100 laid off (1991)
Searle	worldwide	2,250 jobs to be cut (nd)

Source: Scrip, various issues.

It can be expected that these cuts will continue in the industry as reforms to healthcare continue in the industrialized countries. There are few cases of research staff losing jobs, although with greater use of universities, other research institutes and contract research companies, it is likely that substantial transformations in the industry's labour market will occur. Indeed, several companies have indicated they are looking for scientists who can integrate different research projects that are now externalized to other research centres. Such "quasi-integration" has considerable implications for the organizational structure of the industry.

3.2.5 Mergers and Acquisitions

- Mergers and Acquisitions continue to play a role in the industry.
- Brand-name manufacturers are using acquisitions to access the generic market.
- Acquisitions of small, biotechnology-based firms continues.
- Mergers have been brought on by increasing competition, rising R&D costs, longer development times and the need for greater capital investments.

There were 760 mergers and acquisitions in the pharmaceutical and biotechnology industries worldwide between 1988 and 1992 (including research institutions and universities) - 188 of these were completed in 1992 which represents a 60% increase on the previous year (Scrip,19th Oct,1993:10).

Two recent examples of mergers include Hoechst and Roussel Uclaf, who expect cost savings and the elimination of duplication from merging their pharmaceutical operations (Scrip,2nd Nov,1993:9), and Toyama Chemical and Mitsui Pharmaceutical in Japan who merged mainly because of pressures brought on with biennial reimbursement price cuts for antibiotics in Japan (Scrip,4th May,1993:11).

Several manufacturers have used acquisitions to access the generic product markets. Marion Merrrell Dow (MMD), for example, acquired the generic drug business of the Rugby-Darby group, the largest generic drug manufacturer in the US. The move was seen as "a strategic step that builds upon MMD's recognized leadership in marketing pharmaceuticals to the growing US managed care market". In 1992, Rugby had net sales of about $US 280 million with over 87 million prescriptions (Scrip,15th Oct,1993:11).

A more significant, flexible organizational form which companies have been using are collaborative relationships with others and with universities and research institutes. They are considerably more flexible because they provide specific access to skilled researchers, research, technology and markets without the commitment to other 'unwanted parts' of an organization. Mergers and acquisitions may also lead to considerable complexity as firms attempt to unravel the alliances that their partners or acquisitions have developed. When Novo Industri and Nordisk Gentofte merged, for example, each had alliances in 32 and 18 countries respectively (Scrip, 21st June,1991:13).

3.2.6 Collaborative Integration

- Collaboration continues to be critical to the industry.
- Access to resources and the increasing costs of doing business are the key factors for why companies collaborate.
- Some firms have this as an explicit strategy to gain a greater presence in the globalized industry.
- Collaboration is a not a new phenomena, nor is it unique to the pharmaceutical industry.
- While critical to the pharmaceutical industry it is essential to biotechnology-based firms.
- Collaboration is particularly important to firms with weak product pipelines.

The phrase "collaborative integration" covers many different types of "quasi-integrative" relationships amongst firms, research institutes and universities. The popular term is "strategic alliance" but this is an often misunderstood, confusing statement which, to some, also refers to mergers and acquisitions. There are many other phrases (for example, strategic partnerships, collaborative ventures) but the essence is cooperative linkages between 2 or more organizations as they share their resources for a specific purpose.

As with other industries, some firms have a better understanding and capability with these relationships than others. Some firms rely on these linkages for their survival. There is also a question regarding the size of internalized research in large corporations and how this can be effectively managed. A key advantage of a partnership is that it provides access to smaller research units that can do research more effectively outside the large, sometimes bureaucratic organizational structure of brand-name companies. Collaboration became increasingly dominant over the 1980s and is expected to play a pivotal role in the pharmaceutical industry over the 1990s.

Several examples and points illustrate the 'wide' nature and extent of collaborative integration:

- co-marketing (where 2 companies market one product under different brand names) is more common in Europe than in the United States, where co-promotion (2 firms market a single brand using the same pricing and promotional strategy) is more popular. Co-promotion is now taking on in Europe because it provides faster market penetration and greater market share. It is currently disallowed in Italy and Spain. It has uncertain acceptability in Japan, although Japanese companies prefer to license in products from US and Europe firms.

- Licensing helps the internal product pipeline. Europe is regarded as a "rich and unexploited licensing resource" as it is still a mix of a dozen or so complex and different markets. Licensing is also seen as a way of entering into the single European market.

- Forty-six percent of Marion-M-D success is through licensing in (46% of company sales for 1990 - others, Schering-Plough, 32%, Merck 30%, Pfizer,24%). Collaboration is a way to quickly increase or develop geographic or product market presence. It is a popular way for Japanese companies to get an American presence (Hone,1993:44).

- Firms can gain access to research and markets. Chugai (Jp) entered a collaborative relationship with Australia's AMRAD corporation (the Australian biomedical research and development company) - each gets certain rights to each others products in certain regions (Haydock,1994:24).

- Alliances are seen by independent french companies, mainly family concerns, as a key strategy to get the critical mass to counter the dominance of multinationals in France (Scrip,2nd Feb,1993:2; 5th Feb,1993:10).

- US and European firms have sought to gain greater control of their collaborative relationships with firms in Japan while Japanese firms have sought to do the same with their partners overseas (Howells,1990).

- Rhone-Poulenc Rorer is looking for collaborative ties with other firms in a bid to rebound from its fall in profit in 1993. It would like partners in the OTC sector, its core prescription area, and with firms based in the US and Japan. Like other major firms RPR wants to become a leader in cell therapy and genetics (Scrip,14th Jan,1994:6).

- US biotechnology-based company Tularik formed a collaborative relationship with Merck and Yamanouchi. Yamanouchi states that this alliance is part of its strategy for new product development and is part of a broader overseas R&D network (Scrip,14th Jan,1994:12).

- Seeing the potential of the generic market in the US with the increasing role of managed care, the Clinton health reforms and major products coming off patent, Hoechst is now collaborating with the US generic firm Copley Pharmaceutical (Scrip,19th Oct,1993:8).

- With the huge costs, risks and uncertainty of product development, competitors do collaborate. Manufacturers, for example, are pooling resources on AIDS and HIV infection. Fifteen companies from the US and Europe are sharing information and supplies. Companies include Astra, Boehringer-Ingelheim, BMS, Burroughs-Wellcome, DuPont-Merck, Glaxo, Hoechst, Roche, Lilly, Merck, Pfizer, Miles (for Bayer), Sigma-Tau, SKB,and Syntex (Scrip,23rd April,1993:10).

- Chiron has over 200 collaborative relationships with the academic world.

- Between January 1991 and October 1992 Eli Lilly formed 12 new relationships - mainly equity deals with small partners (Longman, Dec/Jan,1992:19).

Several questions can be raised regarding these types of linkages.

- How can industrial policy be developed to utilize these organizational forms for the benefit of local economies?

- What is the most effective form of government involvement?

- Are companies using collaborative ties as part of a long term corporate strategy or are they seen as short term "quick fixes"? What are the implications?

- Is collaborative integration merely a "stepping stone" for eventual takeover?

- Will collaborative ties ultimately lead to greater control (but not ownership) over product development by the large brand-name manufacturers?

3.2.7 Research and Development

The following chapter looks into R&D in greater detail but there are some interesting developments in this part of the pharmaceutical business which should be incorporated into our understanding of corporate strategy.

- The R and the D are beginning to be split up.
- The location of parts of the research phase are being dispersed geographically.
- Japanese firms are expanding their R&D operations.
- Research centres are taking on specific responsibilities for certain products.

- Presently 50% of Ciba-Geigy's research is conducted in Switzerland, but R&D activities will increasingly be undertaken close to markets to also take advantage of cost efficiencies and other local conditions favourable to research.

- In 1992 HLR made each of its research centres responsible for specific therapeutic areas - this, combined with its international integration of clinical R&D should enhance its ability to reduce the time it takes to bring products to the market.

- A survey of Japan by the Kosheisho (Ministry of Health) revealed that 100 out of 120 Japanese pharmaceutical firms conduct R&D abroad, 6 of which have overseas labs. Eighty-percent are planning to conduct discovery research outside Japan and half intend to set up more extensive R&D facilities abroad - mainly in immunology, cancer, cardiovascular and antibiotics (Scrip,9th March,1993:10).

- A satellite system for basic R&D is being developed by Otsuka Pharmaceutical. This involves 11 domestic and 2 overseas research facilities - each of which is relatively autonomous and hopes to take advantage of localized skilled personnel (Scrip,8th Oct,1993:15).

- R&D as a percentage of sales in Japan has doubled since 1980 and is expected to grow further.

- Glaxo has split R&D into 2 new divisions: the Research division and the Group Development and Product Strategy division. This reflects a recognition that there is a close relationship between strategy and marketing and the development process. Research can then focus on identifying new chemical entities (Scrip, Nov,1993:6).

- Sandoz is reorganizing by distinguishing between research and development with the hope that the specific focus will prove more effective - especially if it can reduce the time it takes to get a product to the market (Scrip,17th Dec,1993:7).

- Elf Sanofi is closing 2 R&D centres as part of its restructuring program - which also includes forging collaborative ties with Winthrop and BMS. It has decided to focus [read specialize] in its major therapeutic areas (Scrip,14th Dec,1993:8).

- SKB is rationalizing its research and focusing on core therapeutic areas and technologies applicable to biotechnology, chemistry, biochemistry, molecular pharmacology, cell biology). This, they say, will avoid duplication and enable better focus on rational drug design. It also involves about 150 redundancies in R&D (Scrip,2nd/4th Sept,1992:9).

- Syntex's restructuring program also involves re-prioritizing some of its R&D activities. Syntex currently commits about 18% of sales into R&D but its "worldwide development research organization" is being "redesigned" to help reduce the time taken to move new drugs from the discovery phase to the marketplace (Scrip,6th Nov,1992:9).

- AMRAD (Aust) has several collaborative relationships with major drug companies in a bid to expand its market potential globally. For the drug companies it presents an opportunity to tap into the research capabilities in Australia. Major firms include Merck, Chugai and Sandoz (Scrip,10th Sept,1993:13).

- Boehringer Ingelheim lost $US 30 million in German sales in the first part of 1993. With sales down by 18% BI warned that the German government should not be surprised if the industry started to move its R&D into other countries which reward innovation. 1,896 of BI's 3,677 R&D staff now work outside of Germany and it is increasing its US presence. BIs research will be more focused on a narrower range of diseases - respiratory and cardiovascular, inflammation, CNS immunology, virology and oncology (Scrip,22nd June,1993:8).

There is then, some degree of rationalization in the R&D process. In part this relates to new methods of discovery and to the growing acceptance by firms of the need to specialize on core product areas. Research is moving away from the conventional "shotgun approach" for new drug development and towards rational drug design. The predominant approach to research has been to screen thousands of chemicals and this would be followed by animal and clincial testing. Now, with rational drug design, desirable properties of a potential drug are identified in advance and then research is conducted to develop the necessary compounds. Opportunities exist for countries which have renowned areas of research specialization.

3.3 BUSINESS ORIENTATION IN THE GENERIC DRUG INDUSTRY

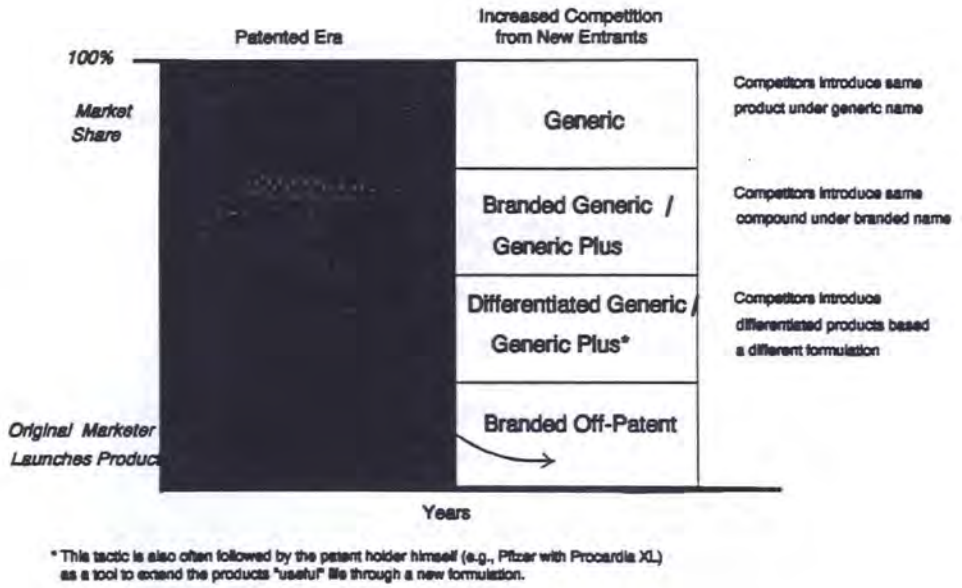
The term generic is used to designate pharmaceutical preparations based on active ingredients that are no longer patent protected and are freely available on the merchant market. Several different types of generic products exist:

Branded Generics: frequently called "branded multisource products" offered under a brand name and actively promoted through a detail force to the medical community. These branded generics can be found in countries like Italy or Finland where patent protection is relatively recent.

Plain Generics: preparations offered with no distinct brand name, sometimes even marketed under the DCI name of the chemical entity they contain. This product is typically supported by only limited marketing and promotion efforts, targeting mainly wholesalers and pharmacists rather than physicians. Plain generics compete primarily on the basis of their low delivered price rather than on product differentiation.

Generic Plus: (also called differentiated generics) typically involve a new galenic formulation providing an improvement in therapeutic effectiveness or patient convenience (e.g. once per day dosage). Generic plus formulations can be offered at a substantial price premium compared to the original branded product, depending on the therapeutic benefits the new formulation provides. The market dynamics are quite different from the other generic drugs and more closely related to innovative (brand) pharmaceuticals.

Figure 3.1 What are Generic Pharmaceuticals?



Source: Polastro,E. and Mellor, N.E. World Pharmaceutical Report, 1992

3.3.1 Forces contributing to the expansion of the generic market

Three main forces have driven the expansion of the generic pharmaceutical market:

1) Cost Containment measures to curb health care expenditure

Generics have been identified as a possible option to reduce the burden on health care delivery systems around the world.

The following initiatives are currently taking place in the European Community:

- substitution guidelines: pharmacists can substitute cheapest available equivalent product
- new reimbursement systems (such as in Germany) based on a flat amount set at the level of the cheapest equivalent product
- pressure to search for more cost effective forms of treatment introduces an element of price elasticity
- the UK has added ten new therapeutic categories which can be reimbursed under the NHS. This will create new markets for generics.

The following cost containment factors are seen as a boost to the North American generic market:

- the growth of managed care - in some programs generic drug substitution is mandatory. The Clinton plan for health care reform favours generics.
- increasing power of third party insurers.
- pressure from powerful unions like the UAW and CAW to reduce drug costs in their benefit plans.
- growth of mail order pharmacies and restricted formularies favouring generic drug substitution.
- the perception that generics are now more closely regulated.
- the impact of DUR (Drug Utilization Review) by US government - this is a weapon against brand companies as physicians will be asked to justify why they continue to use a branded product.

The following factors are seen as possible influences in the Japanese generic market:

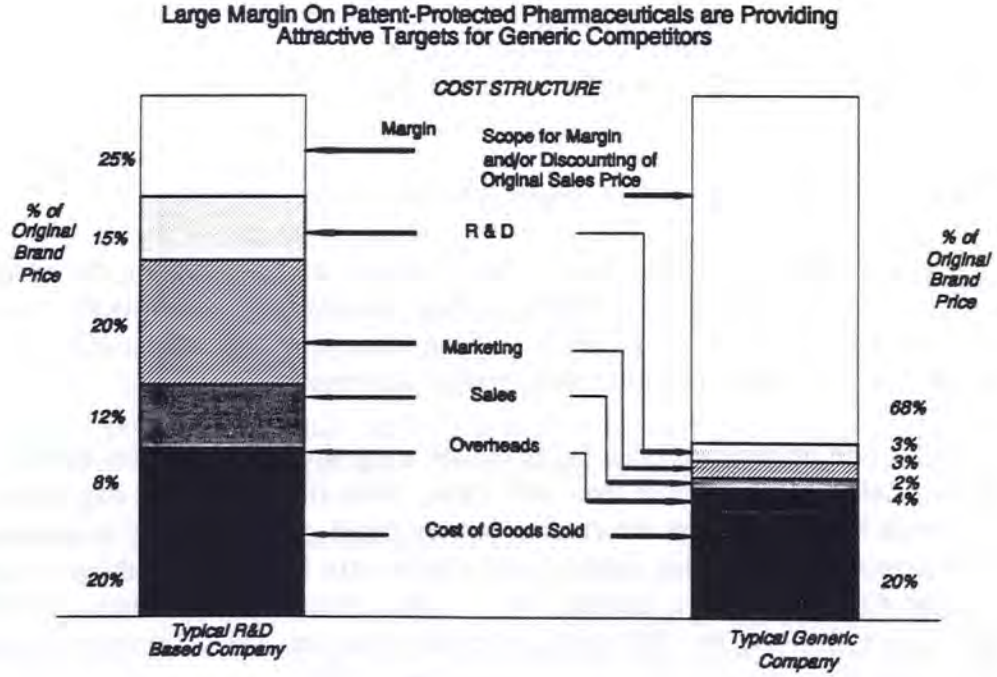
- sales of generics in Japan will be boosted by the expected spread of the flat fee-for-service reimbursement system in certain medical facilities as institutions focus on reducing the drug component of total treatment costs. (Scrip, 24 August 1993: 13) The fixed fee schedule expanded in 1992 applies to medical institutions specializing in in-patient chronic care or treatment of the elderly and hospitals with certain staff/patient ratios.

- In the face of rising costs and official concern over high drug consumption, Daiichi Pharmaceutical president Suzuki predicts the spread of the cost cap system. Japanese firms may have to move into generics to cope with the increased demand for cheaper products.

2) Large margins on patent-protected pharmaceuticals--a powerful driving force

Figure 3.2 illustrates that there is ample room for a generic product to generate large profits. Generic drugs typically have limited overhead, R & D and marketing costs. It is not surprising, therefore that in the EC those countries where pharmaceutical prices are the highest (Germany, Netherlands and UK) the generic penetration is the highest.

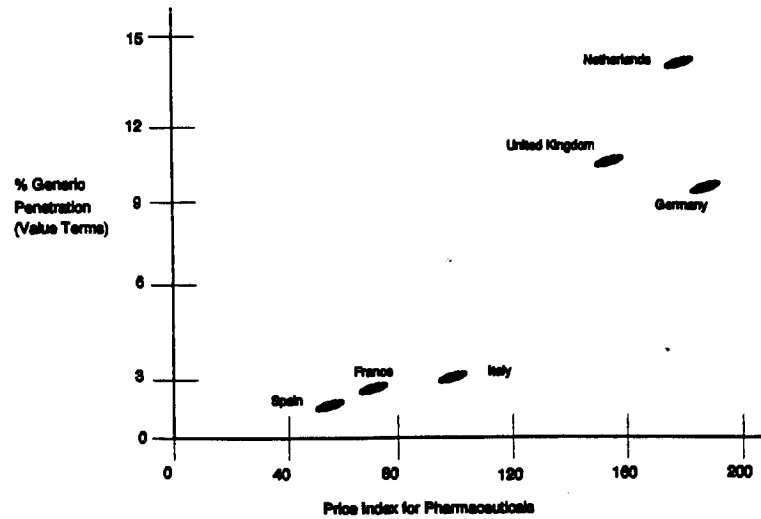
Figure 3.2 Large Margin on Patent-Protected Pharmaceuticals



Source: Polastro,E. and Mellor, N.E. World Pharmaceutical Report, 1992

In Spain, Italy and France the penetration achieved by generic products has been modest due to the limited margin left for generic drug manufacturers to manoeuvre because of lower pricing levels for pharmaceuticals in general. (Polastro, E. and Mellor, N.E., 1992) This is illustrated in figure 3.3.

Figure 3.3 Generic Penetration is Linked to the Level of Pharmaceutical Pricing



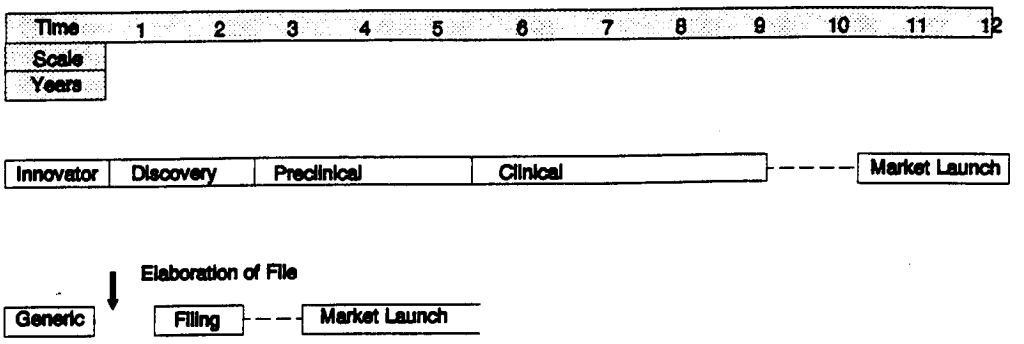
Source: Polastro,E. and Mellor, N.E. World Pharmaceutical Report, 1992

3) The patent expiration of several major pharmaceutical products

This factor constitutes the third driving force behind the development of generics over the past few years. Over the next 5 years, branded drugs worth nearly $20 billion a year in sales are expected to go off patent. (Weber, 1992: 126) A number of top selling chemical entities have lost their patent protection thus attracting generic competition.

The introduction of generic formulation causes a rapid erosion of sales for the original branded product. Sales losses of more than 60% three years after the patent expiration are not uncommon. It must be stressed that the erosion is very rapid, since typically it is immediately or shortly after patent expiration that generic preparations are introduced, taking advantage of short development times required to register those types of products. (Polastro, E. and N.E. Nellor, 1992) Figure 3.4, on the following page demonstrates the differences between the product development times for innovative and brand name drugs.

Figure 3.4 The Product Development Cycle for Generics



SOURCE: Polastro,E. and Mellor, N.E. World Pharmaceutical Report, 1992

Market features

There are some differences in the regulatory environments between the European Community and North America. These differences will have some implications for European and North American generic drug producers.

The Waxman-Hatch Provision

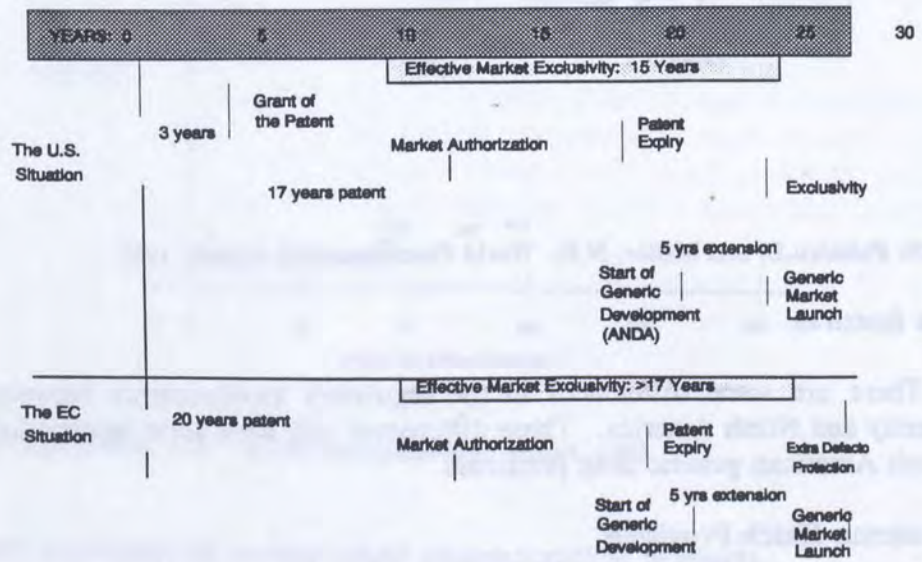
In the US, the 1984 Waxman-Hatch provision explicitly allows generic drug producers to have access to active substances for experimental purposes even during the period of patent protection. This provision permits generic drug producers to start the sourcing, the development and the registration of generic formulations before the expiry of market exclusivity. Consequently, companies can be ready to market generic preparations from the very first day. It also allows producers of bulk active ingredients to start developing a synthesis process to supply and even sell the material provided for experimental purposes.

Supplementary Protection Certificate (SPC)

The absence of explicit Waxman-Hatch provisions in the current European community SPC regulation potentially represents a threat for the traditional players in the EC market. If strictly enforced, the SPC could prevent generic producers from starting the development of generic formulations before the end of the market exclusivity period postponing by 1 or 2 more years the development of a generic formulation. The SPC Regulation is being interpreted as allowing only lab scale studies to be carried out in the EC only during the protection period thus effectively prohibiting European bulk suppliers from early participation in the US market

for new generics. EC-based producers of bulk generics are potentially the most exposed and vulnerable to SPC impact. European producers would no longer be allowed to offer these sample quantities of active, patent/SPC protected products even to non-European customers. Figure 3.5 illustrates the differences induced by the SPC between the US and EC marketing exclusivity period.

Figure 3.5 The Differences Induced by the SPC between the U.S. and the EC Marketing Exclusivity



Source: Polastro,E. and Mellor, N.E. World Pharmaceutical Report, 1992

Expected trends and consequences for the generic drug industry based on this legislation

- the SPC is likely to have far-reaching effects on the local generic industry and Arthur D. Little predicts that SPCs will dramatically reshape European generics market probably leading to a trend in consolidation amongst EC countries within the industry (Scrip, 12th August, 1992:4) The long term outlook for generics in Europe, however, remains very promising due to the fundamental changes occurring in the health care scene.

- the toughest challenges are likely to be faced by the EC-based producers of bulk generics (bulk active ingredients) who, if the legislation is not amended, virtually could be prevented from competing not only in Europe but also in the entire world market.

- most obvious beneficiaries of the changes in the patent regulations are likely to be the innovative pharmaceutical companies. These companies will have not only the opportunity to extend the useful life of their products even beyond the period intended by the authorities but also to develop a bridgehead on the generic drug market, taking advantage of the underlying and emerging regulations in the health care scene.

- EC producers will be at a disadvantage relative to non EC companies and may respond by establishing bases outside the EC or to develop activities in other segments

- US and Canadian producers could take advantage of differences in the existing patent protection between NA and the EC. US companies are ready to launch their own generic versions right after expiration placing them in a position to outpace EC companies (refer to figure 3.4). This could induce some Canadian and US companies to develop a base in Europe reversing the traditional direction of generic drug flows.

- Since US generic drug companies import 80-85% of their bulk material from Europe (primarily Italy) they may be forced to look outside the EC for bulk materials. (Scrip, 16th February 1993: 16)

- possible new source countries include India, China, and Eastern Europe as well as five non EC countries - Switzerland, Austria, Sweden, Finland and Norway. (Scrip, 16th February 1993:16)

- forging of strategic alliances between NA and EC-based companies in quest of economies of scale.

3.3.2 Marketing in the generic drug industry

The marketing strategy for innovative drug manufacturers has been to convince individual physicians to prescribe their products. This strategy requires a dedicated sales force and a focus on individual "relationships". Selling costs account for approximately 15% of total costs.

Marketing in the generic drug industry is very different. Smaller profit margins and a different customer base encourages a different form of marketing. Price and bioequivalence (to brand) are the most important features of the product. Consumers in this sector include: wholesalers (e.g. Medco Containment Services and mail order pharmacies), health maintenance organizations (HMOs), retail pharmacists (because of their ability to substitute under many formulary systems), hospital purchasing groups, therapeutics and formulary committees, third party insurers, and governments. This is an extremely *powerful* customer base which requires a selling approach which focuses on:

- clinical knowledge
- pharmaceutical knowledge for a broad range of products (since breadth of the product line is an appealing feature to this group)
- knowledge of health economics
- knowledge of complex benefit programs

Governments and employers are looking for ways to reduce the costs of their drug plans. One of the ways to do this has been to operate under a "restrictive formulary" which encourages (or insists) on generic substitution. This trend has opened the door to a proliferation of mail order pharmacies in North America.

Mail order pharmacies compete as low cost alternatives to retail pharmacies. The benefits of mail order include:

- breadth of products (including generics and branded drugs)
- free delivery
- no payments from plan members (all payments from third party insurers)
- minimised dispensing fees (in Canada C$5 versus C$11.50)
- 24 hour toll free numbers
- "bundled services" such as consultation, client education and drug profile management

How does a mail-order pharmacy compete?

- purchasing directly from the manufacturer bypasses the "middle man"
- reduces administration costs by reducing the number of claims for long term maintenance drugs (e.g. for heart disease, diabetes, arthritis and birth control)
- uses generic substitution where possible
- offers a broad product line of generics and non generics
- maintains sophisticated computerized records for all customers

Questions:

- the recent emergence of Medi-Trust, Rx Direct Inc. and Pharmex Containment Services demonstrate that Canadian mail order pharmacies are growing. What will this trend mean for other stakeholders (retail pharmacies, governments and third party payers)?

- As the purchasing power of other stakeholders such as pharmacists, third party insurers and governments continues to grow what role will the physician play in the supply chain?

- What can be expected to happen in the next few years as the cost containment efforts intensify?

- What will the Merck-Medco merger mean for the generic drug market?

3.3.3 The multinational drug threat in the generic market

The following factors have contributed to the significant trend of multinational drug companies entering into the generic drug market:

- Multinational companies have few "blockbuster drugs" in the development pipeline. While there are no exact figures available on the number of "blockbusters" the following points provide some insight into where specific companies stand on this issue.
  - Marion Merrell Dow has little hope of a blockbuster drug until 1995 (Gold, J.S., 1993, p.17-20)
  - Glaxo Inc., is often cited as having one of the stronger R&D pipelines. It has 2 new products Imitrex (an antimigrane drug) and Zofran (an anti-emetic). (Mullin, R., 1993, p.24-25)
  - Roche needs a blockbuster product in the post-1996 period in order to sustain superior earnings growth and the two most likely candidates are Pulmozyme (Genentech's recombinant human DNAse) and Orlistat (an anti-obesity drug). (Scrip, 27th August, 1993:12)
  - Roy Vagelos, Merck CEO, doesn't see enough blockbusters in the current and prospective line-up of Merck drugs to continue the firm's historic rate of growth. (Scrip, 20th August 1993:14).
  - Pfizer has a large portfolio of new drug launches (Scrip, 5th November 1993:11).
- By 1995 drugs representing US$15-20 billion in pharmaceutical sales will lose patent protection. (Plisher, E.S., 1992, p.20)
- Currently, major brand name drugs coming off-patent are losing about 50% of the total market (in units) to generic copies in the first year.
- Brand companies will have to be very concerned when they have two profit centres (Raw Materials and Finished Products) to protect. For example, Syntex produces raw materials and the drug for NAPROXEN and it stands to lose 70% of the market when the patent expires in December 1993.
- Associations representing the innovators (e.g. PMA, PMAC) wield enormous power when lobbying governments.

- Prediction that by 1995 60% of all new prescriptions will be for generic drugs. (Scrip, 19th February 1993:16) By the year 2001, approximately 70% of drugs will be dispensed as generics because $22 billion in drugs will be going off-patent. (Employee Benefit Plan, December 1993, p. 14-17.)

- By 1995, over 80 major branded pharmaceutical products may face generic competition. (Thwaite, E., 1992, p.110-112)

- Innovative companies are going to need access to the generic companies' expertise with the Application for New Drug Approvals (ANDA) process needed to compete in this industry.

- If a strong generic is first to market, then it stands a good chance of holding on to a significant portion of its market share when the patent protection officially ends.

- In the US, FDA approval time for generics has fallen to about 4 months— and there is a steady flow of new products. Generic drug approvals are averaging about 15 to 20 per month. On average about 30 new applications are submitted every month.

- The rates of approvals relative to non approvals is rising primarily because generic drug companies are submitting higher quality applications. The average time to complete one review cycle has fallen to about 4 months from 14 months during the late 1980s.

- US managed care buyers are emerging as powerful customers demanding services such as "bundled product offerings". To compete in this arena, a pharmaceutical firm must have a broad product line which includes a sizeable portfolio of generic drugs.

- Restrictive formularies favouring generics are gaining widespread acceptance.

As a result of these changes in the market, many innovative companies are being forced to develop generic drug strategies in an attempt to protect market share after patent expiry. These strategies include but are not limited to the following:

1) Marketing improved versions that are still patented

Under the Waxman/Hatch regulation when a brand name company decides to withdraw a New Drug Application for a product it is no longer interested in marketing there will be a presumption (on the part of the FDA) that the product was withdrawn for safety or efficacy reasons. This regulation could benefit a brand-name drug company who might wish to replace an older product which is no longer patented with an improved version (patented) - this is very damaging to the generic drug companies since there is no way they can fight the presumption of a problem with the product.

2) **Manufacture their own generics and pre-empt the competition by entering the market before patent expiry. This is referred to as "self genericisation" and the product offering is sometimes referred to as a pseudo-generic.**

Generic drug companies believe this practice threatens economic viability of smaller generic drug producers. The multinational could release a generic version several months before patent expiry, fill the inventory pipeline and cut the first year sales for everyone else However, some industry analysts say that when an innovative drug firm launches it own generic several months before patent expiry it causes the following chain of events:

- cannibalizes its own brand
- loses profits for two quarters before patent expires
- speeds up the generic product erosion
- confers legitimacy on the generic drug industry

A generic product may be manufactured at the same plant using excess plant capacity. The only difference between the generic and the brand name drug may be the trade dress (colour, imprint and size). It is interesting to note that Merck is the only company that markets its generic in the same trade dress as the brand. In view of Merck's influence on the industry this may become the norm.

Question:

- What will this mean for the industry if trade dress becomes consistent between generics and brands? How else will companies differentiate their products?

There are some circumstances where a generic manufactured by an innovative drug manufacturer could command a premium price.

Example

Marion Merrell Dow (MMD) and Rugby have an arrangement for generic diltazem (CARDIZEM). MMD lost exclusivity in 1992 but one month before this date it authorized Rugby to sell a generic version manufactured by the new MMD subsidiary, Blue Ridge Laboratories. The generic was priced at 70% of brand.

In 1992, several US pharmaceutical companies had independent generic units (either manufacturer or distributor). This is illustrated in Table 3.3.

Table 3.3 US pharmaceutical companies with independent generic units (manufacturer or distributor) in 1992

Company	Generic Unit	Company	Generic Unit
AHP	Elkins-Sinn	Lederle	Lederle Standard Products
B Ingelheim	Roxane	Marion Merrell Dow	Blue Ridge Labs
Bristol Myers Squibb	Apothecon	Merck	West Point Pharma
Ciba-Geigy	Geneva	Searle	Schiaparelli Searle
Du Pont Merck	Du Pont Multi-Source Products	SmithKline Beecham	Penn Labs
Forest	Inwood Labs	Syntex	Hamilton*
Fujisawa	Lyphomed	Upjohn	Greenstone
Ivax	Goldline	W-Lambert	Warner Chilcott

Source: Faigen, N.; The Multinational threat in the generic market, SCRIP Magazine, April 1993

*Hamilton received ANDA approval for three strengths of Naproxen in October 1992 but Syntex has not confirmed that the new affiliate will be a generic drug marketing subsidiary.

3) Form a strategic alliance with a generic company to produce a generic

Table 3.4 represents the known strategic alliances between brand name and generic drug companies in 1992.

Table 3.4 Known strategic alliances between brand name and generic companies (in 1992)

Company	Partner	Product
Syntex	Rugby	Generic version of Norinyl (marketed as Genora)
SmithKline Beecham	Rugby	Generic version of Dyazide

Company	Partner	Product
MMD	Rugby	Generic version of Cardizem (produced by MMD's Blue Ridge Labs)
Upjohn	Geneva	Generic versions of Halcion & Xanax (from Upjohn's Greenstone subsidiary)
Zeneca	Goldline	Generic version of Tenormin (produced by Zeneca's IPR subsidiary)
Ciba-Geigy	Geneva	Generic versions of Lorpressor and Voltaren after US patent expiry
Sandoz	Danbury	Generic version of Pamelor

Source: Faigen, N., SCRIP Magazine, April 1993:13

4) Acquire a known generic drug company and operate as a subsidiary.

Some companies have reached the conclusion that it makes sense to acquire an established generic drug company. As a result, generic drug firms should expect to receive offers from large companies.

Advantage of operating a separate generic unit

- can keep the generic drug business at arm's length from established brand name franchise

Hoechst's acquisition of Copley Pharmaceuticals is seen by industry analysts as a clear indication that the US pharmaceutical marketplace is changing so rapidly that brand name companies believe it is essential to "purchase" generic drug expertise in order to become a major force in the generic industry. Hoechst paid multiple of sales (7.5 time calendar 1994) and earnings (42 times calendar 1994) to be a major player in the generic industry. This leads analysts to predict that further generic drug company acquisition activity will happen (at prices many feel are unjustified). (Scrip, 29th October 1993:24)

Potential acquisition targets

If Hoechst's acquisition of Copley is regarded as a leading indicator of possible future acquisition activity in the industry it is important to look at potential acquisition targets for brand name producers. One industry analyst feels that the following companies may be targets:

- Biocraft: seen as undervalued on a takeout basis. The downside in acquiring this company would be that the top management would probably not come with it. It is likely that any company interested in acquiring the company would have an established generic drug business.

- Mylan: at least seven brand name companies have approached them. It is expected that, at the very least, Mylan will develop an exclusive alliance with one or more brand companies to be the generic "leg" in packages companies offer the managed care market.

- Teva: is unlikely to allow itself to be acquired. It is an obvious partner for Merck as the two have had a close business relationship for years and it is therefore likely that Teva will sign up as the main generic drug supplier to Merck.

(Scrip, 29th October 1993:24)

Gruntal Investment Research analyst, David Saks has listed six companies as the most likely takeover targets -- Biocraft, Ivax, Marsam, Mylan, Watson and Zenith-- because of their solid infrastructure, manufacturing, distribution and new product attributes. Several other publicly traded companies are not mentioned as prime takeover targets because they have yet to resolve difficulties with the FDA (Barr Labs) or are largely owned by a foreign entity--Lemmon (Teva), A L Labs (A L Oslo) and Purepac (FH Faulding).

There is also some speculation that some private companies are possible takeover targets. These include Danbury Pharmacal (a division of Schein), Clay Park Laboratories, Eon Laboratories, Lennett Co, OHM Laboratories, Sidmak, Thames Pharmacal and URL (a distributor/manufacturer). (Scrip, 29th October 1993:24)

Hoechst has forecast that the US generic drug market will grow from the current $4 billion to $11 billion by the end of the decade. One must ask where the growth will come from? It appears that the brand name manufacturers are positioning themselves to ensure that market share is protected if the growth is at the expense of their own brands.

Some analysts predict that within a few years two thirds of the members of the Generic Pharmaceutical Industry Association (GPIA) will be owned by Pharmaceutical Manufacturers' Association firms!

5) Acquire a company with expertise in generic product distribution

Brand name producers do not necessarily have to acquire a generic drug manufacturer. Most large companies have excess manufacturing capacity in house. The company could leverage this excess capacity by acquiring a leading distributor. Marion Merrell Dow (MMD)

did this when they paid an estimated $280 million to acquire Rugby-Darby, the largest distributor of generic products in the US. MMD is now considered to be in a dominant position in the generic drug market.

6) Filing law suits claiming infringement of manufacturing processes

For example, MMD and its supplier Tanabe, sued three companies--Mylan, Copley and Lederle--claiming infringement of Tanabe's US patent rights on the Diltazem production process (generic of Cardizem). (Scrip, 19 February 1993:1) The US Federal Trade Commission (FTC) is concerned about "frivolous" litigation and use of regulatory proceedings simply to delay market entry of generic drug competitors. A company may forfeit its right to take regulatory or judicial action if these processes are used as an anti-competitive weapon.

3.3.4 What do these strategies mean for the generic industry in the future?

Hemant Shah, an analyst with HKS, expresses scepticism about strategic alliances. He feels that the innovative companies have reacted impulsively to the generic drug threat without recognizing long term consequences for the market. He feels that to sell a generic effectively a brand company would have to develop an infrastructure, maintain a salesforce and establish ongoing relationships with customers. (Scrip, 19 February 1993:16)

Other analysts predict that in four years the US generic drug industry will no longer exist as a separate industry from the brand name. Competition among the larger companies to acquire a quality generic drug house will continue to increase and companies will either purchase or make alliances with these generic drug companies rather than develop generic drug expertise internally over a period of years (and risk missing the boat!) Those that will be the most successful in the new "hybrid" generic drug market will need to focus on specialty businesses, primarily new drug delivery systems, improved purity of drug substances and other novel, proprietary methods involving the manufacture and development of pharmaceuticals.

The Federal Trade Commission has begun investigating the potential anti-competitive effects of mergers between brand-name and generic drug companies. Such mergers could reduce competition either because the products marketed by the merging companies overlapped or because the merger eliminated competition outright.

Table 3.5 illustrates the current or potential strategies being used by major US innovative firms (at the end of 1993) to compete in the generic drug industry. It is clear by comparing it to Table 3.3 (1992 activity) that there has been a great deal of activity during the last year.

Table 3.5 U.S. Generics: What to Watch

INNOVATIVE COMPANIES	CURRENT INVOLVEMENT WITH GENERICS	POTENTIAL INVOLVEMENT WITH GENERICS
ABBOTT	Major manufacturer and marketer of generic injectables	No presence in oral generic market and nor likely to have one
AMERICAN HOME PRODUCTS	Produces and markets generic injectables through Elkin-Sin	Planning to launch generic versions of some female health products
BAYER	Formulating a strategy for generic market	Potential acquirer of a major US generic firm
BRISTOL-MYERS SQUIBB	Generic operation Apothecon and certain multisource drugs from Bristol	Rumoured to be seeking to acquire a leading generic house
CIBA-GEIGY	Early mover in the generic market with the acquisition of Geneva and Cord	Understands the US and global generic business and is willing to commit to it
GLAXO		Thought to be interested only to the extent to prevent losses for major products
HOECHST	Has become a major player with its purchase of Copley	
JOHNSON AND JOHNSON	No involvement in the generic industry	Currently no active plans to enter the market
LILLY	Actively exploring the feasibility	Not believed to be interested in acquisition. Will probably compete aggressively with its own off patents
MARION MERRELL DOW	Recently acquired the generic drug business of Rugby, the largest distributor in the US	In a dominant position
MERCK	Currently markets generics of its own off patents	Success thought to depend on the breadth of the portfolio. Recent purchase of Medco will give advantage in managed care.
PFIZER	Formulating a strategy	Generics may be a low priority because of a large portfolio of new drugs
RHONE POULENC RORER	Launched a generic version of a drug which lost patent protection	Will need breadth in a generic portfolio to compete
ROCHE	Exploring several generic drug strategies	
SANDOZ	Recently began to market a generic version of one of its own products	Approach may be too limited to be successful
SCHERING PLOUGH	Developing a strategy	Not expected in the near term
SMITHKLINE BEECHAM		Expected to announce a "bold" strategy as Tagamet goes off patent in May'94
SYNTEX	Marketing generic versions of Naproxen and Anaprox	Not expected to be successful
UPJOHN	Will be unable to supply drugs at low enough prices	Geneva will market generic versions of Upjohn's products
WARNER-LAMBERT	Already a major player in the generic industry	Growth has been slow due to regulatory problems
ZENECA	Has launched a generic version of Tenormin	Future strategy unclear

Source: SCRIP, 5th November 1993, p.11

Question:

What will it mean for the consumer if there is a consolidation of the US generic industry ? If innovative firms were to dominate the generics and the medium sized companies to disappear, would the major companies influence both pricing and new product development policies and would generic drug prices rise?

What will it take for generic drug manufacturers to compete successfully in this market?

William Haddadd, president of the GPIA, believes that fully integrated, multisource, financially secure companies will have the advantage in the industry. What leads to a fully integrated generic drug manufacturer?:

- a national distribution system and manufacturing capabilities in the growing hospital market and the traditional solid dosage form market
- manufacturing capability in or access to topicals and liquids
- backward integration into the manufacture of raw materials (which account for approximately 60% of the finished price of the product)
- restructuring of entrepreneurial companies into rational corporate environments
- hiring of new scientific, administrative and marketing personnel from the brand name side (want the competenca and experience but tell them to leave their structured thinking behind) (Haddad, W., 1992a, pp.26-29.)

3.4 ANTICIPATED GROWTH AREAS

3.4.1 Regional

Eastern Europe

With a population of around 400 million eastern Europe and the former Soviet Union represent a relatively untapped market. There is a high demand for western goods but there are high risks for western firms - legal, political and economic uncertainty, local currency conversion problems, lack of local entrepreneurial skills and difficulty in finding suppliers.

Glaxo has formed a separate unit to expand in eastern Europe. Glaxo Eastern Europe Srl is based in Rome but has subsidiaries in the Czech Republic, Hungary and Poland, and numerous branch offices throughout the rest of the region. Merck is also expanding in eastern Europe and the former Soviet Union.

Many firms are investing heavily in eastern Europe - Bayer, HLR and Glaxo are investing directly in research projects with Russian research institutes (and gaining rights to new products). Other firms are forming alliances and entering the market with drugs produced outside Russia. Others, such as Merck (which plans to produce children's vaccines and medicines) and Novo Nordisk are building production plants in Russia. Hoechst is using a mix of 3 strategies

research alliances, importing and manufacturing plants. Wellcome is converting a missile production facility into a packaging plant. In 1992 RPR began to focus on 5 eastern European countries - Russia, Ukraine, Hungary, Poland and the Czech republic, mainly through the formation of partnerships with local firms. The German company Knoll plans to collaborate with 2 Russian companies and the Russian Health Ministry to manufacture Knoll's Isoptin - a calcium antagonist.

Many firms are playing it cautious at the moment still waiting to see if the political, economic and social upheaval in the regions begins to improve. Others have clearly perceived the opportunities outweigh the costs, and the region will continue to pose strategic implications for the brand-name manufacturers over the 1990s.

Southeast Asia and China

With greater patent protection now being provided there are new opportunities for brand-name manufacturers to expand into the Japanese and other southeast Asian markets. Some American and European firms have had a presence in Japan for some time but they are now taking more ownership of the industry, developing further linkages with Japanese firms and in some cases developing their own distribution networks as they gain more experience with the market. Other firms are just beginning to make commitments in Japan. China also represents a huge market and firms are developing strategies to take advantage of this potential.

There are significant opportunities for foreign firms already in Japan to capitalize on the aging population market. Recognizing this potential there are several prospective newcomers to the industry including other Japanese firms in chemicals, textiles, cosmetics and beer industries, and foreign multinationals that still do not have a "critical mass" in Japan (Maurer,1994:30).

Recent activities in Japan include the following:

- Bayer, Glaxo, Merck, Roche and Syntex have all set up R&D facilities recently. Pfizer has recently expanded its research (has been in operation in Japan since 1955.Scrip,20th May,1992:13; 16th March,1993:14).

- Ciba-Geigy is moving into the market through collaborative integration. It wants to move from 23rd in sales to the top ten by the year 2000 (Scrip,12th March,1993:12)

- Increasing numbers of foreign drug companies are beginning to market their products directly rather than distribute them through alliances with Japanese firms. Over the past 20 years firms have had to form alliances but they now have experience and benefits of long range planning. Building production facilities in Japan also reinforces commitment to staying in the country (World Pharmaceuticals Report,15th July,1993:8).

- Upjohn regards Japan as its leading drug market and plans to begin launching new products there in 1995. It is increasing its services to the medical community and wholesalers and developing better computerized ordering systems. It will also take on the independent distribution of its products in Japan in 1995. Upjohn will focus on key therapeutic areas for the Japanese market and has said it will be keeping its workforce at "the right size" (Scrip,28th May,1993; World Pharmaceuticals Report,15th July,1993:9).

- Sandoz is expanding its own distribution network and this is likely to be the trend of other manufacturers (World Pharmaceuticals Report,15th July,1993:9).

- In Japan, contract research organizations are called "in-country caretakers". These did not exist before 1986 but came into effect as result of US-Japanese IPP negotiations, which enabled the development of a drug in Japan at the same time as being able to establish a marketing partner (Maurer,1992-3:25)

- The consolidation of wholesalers in Japan has also begun to weaken the power of the manufacturers, and foreign companies are also moving to establish independent distribution networks (for example, Rhone-Poulenc Rorer) (Maurer,1993c:33).

Recent activities in China include the following:

- Chugai and Otsuka (Jp) are active in forming collaborative ties (Scrip,8th Oct,1993:15; Haydock,1994:24).

- Both Ciba-Geigy and HL-Roche have recently announced collaborative investments through the development of advanced manufacturing technology plants in Shanghai and Beijing (Scrip,14th Jan,1994:6).

- BMS is expanding to boost manufacturing capacity in its Shanghai plant through a $US13 million expansion program (Scrip,8th July,1992:11).

- Pfizer established a new manufacturing facility in China in 1992-3 (Scrip,27th April,1993:13).

In South Korea the market is opening up to foreign investment and research. Although presently very small by world standards, the market is expected to increase. Korean firms are also expanding into overseas markets.

- Korean firm Dong-A, for example, claims 4% of turnover will be invested in R&D and it has already set up a US subsidiary (1992). Another firm, Il Yang, plans to expand more into eastern Europe and Chong Kun Dang is expanding overseas as well.

- Many overseas firms have invested in South Korea through alliances (for example, Johnson and Johnson, Green Pharma, Pfizer, Glaxo, Bayer, Upjohn, BI, Squibb.and Hoechst).

- The South Korean government established the Genetic Engineering Research Association. This is a $6 billion project as part of the government's R&D program to move SK in line with the science and technology of G-7 countries by the year 2001 (Scrip,29th July,1992:17).

3.4.2 Sector

Key trends:

- increasing specialization
- biotechnology-based products
- computer technology and contract research organizations
- managed care (US)
- attention on wholesaling and distribution
- over-the-counter markets

Specialization

The costs of conducting basic research, developing preclinical and clinical trials and conducting post-marketing surveillance have been increasing to the point where many in the industry believe it is more efficient and cost effective to contract this work out or develop collaborative linkages with other organizations more specialized that can, in effect, operate profitably with the appropriate economies of scale. In that sense globalizing research and production becomes more imperative but it is also quite possible with the advanced communications and computer technologies. By necessity these technologies also require and enhance greater levels of specialization.

Biotechnology-based products

Computers have revolutionized research as well as other phases of the production process in the pharmaceutical industry. But they have revolutionized research particularly in the field of biotechnology and this will likely be the focus of research projects in the future. In the process of drug discovery the traditional (and costly) "random" approaches are being substituted for rational drug design, which is possible through the cloning of 'appropriate drug receptors' developed through genetic engineering.

More generally, biotechnology has not become the mechanism by which massive profits have developed for the industry. Sales of biotechnology-based products in the pharmaceutical industry have reached an estimated US$20 billion a year and are expected to reach US$60 billion by the year 2000 but they have not fulfilled the expectations of the investors in the 1970s and 1980s. R&D spending by biotechnology-based companies was at US$2.5 billion in 1992. There are about 1,230 biotechnology companies in the US, and 300 in Europe. Of the American firms 470 are developing pharmaceuticals while only 50 are doing so of those in Europe (Polastro et al,1992-93:14; Scrip,25th May,1993:12).

Biotechnology-based products have had the most impact in vaccine development (for use in diseases such as hepatitis B, AIDS, and malaria and also for generally better and safer vaccines), and diagnostics. In the more developed US biotechnology research climate the focus has been on recombinant DNA and gene therapy, while in Europe the focus has been on synthetic chemistry and peptides and rational drug design. Other major areas of therapeutic focus have been neurology, anti-infectives and cardiovascular products.

On the business side, there has been much concern expressed with President Clinton's plan to deny coverage of new drugs under Medicaid if their launch prices are regarded as excessive as this could lead to disinvestment in firms developing biotechnology-based products (Scrip,28th Sept,1993:15). Despite these concerns sales from biotechnology-based pharmaceutical products have increased over the past few years. Organizationally, the biotechnology-based companies are moving toward "virtual integration" whereby "Companies large and small are paring down to their essential strengths, outsourcing functions, divesting divisions and spinning out product groups" (Scrip,28th Sept,1993:17).

Computer Technology and Contract Research Organizations

Computer technology is integral to corporate strategy and indeed, product markets in the pharmaceutical industry. An example of the role of computers is the UK company *Oxford Molecular,* which markets computer software for rational drug design and has recently taken over its main competitor *Biostructure* of France. The new company will be one of the top computer-aided molecular design firms in the world. *Molecular* likes to see itself as an integrator between academia and industry as it develops packages that can be user-friendly to many different scientists.

The two firms are part of what is known as the world computational chemistry market, which is valued at around $US320 million annually. The company's specialization in rational drug design is based on the belief that this is the way drug research will be conducted in the future, particularly as it becomes ever more expensive to discover drugs on a random basis. Since it was formed in 1989 the company has created linkages with Glaxo, British Biotechnology, Hoechst, Roussel, Pfizer and SKB (Scrip,10th Aug,1993:12). Similarly, Paraxel (a contract research organization) has aligned with IBM to develop information systems for clinical research in the pharmaceutical and biotechnology industries (Scrip,22nd May,1992:7).

Although there have been some bad experiences with contract research organizations (CROs) there are considerable advantages to their involvement in the pharmaceutical industry. These bad experiences have included cases where CROs have been involved in disasterous clinical trials, other cases where they have considerably over-charged for their services, and instances where CROs have been financial failures. Many companies still consider CROs as risky and expensive (Patterson et al,1993).

With increasing complexity in pre-clinical and clinical trials and the high costs involved, however, brand-name manufacturers may look more to CROs for externalizing their operations. Another area where CROs can expand is in peri and post-approval trials as these can strengthen submissions for regulatory approval. To a pharmaceutical firm they may represent one-off projects but to a CRO economies of scale give it considerable cost advantages and operational efficiencies. CROs are probably more appealing to small and mid-size pharmaceutical firms that do not have the financial and/or technical resources to conduct trials internally.

The total CRO market is forecast to double its size between 1991 and 1996. It is no longer perceived as a "cottage industry" especially as trials are conducted on a globalized basis in the industry today. It is estimated that there are over 1,000 CROs around the world and some of these are themselves multinational (Barrow,1993:15; Patterson et al,1993:16).

Managed Care

Managed care and hospital groups are becoming increasingly powerful. It is estimated that 40-45% of US population are covered by some form of managed care health plans, with 23% of all prescriptions dispensed under such plans. Drug volumes to group purchasing organizations has been rising by 19% annually since 1985. Now, 20% of company sales in the US are to managed care organizations (Longman, Dec/Jan1993:19; Scrip,12th Jan,1993:8).

Managed care organizations are expected to gain greater purchasing power and deepen the "black hole" (i.e. those pharmaceutical sales that are being discounted). They are exerting pressure on the pharmaceutical industry with the rising use of formularies and associated use of generic products. Physicians are increasingly tied to managed care organizations and this is influencing the marketing approaches of the brand-name manufacturers. In essence, the "customer base" is changing. Whereas the physician was once the customer it is now group formularies and group health plan managers.

The US managed care sector is a "shifting market" that requires different mind sets skills and culture, claims the COO and President of Schering Plough (Scrip,18th May,1993:10). Managed Care is interwoven into SP's operating units and all business strategies. Many other firms, such as Eli Lilly and Merck, have developed agreements with managed care organizations and long term care institutions (Scrip, 16th July,1993:9; 30th July,1993:14). BMS is reorganizing its US business - the sales force will be divided into 12 regional units and this will have an additional managed care unit which reflects the changing nature of health care in the US. Pfizer has expanded its medical and marketing unit which focuses on the managed care industry and plans to increase this further (Scrip,27th April,1993:13).

The increased importance of the managed care sector is indicative of the trend away from the brand-name manufacturers determining how "their" market should be structured. In particular, their marketing and promotional practices will be transformed as the role of the physician is itself transformed and integrated medical care becomes the norm. There are competitive issues also which relate to the role and extent of generic products and how costs can be decreased through over-the-counter medication. Brand-name manufacturers are increasingly price-takers and not price-givers as profitability becomes more a function of volume of sales as opposed to high priced products.

Wholesaling and distribution

Brand-name manufacturers are looking to other avenues to maintain and/or enhance their profitability. Wholesaling and distribution operations are also likely to receive increasing attention from the brand-name manufacturers as they provide a more direct link to the consumer (patient) and the physician and pharmacies.

In Europe wholesaling and distribution companies are basically local but that is changing with the emergence of a large number of international groups supported by smaller localized firms. In wholesaling there are increasing numbers of mergers and acquisitions and greater use of collaborative integration. Pharmaceutical manufacturers are concerned that they will be unable to control the practices of the wholesalers. But wholesalers are also under pressure from some European countries that seek to reduce the wholesale bill in a bid to lower health care costs, and from manufacturers as they see that wholesalers' profit margin can be reduced instead of their own.

It would be very expensive for manufacturers to make significant in-roads into the wholesale market, but perhaps the most effective route is for the manufacturers and wholesalers to work in partnership to provide better, more effective services (Scrip,25th May,1993:6).

Wholesalers margins are high in concentrated markets like the Netherlands, UK and Germany. In France there is a low margin but instead there is a high level of drug consumption. In France the top 3 firms account for 76% of wholesale market (OCP,CERP,IFP), while in Germany the top 3 account for 93% of the market (Sanacorp Group, Merckle Group, Gehe) (Scrip,3rd/7th Aug,1993:4).

Major European wholesalers are forming alliances throughout Europe to combat the potential rise in brand-name manufacturers interest and to consolidate their competitive position vis-a-vis a Pan-European market. The following companies, for example, have been formed through the collaborative linkage of firms from different nationalities in a bid to spread their market share across the European market (Scrip,25th May,1993:7):

- ***Tredimed*** (OCP (Fr), ACH (UK), Gehe (Grmny)
- ***PAG*** (Unichem (UK), OPG (NL), ANZAG (Grmny), Egwa-Wiweda (Grnmy)
- ***ORPE*** (CERP Lorraine (Fr), Hafame (Sp), Negri Martini (It), Internos (Belg), Piraeus (Gr), Bottani (Gmny).

There are some new relationships and organizational forms being developed in the distribution and delivery of pharmaceutical products. Some major brand-name manufacturers have shown substantial interest in developing a stronger market presence in this area as they move toward what have been termed "customer-focused alliances" (i.e. to the physicians). This is an increasingly popular trend in the pharmaceutical industry.

Bristol-Myers Squibb, for example, has formed an alliance with Axion Pharmaceuticals - a US distribution company specializing in anti-cancer products. Some analysts compare this collaborative linkage to the Merck-Medco deal as firms focus on increasing sales volume to improve earnings. By linking with distributors like large mail order "supermarkets" such as Medco or by collaborating with specialists such as Axion, sales volume can be increased (Scrip, 17th Sept, 1993:11).

The Merck Acquisition of Medco

In July 1993, Merck purchased Medco Containment Services Co. for a reported *$6 billion*. Medco currently manages more than $4 billion in drug expenditures on behalf of almost 3,000 clients, which include corporations, state and federal health plans, union groups and major insurance carriers. It also has a rapidly growing mail-order pharmacy business.

Merck-Medco will be the first huge, vertically integrated enterprise in the US pharmaceutical industry. This move virtually assures Merck of an "inside track" on competitive bids in dealing with Medco and eventually most of the Medco formulary products will be supplied by Merck. The Merck-Medco combination promises a further major consolidation of the industry and the rise of other vertically integrated pharmaceutical firms. Some analysts predict that other companies will be forced to emulate Merck in buying large wholesale vendors so they too can stretch from the research laboratory to the corner drugstore and the giant mail order pharmacy which sends out hundreds or thousands of customer prescriptions every day.

Factors that led Merck to this historic acquisition:

- the company didn't see enough blockbusters in the current and prospective line-up of drugs to continue its historic rate of growth. By buying one of the largest wholesalers Merck has expanded the market for its existing drugs.

- Merck has bought a company with its own formulary system which can be reshaped to favour its drugs at the expense of competitors. Merck has one of the broadest lines of drugs in the industry and with its plan to expand its in-house generics business (West Point Pharma) it would theoretically work with Medco to assemble an entire formulary for a managed care plan at very competitive prices.

- Merck will get full access to Medco's extraordinarily rich supply of data on physicians' specific prescriptions for individual patients. Merck's marketing efforts can be aimed at specific prescribers and specific diseases in a way that has never been available before. There has been speculation that this may result in a shift of some Merck research funds from pharmaceutical discovery and development to sales planning and development through intensive analysis of the Medco prescription "treasure trove".

- the Clinton-inspired reorganization of the US healthcare system is predicted to open huge markets for an organization like Medco. States will be anxious to make deals with organizations like Medco which will offer to supply all of a state's medicine in return for reduced prices.

Questions:

- In light of this merger, Merck Frosst Canada is said to be evaluating its options regarding the best way to approach the Canadian market. What are the implications for the Canadian industry?

- Is it possible that individual provinces will follow the lead of some US states and enter into agreements with Merck-Medco to supply all of the provinces' medications in return for reduced costs? What are the competitive or "anti-competitive" implications of this type of arrangement?

- Prior to the merger the Canadian mail order company Medi-Trust reportedly approached Medco as a potential partner and was turned down. What might this mean for the Canadian generic drug producers and mail order pharmacies if Merck-Medco enters the Canadian market?

- What implications does Merck's access to individual physician prescribing habits have for privacy in the industry?

Medco, a huge mail order delivery organization, makes agreements with drug companies to receive special discounts in return for labelling one or more of their products a "preferred product". Tagamet is a preferred product. So, for example, when Medco gets a prescription for another anti-ulcer compound it contacts the pharmacist to see if he/she can get it changed to Tagamet, asking that the pharmacist explain to the doctor that this will reduce the cost for the patient or his/her employer (Schwartz,1993:10).

OTC (over-the-counter)

The extended life provided to a product through OTC sales provides the brand-name manufacturers opportunities for growth in new markets. OTC switching provides a product with direct consumer (patient) contact and loyalty and is less susceptible to generic competition. Smoking cessation products, which did not exist as OTCs until recently, are now one of the largest selling products in the sector. OTCs are also attractive to cost conscious governments

eager to reduce reimbursements for drugs. The pharmacist may develop the role of "gatekeeper" while generally there is enhanced consumer awareness and public involvement with OTC medication.

The OTC market is not easy. It requires more expensive and different forms of promotion and advertising from ethical products and new dosage levels, indications and combination products will need examination. Short term profitability is low although over the long term the returns are very attractive. But with generic prescribing becoming more common, rising prescription charges, increased price constraints and major drugs coming off patent the OTC market looks very attractive to the major brand-name manufacturers (Darbourne,1993).

The worldwide OTC market is estimated at about US$30 billion (US 40% and Europe 30%). Traditionally the market has been very nation specific in Europe, but now the trend is toward greater internationalization, particularly as OTC manufacturers have consolidated with the emergence of pan-European brands (Dudley, 1992:25).

One of the advantages of OTC switching is that a product will receive patent extensions in the US while clinical trials conducted to make the switch are in progress (up to 3 years extra protection). A company's image can also be enhanced by the switch. The US is regarded as further advanced with switching than is Europe. Of the 10 best selling OTCs in US in 1991, 9 were switches and the other switch-related. Most US switch products achieved sales of over $30 million in 1991 (eg, advil, nuprin, benadryl) (Dudley, June,1992:27).

Recent corporate activity in OTC's include the following:

- Warner-Lambert has recently developed alliances with Glaxo and Wellcome for OTC switches. WL receives OTC rights to Zantac and Zovirax - currently the 1st and 8th biggest selling drugs. They could each generate up to US$200 million in their first year as OTC products. WL has been expanding its OTC and consumer products business over the past 2 years (Scrip,3rd Aug,1993:9; 6th Aug,1993:10). Other drugs may follow in the agreement between Glaxo and WL.

- Merck and Johnson & Johnson have formed a new OTC venture in the UK which will develop and market Merck's and J&J's prescription products. The agreement expands upon a similar linkage in the US market (Scrip,12th Oct,1993:7). J&J and Merck's collaborative OTC link itself acquired the french firm Laboratories JeanPaul Martin and this is seen as part of its strategy to expand further in the European self-medication sector (Scrip,17th Oct,1993:7).

- In 1992 Hoffman-La Roche established a new OTC division and this has become one of the leading suppliers of OTC products in Europe, Asia and Australia (Scrip,22nd June,1993:15).

- Wellcome is looking to expand its OTC business through some form of collaborative relationship (Scrip,2nd April,1993:10).

- In line with Pfizers global strategy the French subsidiary plans to move into the OTC market. (Scrip,10th,Nov,1992:7).

There is considerable activity in the OTC sector as manufacturers seek new approaches to maintaining profitability. There is considerable investment involved but the long term rewards are such that, given the social, political and economic context of the major markets today, it is inevitable that the involvement of brand-name manufacturers becomes more extensive.

Alliances are perhaps the most effective mechanism by which to develop a strong OTC presence. But over the longer term the transition to other parts of the value chain will require, and lead to, transformations of the internal organizational structure of the pharmaceutical firm. Again, the implications of this await further exploration. What, for example, will be the effect on employment patterns in the respective countries in which the manufacturers operate?

3.5 THE ROLE OF TECHNOLOGY AND MANAGEMENT PRACTICES

3.5.1 Manufacturing in the Pharmaceutical Industry

Until recently, pharmaceutical companies had rarely considered the positive contribution that the manufacturing process can make to profits. (Byrne, F., 1993) In the 1980s, however, manufacturing costs increased as a proportion of sales (rose from 10 to 20% to 20-25% and continue to rise). Drug companies are only now beginning to understand the contribution that manufacturing can make to reducing costs and improving competitive advantage. Higher return from the manufacturing function will help to compensate for decreasing margins. This can be accomplished by:

- faster introduction of new products
- reduced manufacturing costs
- greater efficiency
- improved contribution to competitive positioning

Pharmaceutical companies expecting reduced manufacturing costs to help make up for decreasing profit margins must understand the factors which are driving their cost structure upwards. A number of industry-wide trends have had an impact on the manufacturing function:

- **Greater variety within a product line**

The same basic formulation is now usually available in a wider range of strengths, packaging and pack size. While this may meet the needs of the end use customer (patient, practitioner and pharmacist) it means smaller batch sizes, higher stocking cost and greater "complexity" costs.

- **Manufacturing volumes are often lower**

Higher potency products - formulations taken once a day mean fewer pills to be produced and a higher per unit overhead burden. Many indirect costs are batch related and batch numbers have increased. Companies are only just beginning to address the economies of scope afforded by computer-integrated manufacturing.

- **More technology within the sector**

This is partly to service the increased variety of products, but also to meet tighter standards and legislative requirements. This technology often consists of "one use", specialized equipment, made redundant by a switch in product or packaging. This trend has been accompanied by a significant increase in engineering and maintenance functions and hence indirect costs.

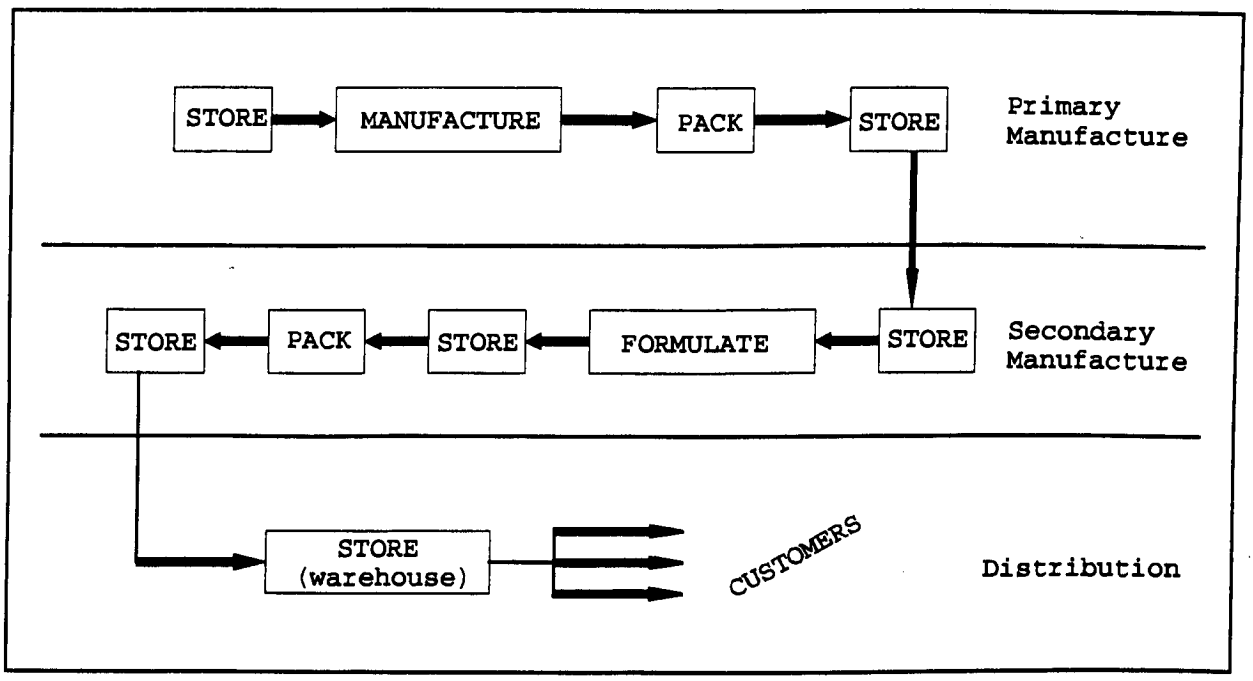
- **Size of the Manufacturing Asset Base**

Manufacturing capacity in plant and equipment may be considerably greater than what is needed leading to an under-utilisation of the asset base.

- **More Complex Supply Chains**

The processes involved in the international supply chain are very complex. Figure 3.6 shows the steps in the chain from active ingredient manufacture (often referred to as primary manufacture), formulation (or secondary manufacture) and distribution. Inventories are higher and slower moving in the pharmaceutical sector than in almost any other industry. In a multinational pharmaceutical company, the time taken for a quantity of raw material to pass through the chain can take over 300 days. This presents an opportunity to improve since raw material is only being worked on for about 25 days. (Forrester, 1992: 12) Large sums of money (potentially hundreds of millions of dollars) can be realised by managing the supply chain as one continuous process, with each point in the chain recognising its role as internal customer/supplier.

Figure 3.6 International Supply Chain



Source: **Adapted from: Forrester, P., Scrip Magazine, July/August 1992**

- **Quality-related costs**

Costs have been driven upward by the "need to comply" with regulatory agencies but the productivity of the quality function is rarely questioned (e.g. documentation process, staff requirements, etc.).

- **Lack of Investment**

Lack of investment in appropriate performance measures and management information systems to reflect the changing environment.

3.5.2 Changes ahead

Pharmaceutical companies will have to start looking at their manufacturing functions as vehicles for the creation of value. The historic mission of "no recalls and no stockouts" will no longer do. Companies with a manufacturing strategy which is aligned with their development portfolio, marketing strategy, and distribution capability will achieve the gains needed to compensate for decreasing margins and increasing costs.

The contribution of manufacturing can be increased over the whole of the product life cycle by maximizing the effectiveness of elements such as cost, market responsiveness, regulatory compliance and time to market. At the strategic level, there is a need to significantly reduce the number of plants and to increase overall asset utilization. Improving the productivity of existing plants is another possibility.

International manufacturers in virtually every sector are faced with similar challenges however, unlike the pharmaceutical companies many of these businesses are in trouble. It may be easier to see the need for change when survival is threatened. Successful companies have built a competitive manufacturing strategy by addressing gaps and weaknesses in eight decision categories sometimes referred to as the "bricks and mortar" of manufacturing. These categories are:

- Capacity, Facilities, Technology and Vertical Integration (structural categories or "bricks")
- Workforce, Quality, Production Planning/materials Control, and Organization (infrastructural categories or "mortar")

Pharmaceutical companies are beginning to examine these categories in light of their business strategies and the growing pressure to decrease the "time to market". Manufacturing is increasingly finding itself on the critical path of "time to market" but few companies have grasped this. Over the past two years 60% of US pharmaceutical industry pre-approval inspections have "failed" both for good manufacturing practice reasons and physical/paper process variations. There are also a number of companies which have medically approved products but are unable to scale up production or gain manufacturing approval. (Byrne, September 1993: 32)

There are substantial benefits to be gained from considering manufacturing implications early in the development of a new product and tailoring development for cost-effective manufacture. (Byrne, September 1993: 32) This is referred to as concurrent (or simultaneous) engineering. Concurrent engineering is a major trend in manufacturing which involves early and continuing involvement with new products by production, materials planning and engineering support groups to ensure that the products are effectively managed from design to delivery. While it sounds quite logical it has only recently received acceptance in the pharmaceutical industry.

Design for Manufacturability is one way to take advantage of this interface between product development and the manufacturing function. In translating a product design (or drug formulation) into a manufacturable product, development and manufacturing should consider the discrete steps in the process. Designing the product for manufacturability is quite simply designing the product so that it is easy to make. In electronics manufacturing this would involve minimizing the number of separate parts or components. In the pharmaceutical industry it means simplifying the process, such as minimizing steps in either primary or secondary manufacture, thereby reducing the complexity of the manufacturing and quality control functions.

Improved market responsiveness can also increase manufacturing's contribution to profitability. With the more complex marketing and customer service issues now facing industry, and the emergence of different purchasing, distribution and customer structures, manufacturing can support the market effort by taking a more proactive role in understanding customer needs and responding to them.

Within manufacturing the challenge is to achieve the fastest possible launch following regulatory approval without damaging the production of existing products. Changes arising from slippage in regulatory approval dates, problems with packaging or difficulty moving from the lab to production can cause problems for manufacturing.

How Manufacturing Can Help Reduce"Time to Market"

- Consider the value chain to be one process and determine where value is added
  - concentrate efforts on eliminating bottlenecks and reducing non value added activities

- Decrease throughput time by:
  - working throughout the development process to design for manufacturability
  - re-engineering (redesigning the process)
  - automate (after re-engineering)

- Reduce Delivery Time
  - Just in Time deliveries
  - use of Electronic Data Interchange (EDI)

- Reduce Engineering Time
  - Concurrent engineering
  - Design for manufacturability

- Reduce Procurement Time
  - EDI
  - alliances

According to a recent survey on manufacturing in the UK (SCRIP, 22nd May 1992: 5), the pharmaceutical industry has seen the introduction of the following programmes:

- lead time/cycle time reduction (75% of companies surveyed)
- planning and control technologies (65% of companies)
- value chain integration (40%)
- initial rationalisation of the product portfolio (30%)

These steps have led to more efficient use of working capital with 73% and 82% of companies reporting lower raw material and finished goods stock than in 1989 but the pharmaceutical industry still lags behind many other sectors in terms of management of inventories according to the survey.

75% of manufacturers are expecting a reduction in their manufacturing costs as a result of these and other programs such as continuous improvement or total quality management, and new process technologies.

Time taken to reach the market was cited as the major constraint to enhancing profitability by 73% of the companies (a much bigger proportion than any other sector). In the past three years, only 34% of companies have succeeded in reducing the time taken to bring a new product to market, while 27% saw an increase. Increased regulatory requirements were seen as another key factor in limiting performance, ahead of long delivery lead times.

3.5.3 Technology in the Pharmaceutical Industry

The pharmaceutical industry has prided itself on having the latest and the best process technology - this often resulted in a profusion of differing technologies doing the same task. The result is a wide range of technology deployed, a high level of support staff (which may have a shallow competence in many areas) and a technological focus rather than a production focus.

In comparison with other UK industries, pharmaceutical companies lead the way in terms of process technology development: since 1989, 80% have introduced at least one new technology and 36% ten or more.

What are the information systems requirements in pharmaceutical manufacturing?

Within pharmaceutical development the different functions tend to be discrete with separate systems dedicated to each part of the development process such as toxicology, analytical chemistry and stability. Manufacturing is characterized by a large number of closely related functions, which are usually translated into highly integrated systems. Unfortunately, many manufacturing information systems are designed to handle repetitive processes and overlook non-routine requirements unique to pharmaceutical manufacturing.

Most manufacturing information systems cover business requirements such as forecasting, planning, scheduling and procurement; the storage of raw materials and finished goods which includes warehousing and inventory control; sales order processing such as orders, despatch and invoicing; and general accounting. Within pharma manufacturing it is a challenge to achieve the fastest possible launch following regulatory approval without damaging the production of existing products. Changes which arise from slippage in regulatory approval dates, problems with packaging, or the difficulties moving from the laboratory to commercial operations are difficult to track with "off-the-shelf" systems. The pharmaceutical industry needs information systems capable of handling batch traceability and linking bills of materials with work orders. Interfaces to laboratory information systems and quality assurance and control are also essential.

Pharmaceutical manufacturing has not embraced automation with the same enthusiasm as other sectors. This is partly because manufacturing costs represent a smaller percentage of overall costs in pharmaceuticals than in other sectors so the drive for efficiency is less pronounced. The asset base is generally under-used compared to similar industries (80% for bottling plants and food processing compared to 40% in pharmaceutical companies). (Owen, C., 1993:40)

The special features which govern pharmaceutical manufacturing such as stringent regulations and the need for a technically trained workforce indicate that there is relatively little technology transfer in from other industries. As a result the pharmaceuticals sector has yet to realize the benefits of robotics and integrated process control.

Some of the barriers to the widespread use of information technology in the pharmaceutical industry include:

- the wide differences between companies in the process sector (paints, foods and chemicals as well as pharmaceuticals) and their differences in requirements has meant that software companies have not invested in packages within the process industry and the sector in general has been poorly served.

- the pharmaceutical sector has special requirements which are not found in other process-based industries. For example, batch traceability and labelling requirements.

- system validation is an issue. General systems for the process control industry are not usually written to the high standards required within the pharmaceutical industry where systems must be validated to GMP requirements. Faced with the possibility that product licenses could be withdrawn because of regulatory control problems, many manufacturers have tried to minimize their reliance on information technology and therefore still depend on validated manual systems to back up their regulatory submissions. (Owen, C., Scrip Magazine, September 1993: 41)

- most pharmaceutical manufacturers have had to modify software which has not been designed to meet their requirements. This can be a frustrating business.

- absence of well-designed packages for the industry and the difficulties of tailoring to fit means that successful implementation is not without problems.

Examples of Technology Application in the Pharmaceutical Industry

Cellular Technology

Warner-Lambert, a developer, marketer and manufacturer of quality health care and consumer products, has integrated the manufacturing process at its Pennsylvania plant. In doing do, several tactics were employed:

- integrated manufacturing cells were designed and implemented for each product family
- the team set standards for specific off-the-shelf hardware and software, communication networks and auxiliary equipment
- the planners insisted on open system architectures
- all processes and procedures were simplified before integration
- internal and external alliances were created
- a core implementation group was formed to maintain continuity and consistency
- skill training became a high priority
- communication was given constant attention

Using the cell control strategy the plant is moving toward an innovative, integrated, continuous process-packaging cell. The core implementation team is now working with a different group of production personnel on developing a new cell.

MRPII

In 1992, Stanley Pharmaceuticals Ltd., a subsidiary of Novopharm, showed a 50% increase in revenue per employee. Production increased from 7 million units and profit rose 126%. The company's business is 3 times larger than it was in 1989, while staff has grown modestly from 111 to 178. Stanley has expanded from one location to 2 plants and an administrative centre in North Vancouver and a warehouse in Toronto. One of its biggest customers, Shopper's Drug Mart, for which it makes 160 Life brand products, has awarded Stanley two more product lines. This success has been attributed to the adoption of a local area network-based (LAN) Manufacturing Resource Planning (MRP II) system. MRP II is a total, company-wide system (buyers, marketing staff, production, and accounting) which is able to simulate the manufacturing system to plan and test strategies. Stanley's system runs over 60-station LAN with 25 workstations each at the administrative centre and the main plant. Four dail-up stations are located in the 2nd plant, with another four in the Toronto warehouse.

Data Collection

The data collection system at Abbott Laboratories provides plant management with a tool to reduce production costs and build quality into its products. To support accountability by work centre, a cost master was developed, with labour and material standards staged on the basis of expected yields at each routing operation. Next the time clock system was converted from the manual system to one that would process bar coded employee badges read by terminals. The new data collection system collects data from manufacturing divisions in three Canadian provinces: Ontario, Quebec and Saskatchewan. The data collection system reviews yields, labour costs, machine downtime, and in-process scrap on a daily basis so that action can be taken to determine problem causes and ensure that corrective action is taken.

Work Flow Management

Workflow is the name given to procedures that involve the movement of tasks from person to person in sequence allowing each to make a contribution before passing them on to the next stage. Such procedures are used for processing the documentation for clinical trials. For pharmaceutical firms, automated workflow can improve the productivity, accuracy and speed of data processing. Workflow and imaging software can help to manage and control the huge volume of paper-based information which is generated while providing the necessary control and management of information (It is not uncommon for a new drug application to include over 100 kg of accompanying documentation).

Several leading pharmaceutical companies including Burroughs-Wellcome, Warner-Lambert and ICI have introduced workflow software into their data processing departments.

In the next few years dramatic changes are expected in the way in which these are carried out.

- reasons for this include the high administration costs and levels of accuracy and quality required

- emergence of workflow development software that will automate many of the tasks involved.

What are the shortcomings of the current manual workflow system?

- manual systems rely on individual's memories and verbal agreements which can lead to incomplete or incorrect documentation that could delay the approval of a new drug and potentially cost the company millions of dollars.

- problems of interpretation can arise

- time consuming and labour intensive

Computer Assisted New Drug Applications (CANDA)

The growing trend towards the submission of Computer Assisted New Drug Applications (CANDAs) to regulatory authorities offers pharmaceutical companies a unique opportunity to develop a streamlined and integrated approach to the management of information about drug products. The use of CANDAs is increasing because of the benefits derived from getting high quality products to market more quickly.

Emerging standards for CANDAs currently allow packages ranging from text image systems to complex database systems. This flexibility means that companies are developing their own, quite different, sophisticated systems to gather, analyze and collate information for use in licence applications. This information is then formatted according to the needs of a given regulatory body and published in a variety of media, including optical disk, magnetic disk and paper.

The fundamental goal of developing standards for CANDA is to concentrate effort on achieving integration for the purposes of data exchange. This integration will not only improve the license submission process but will provide massive benefits to the whole portfolio of clinical and research systems. The question that remains is who will develop the standards. It seems logical (but highly unusual) that the industry and the regulatory agencies must work together to develop the standards for this technology.

Electronic Data Interchange

Today more than ever, organizations are reviewing the costs associated with conducting business between their trading partners. Spiralling costs, information overload and redundancy of paper work have inspired more economical and effective methods of processing routine business transactions. Electronic Data Interchange is one of these methods.

Electronic Data Interchange (EDI) is the inter-company computer-to-computer exchange of business information between any multiple of business partners. EDI is gaining widespread acceptance in many industries. The pharmaceutical industry is no exception.

Bristol-Myers Squibb is online with the computer program POWERnet from Strategic Technologies Inc.'s Numerax subsidiary. The program has made a great difference in the way BMS tracks freight. Access to POWERnet is through a value-added network or directly into Numerax. Bristol-Myers now requires that a carrier have EDI tracking capability before it receives a piece of the company's business. (Bowman, 1993, p 61-63)

In March 1991, Bergen Brunswig Drug Co. and Marion Merrell Dow (MMD) successfully implemented an advanced form of financial electronic data interchange (EDI). MMD believes that EDI improves its relationships with its trading partners, since implementing EDI requires that two partners examine and understand each other's ways of doing business. Bergen Brunswig has seen the following benefits from this arrangement:

- savings in document processing time, staff hours and document storage costs
- improved accuracy
- document transmission speed
- increased customer satisfaction

Just-in-time and "Stockless" Supply Delivery

Advances in information technology have paved the way for Just-in-time (JIT) and Stockless supply delivery from pharmaceutical manufacturers and wholesalers. JIT is defined as the reduction of inventory from an end users' (e.g. hospital or pharmacy) storage areas through daily deliveries from the distributor(s) in bulk or case lots. (Kerr, 1991) A "stockless" system is designed to eliminate centralized inventory at the customer level (may be wholesale or final end user level). The distributor provides daily (or more frequent) replenishment of supplies on a unit of use basis. This system assumes that the customers' in-house inventories are non existent and that buffer stock is at an absolute minimum. A stockless system places the responsibility for stocking shelves and bins with the distributor as part of the "bundled" service.

Stockless and JIT delivery systems are becoming very common in the hospital sector within North America. Distributors benefit from reduced competition, paperwork, fewer sales calls and a higher price mark up (because of the bundled service). End users realize savings through decreased staff requirements and lower holding costs for the inventory. In addition to the cost benefit, obsolescence, product damage, shrinkage and theft becomes the responsibility of the distributor.

Baxter Healthcare Corporation and Abbott are leaders in the area of JIT and stockless delivery systems in Canada and the US. As prime vendors, they supply customers with all pharmaceutical and medical/surgical products.

Electronic Territory Management Systems (ETMS)

By the end of this decade, information technology will be an increasingly important strategic tool in the pharmaceutical industry's promotional and marketing activities. Modern electronic territory management systems (ETMS) will support and extend the sales representative's role, while decision support systems and expert systems will be used in setting prices and building strategies. These developments in IT will have far-reaching implications for corporate structures and management.

The 1990s will be the era of information-based selling. Today, direct information is available about all sales-related activities. There are in-house sales data, IMS sales data at the regional and geographical level, prescription based services like SOURCE in the US and prescriber-linked prescription databases such as SCRIP TRAC in other European countries. The growth of these databases have been accompanied by the development of personal computer (PC) technology for the sales force.

The computer allows sales force to micro-market, that is:

- address each customer with a specific message or marketing mix tailored to particular needs

Electronic marketing instruments and multi-media applications to promote the company's portfolio are becoming a major part of the marketing mix in all segments of the pharmaceutical industry. Each of the segments of the pharmaceutical industry --truly innovative, semi-innovative, multisource and generic--require a different composition and application of the marketing mix and the need for sophisticated IT instruments will vary.

Since price is a major factor in purchasing decisions in the generic drug segment, this section of the market has the least need of an IT-driven marketing mix. In the truly innovative segment it is the extra innovation versus competitor products which will decide the battle for the prescription and there is no real evidence that heavy application of IT is necessary to support this.

3.5.4 Total Quality Management

Total Quality Management is managing an entire organization so that it excels in all dimensions of products and services that are important to the customer (both internal and external). In the pharmaceutical industry, external customers include: prescribing physicians, patients, pharmacists, therapeutic committees, third party insurers, wholesalers, government/policy makers, fund managers, shareholders, the media, regulatory bodies, etc. The purpose of the business is to satisfy the diverse needs of these customers. This is achieved with outputs (pharmaceutical products) that are the result of a complex chain of internal customer/supplier relationships. (Figure 3.7)

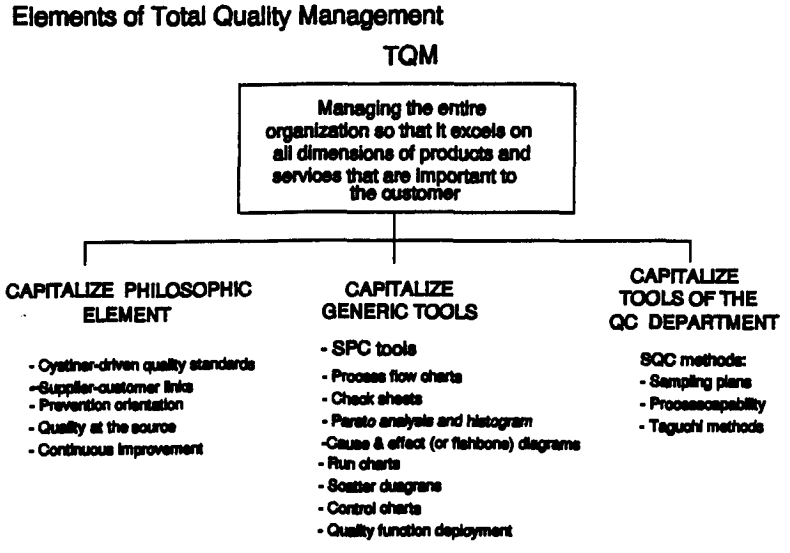
TQM has three components: a philosophical element, generic process improvement tools and tools of the quality control department. Traditionally the pharmaceutical industry has focused its efforts in the quality control area in concordance with Good Manufacturing Practices.

A lack of quality has never been an issue in the pharmaceutical industry, which has been obsessed with quality long before it became important elsewhere. In the US the FDA approves the release of new drugs and also audits and approves the quality of pharmaceutical manufacturing processes. The top priority in pharmaceuticals is quality assurance, with or without TQM. Quality assurance depends on information technology (IT) which aids in the development of safe, new products and in getting products to market quickly.

In the pharmaceutical industry, for example, manufacturing makes the product, packaging packages the product, and distribution warehouses and ships the product. Distribution cannot ship the product until quality releases the product. At Marion Merrell Dow, the packaging engineering department sets the specifications for all packaging material commodities. Packaging materials test each order received against these specifications. Data are acquired and stored in databases which can evaluate line performance and Statistical Process Control (SPC) data on commodities as they are received. This statistical process control program complements the company's new integrated manufacturing prioritizing system.

The industry's necessary obsession with product and process quality assurance has kept most companies from committing to the other elements of TQM --namely, the philosophical element of continuous improvement and the application of generic statistical quality tools. This is changing and pharmaceutical companies are expected to continue to adopt elements of TQM.

Figure 3.7 The Concept of Total Quality Management.



Source: Chase and Aquilano, 1993

At Johnson & Johnson's plant in Sherman, Texas, a shared vision keeps the facility profitable for its management, union members and the small town supported by it. During 1990, the continuous improvement efforts by quality improvement process teams throughout the plant generated $2.6 million in savings. Hundreds of small success stories convinced plant management of the competitive values of continuous improvement teams.

MMD was the first drug company to recognize the individual private doctor is no longer the primary drug-buying decision maker. After benchmarking the way AT&T deals with its big buyers, MMD increased its special marketing and sales groups to cater to government accounts and managed care companies. John Aitken, MMD's vice president of quality performance improvement, credits the company's early experience with TQM for its current jump on the competition. When MMD was formed from a merger with Marion Labs, the merger steering committee determined that quality initiatives would be integrated throughout the company. MMD began commissioning research on how managed care groups buy drugs. MMD is also improving the way it answers customer questions. Emulating Hewlett-Packard, MMD is creating a toll-free number staffed by pharmacists and physicians who can field queries around the clock.

3.5.5 Marketing

In the past, the marketing philosophy for the pharmaceutical industry has been that they will be able to sell what they choose to produce. Marketing has been largely a peripheral business. Now faced with a market place that is increasingly shaped by customer-driven demands, marketing is rapidly being transformed into the industry's driving philosophy.

Surprisingly few companies recognize the power of marketing or have realised the extent of the changes necessary to compete successfully in the 1990s. Two forces that have been profoundly affected are:

- pharmaceutical sales forces
- distribution channels

These two factors (together with promotion and pricing) have changed very little in 40 years. By the early 1990s, however, this comfortable position has been threatened by:

- a more powerful and sophisticated customer base
- intensifying competition
- growing concentration in the distribution channels

As a result there has been a fundamental shift in the strategic role of the marketing mix components. The sales force (long the main promotional medium) is at the forefront of these changes-- the traditional primary selling relationship between the sales force and the individual physician has been changed by a number of market factors which include:

- an increasing trend towards group practice and closer links between physicians and insurers has led to concentrated buying decisions in the hands of fewer but more professional purchasers.

- By 1991, 75% of all HMOs in the US operated some kind of restrictive formulary and 30-40% of all hospital drugs were bought this way.

- In the UK, fund-holding partnerships of doctors are co-ordinating their prescribing behaviour with community pharmacists or in-house dispensaries. The Netherlands uses computerized prescriber-dispenser networks.

- Companies are now being forced to develop relationships with pharmacists to take into account their growing ability to substitute products and automatically refill prescriptions. There is also an important trend towards switching products from prescription-only status to OTC.

- One of the most important strategies a pharmaceutical marketer can implement is to recognize pharmacists as integral members of the health care team. Pharmacists play a critical role in drug purchase decisions .

- Pharmaceutical companies are facing more competition from retail pharmacy "private label" brands, generics and OTC products manufactured by the wholesalers, particularly in Germany and the Netherlands. Companies must also be aware of the involvement of new decision makers such as nurses and the growing influence of patients on both prescribing and dispensing.

These trends necessitate a change for the sales force. Emphasis should be placed on:

- product features and benefits
- relationship selling with a long term focus
- emphasis on effective account management
- value added selling

Since the customer groups are not evolving at the same rate, companies will have to include all types of selling. As few representatives have the breadth and depth of clinical, pharmaceutical and health economics knowledge necessary to deal with the issues raised by sophisticated buyers, team selling is taking a central role. Approximately twenty companies in the US, and Glaxo and Rhone-Poulenc Rorer in the UK have adopted team selling to large user/buyers.

In the top eight markets (US, Japan, Germany, France, Italy, Spain, the UK and Canada) the minimum mass necessary to enable a sales force to maintain a competitive share of voice for a limited product range was around 2,900 representatives in the early 1990s. At a cost of US$100,000 per representative, sales force costs would be about US$290M. Given that selling costs represent around 15% of total price, a company would have to achieve sales of US$2 billion to fund a minimum sales force. Few companies worldwide achieve this level of sales. (Darbourne, A., p. 13)

Companies are therefore, thinking their strategies through carefully. Syntex has confined its sales force growth to the US while others have implemented co-promotion and co-marketing strategies and selective out-licensing to gain market access at a reasonable cost. A third approach is to focus marketing efforts on prescribers in specialist areas.

Significant among the new players are the specialist purchasing agents and mail order suppliers which have become major direct buyers in the US. As the demographics continue to shift, nursing homes, long-term care facilities and clinics are also emerging as direct buyers.

In Europe, wholesalers are negotiating cross-border acquisitions and setting up buying consortia to take advantage of the single European market. They are also integrating backwards into the manufacture of generics and in some cases, forwards into the formation of retail pharmacy chains.

Wholesalers are also moving forward into direct hospital supply with Just-in-time arrangements for stockless hospitals and in-hospital management agreements. This is a prime feature in the US where 85% of hospital pharmacy arrangements are done on a prime vendor contract.

In the UK where about 50% of hospital drug purchases are supplied through wholesalers, nine manufacturers including Merck and ICI, have wholesalers as their sole hospital distributor. (Darbourne, A., P. 14)

Individual pharmacists are gaining greater power to make decisions at the point of sale as a result of increased pressure from insurers and governments for generic substitution and prescription-only to OTC switches. As an added complicating factor, supermarkets and large discount stores are moving into the retail pharmacy and are constructing in house chains.

As the distribution channels change from a formerly passive role to powerful, fully involved participants in the supply chain, pharmaceutical companies are redefining their channel strategies and relationships. Some major companies are evaluating "seamless logistics" fully integrating the upstream manufacturing to the down stream supply process to encourage greater efficiency.

How the pharmaceutical companies choose to respond to the new marketing environment, survival and growth in this customer-driven market will be determined by how well and quickly they adapt to the new conditions.

Mail-Order Drugs

New mail-order pharmaceutical providers have staked claims to the lucrative drug market, once the exclusive domain of traditional drug store pharmacists. Operating out of warehouses, providing free delivery within 24 hours and maintaining computerised records of all of their customer's health care needs has enable mail-order to penetrate the market, especially in the area of long-term maintenance drugs for heart patients, arthritis sufferers and diabetics where often the medication is not needed immediately or can be ordered in advance.

The lower costs of mail-order prescriptions have appealed to companies offering employees prescription drug benefits since mail-order providers directly bill companies and patients are not required to outlay any money. The pharmacies are worried and that means they have cause to worry--"it means mail-order has really found its place in the corporate market".

Some Dutch private health insurance companies are investigating the possibility of dispensing prescription drugs directly to their clients through the mail as a way to cut costs. Currently, those people with private health insurance policies have to pay pharmacists for their prescription drugs and then place a claim with the insurance company for reimbursement.

One of the areas of concern with mail order pharmacies is security - they must be able to guarantee safety and ensure mail-order drugs do not fall into the wrong hands.

3.6 SUMMARY

To understand the success and/or failure of the pharmaceutical industry in different countries, and the competitiveness of pharmaceutical firms, also requires an examination of the geographical structure and industry dynamics at a different scale other than just national.

There are many discussions on the structure of the industry, its key characteristics, leading firms and so on. There is little research, however, which investigates the industry or firms on a micro-scale. In Canada, for example, there are geographical agglomerations in the greater Toronto area and also in and around Montreal. Are there similar agglomerations in other markets, and if so, to what extent do they contribute to the effectiveness of those national industries?

These questions raise further questions! When we speak of an industry's competitiveness what do we mean when we know that the national industry is dominated by foreign capital and whose decision-making authority is vested in other national jurisdictions? Is it more accurate perhaps to focus on determining those characteristics which contribute to a profitable, research oriented industrial base for pharmaceuticals? What then can Canada learn from other nations strategies to promote R&D generally, and in the pharmaceutical industry more specifically? Moreover, what factors are central to the locational decision-making of pharmaceutical firms?

At the same time, we must recognize the historical context in which the pharmaceutical industry has emerged. It had its origins in Europe and later developed in the United States, and this has clearly been an important factor in the continued dominance of these regions today. But how has Japan emerged as an influential location for R&D investment and how are other countries attempting to develop and attract R&D capabilities?

This chapter has provided a snapshot of corporate strategy and the competitive issues characterizing the industry at the beginning of the 1990s, and has identified and suggested trends that will impact upon the industry through the 1990s. The "driver" for corporate strategy and competitiveness, however, is the nature and extent of research and development that the manufacturers possess. Our understanding of this requires an examination of the nature of R&D in the industry and the locational elements of R&D - the focus of Chapter Four.

CHAPTER 4. R&D IN THE PHARMACEUTICAL INDUSTRY

4.1 INTRODUCTION

This chapter consists of six sections. The first reviews the extensive literature on the location of R&D activity by multinational corporations and suggests ways of analyzing the implications of recent developments for Canada. The second section provides an overview of pharmaceutical R&D spending trends in Canada, with the view to assessing the impact of the recent modifications of the Patent Act. The third section makes a brief comment on salient characteristics of pharmaceutical R&D in Europe. The fourth section provides an overview of pharmaceutical R&D on a global scale. The fifth section summarizes the key features of R&D in biotechnology and its relationship to pharmaceuticals. This is followed by a brief discussion of selected policy issues, and a concluding section which reviews the problems associated with definitions of research and development.

4.2 LOCATION OF R&D ACTIVITY BY MULTINATIONAL CORPORATIONS: THEORIES, TRENDS, AND EMPIRICAL EVIDENCE

4.2.1 Introduction

This section presents an analytical overview of the patterns of international location of R&D activity and their determinants. The traditional patterns are discussed together with the emerging trends and theories attempting to explain the reasons for the observed changes and possible future developments. Given the time constraints on the completion of this report, most of the discussion in this section relates to industrial R&D in general, across a whole spectrum of industries. The applicability of the analysis to the pharmaceutical industry in general and to its Canadian operations in particular is explored only to a very limited extent. A more detailed treatment will require discussion with corporate management, both in Canada and in the headquarters of selected multinational corporations.

The following paragraphs draw heavily on an excellent recent review of a large volume of literature on "internationalization of R&D" by Granstrand et al. (1993). The review discusses factors contributing to centralization of R&D in the "home country" of the multinational corporation together with factors encouraging decentralization. Each set of factors are, in turn, divided into those on the "demand side" and those on the "supply side". While much of the academic literature on the subject is based on U.S. data, Granstrand et al. make an effort to include in their analysis empirical evidence from European multinational corporation as well. They show that such a broadening of the data base leads to conclusions suggesting that a rethinking of the conventional wisdom on several aspects of the location of R&D activity may be in order.

4.2.2 The Main Trends

In the traditional view of a large cross-section of industries, the central management of a multinational corporation has the task of controlling and coordinating the various largely independent national subsidiaries. In this model, R&D activities tend to be highly centralized in the home country, close to the corporate headquarters and major production facilities. Empirical analysis of data for U.S.-owned multinational coporations largely confirmed the validity of this pattern. In most other countries as well, foreign R&D activities of multinational corporations are still more the exception rather than the rule. The bulk of R&D is still performed in central home-country based laboratories (Grandstrand et al., 1993, p. 422).

Recent theory, by contrast, emphasizes the "network character" of the multinational corporation and its operation as an integrated whole. In a similar vein, recent literature on R&D in foreign subsidiaries differentiates between the various types of tasks performed under this heading. Firms are under increasing pressure to shorten market penetration times and shorten the period of R&D and product development.

Evidence based on patent data shows that, for example, large Belgian and Dutch multinationals performed more of their R&D activity outside their home country than inside. Canadian, British, Swedish and Swiss multinationals performed between 30% and 42% of R&D in foreign countries. The role of overseas R&D of Japanese and U.S. multinationals has been increasing in importance as well. In a recent survey, Japanese and U.S. executives ranked increased "internationalization of R&D" as one of their top priorities (Grandstrand et al., 1993, p. 414).

The U.S.-based pharmaceutical industry seems to be a part of this general trend, as illustrated by the breakdown of R&D spending data for member companies of the Pharmaceutical Manufacturers Association. It shows that the R&D spending abroad as a proportion of total company R&D[1] grew from 8.4% in 1970 to 21.6% in 1980, levelled off somewhat during the 1980s, registered 19.9% in 1988, and was expected to reach 17.6% in 1994 (Source: Table 4.1).

Table 4.1 Trends in R&D spending of American PMA member companies, ethical pharmaceuticals

Year	Total R&D $ mill.	Domestic U.S. R&D $ mill.	R&D Abroad $ mill.	Abroad as % of Total	Canada as % of Abroad
1994*	13,802.9	11,375.6	2,427.3	17.6	N.A.
1993*	12,633.3	10.330.9	2,302.4	18.2	N.A.

[1] Since the nature and composition of R&D performed in the home country (U.S.) is different from that performed in the foreign subsidiaries, the magnitude of "R&D abroad as a proportion of total" should be interpreted with caution. The time trend is, however, of considerable interest.

Year	Total R&D $ mill.	Domestic U.S. R&D $ mill.	R&D Abroad $ mill.	Abroad as % of Total	Canada as % of Abroad
1992	11,467.9	9,312.1	2,155.8	18.8	N.A.
1991	9,705.4	7,928.6	1,776.8	18.3	7.4
1990	8,420.3	6,802.9	1,617.4	19.2	N.A.
1989	7,330.0	6,021.4	1,308.6	17.8	10.4
1988	6,537.5	5,233.9	1,303.6	19.9	6.3
1987	5,502.2	4,504.1	998.1	18.1	7.6
1986	4,740.1	3,875.0	865.1	18.2	7.5
1985	4.077.6	3,378.7	698.9	17.1	7.3
1984	3,578.8	2,982.4	596.4	16.7	N.A.
1983	3,217.6	2,671.3	546.3	17.0	7.0
1982	2,773.7	2,268.7	505.0	18.2	6.1
1981	2,339.5	1,870.4	469.1	20.0	5.5
1980	1,976.7	1,549.2	427.5	21.6	4.0
1979	1,626.8	1,327.4	299.4	18.4	5.0
1978	1,404.0	1,166.1	237.9	16.9	5.1
1977	1,276.1	1,063.0	213.1	16.7	5.8
1976	1,163.7	983.4	180.3	15.5	N.A.
1975	1,061.5	903.5	158.0	14.9	N.A.
1974	980.4	793.1	147.7	15.1	N.A.
1973	825.0	708.1	116.9	14.2	N.A.
1972	726.1	654.8	71.3	9.8	N.A.
1971	683.8	626.7	57.1	8.3	N.A.
1970	618.5	566.2	52.3	8.4	N.A.

Sources:
Pharmaceutical Manufacturers Association, Backgrounder: U.S. Pharmaceutical R&D and Sales, February 1994
Pharmaceutical Manufacturers Association, Annual Survey Report, Various Issues; personal communication (Canada 1977-1981)

4.2.3 Factors Responsible for the Geographic Centralization of R&D

Several factors favour centralization of R&D in one, or a few, locations, regardless of the country; there are, however, also reasons why this location should be specifically in the home country, in the proximity of corporate headquarters. They include the following:

- Centralization of R&D reduces the number of organizational units and personnel dealing with R&D results, and thus facilitates the task of **protecting firm-specific technology** (reduces the potential for leakage to competitors). Home country location is indicated only if the domestic R&D personnel are deemed more trustworthy than their foreign counterparts.

- Increasing organizational and technological **complexity** of R&D activity increases the difficulties of coordinating information flows; centralization of R&D (not necessarily in the home country) may thus be an advantage.

- Firm-specific technological advantage often derives from the **quality and sophistication of the domestic market**. In such cases, continued close contact with the domestic market customers and location of R&D facilities in the home country is preferred.

- If **economies of scale in R&D** are important, a certain minimum critical size of R&D facilities is required. For the pharmaceutical industry, Burstall et al. (1981, p. 43 and 71) estimated almost two decades ago such a minimum to be between 200 and 300 scientific R&D personnel. They report that in 1975, the average size for a sample of 25 U.S. laboratories was 271 professionals plus 289 technicians; in the six leading German pharmaceutical companies, the average number of researchers was 267 and for a sample of nine French companies, the average number of R&D personnel was 380.

  Some components of the R&D process may, however, be easily performed in smaller units. Moreover, developments such as the use of electronic networks in R&D give the smaller units access to specialized equipment and expertise without the need for physical centralization. [An update on the average size of pharmaceutical R&D laboratories in a sample of countries would shed some light on the importance of economies of scale as a barrier to growth of the industry in Canada]

- Another argument for centralization is based on the need for exchange of information between R&D units and the rest of the corporate functions, as well as between R&D units to **avoid duplication** of effort. Some of this information tends to be unstructured, requires negotiation and common problem-solving and thus face-to-face contact, which is facilitated by geographic proximity. The recent literature on inter-firm R&D cooperation suggests, however, that the advantages of cooperation may be outweighed by the disadvantages of the lack of competition.

Some larger corporate structures with several independent R&D units implicitly recognize the stimulus of competition and require only a minimum coordination among them. This was the case, for example, within the structure of the American Home Products organization which contained several pharmaceutical companies. (Source: Interview with management personnel at Ayerst McKenna Laboratories, Montreal, circa 1975).

- **Historical reasons** remain the most important determinant of centralization, although an explicit rationale for a currently existing location may not be easily formulated.

4.2.4 Factors Responsible for the Geographic Decentralization of R&D Demand-Oriented Factors

"Demand-oriented factors", or characteristics of the markets the company serves may favour decentralization of R&D facilities in order to facilitate interaction with customers.

- Historically, the establishment of an R&D facility outside the home country was usually preceded by attainment of a market share first through exports and subsequently through sales and manufacturing subsidiaries. **Transfer of technology** from the parent company as a demand-oriented factor usually required product and process adaptations which are sometimes best performed in a local R&D unit. Cooperation with customers and contact with local market trends and idiosyncratic aspects of demand strengthen the competitive position of the subsidiary, facilitate recruiting of qualified personnel and lead to a further growth of the R&D unit. This "sequential evolutionary" model of internationalization of R&D is increasingly inadequate to explain the developments in the 1990s.

- The pharmaceutical industry is usually cited as an example of **government regulations** as a demand-oriented factor, requiring local R&D in order to perform clinical testing.

4.2.5 Supply-Oriented Factors

"Supply-oriented factors" favouring decentralization include the availability of skilled personnel or lower R&D costs in various local markets, and access to universities and other research establishments. One reason for greater reliance on universities is that industrial R&D is becoming increasingly science-based (Grandstrand et al., 1993, p. 423). In the pharmaceutical industry, this trend takes the form of a shift from the traditional "shotgun" approach to new drug development (which starts with the screening of thousands of chemicals for biological activity and proceed to animal and human testing) toward a "design" approach (where the desirable properties of a future drug are specified in advance and researchers are then charged with the responsibility of synthesizing the appropriate compounds).

While the theoretical arguments may appear convincing, the empirical support testing the importance of the supply-oriented factors as determinants of R&D location is still rather limited (Grandstrand et al., 1993, p. 422).

Recently, a new pattern is emerging as a consequence of the escalating pace of technical progress and rising costs of R&D: Competitive advantage requires access to a wider range of sources of leading-edge technologies, R&D skills and knowledge than is available in the home market. R&D units located in foreign countries have thus acquired a new range function:

- R&D units abroad help **create and renew the core technological capabilities** of the firm. Some of these new types of foreign R&D units help the parent company **diversify** into new product areas and technologies, for example, through acquisitions of (foreign) biotechnology firms by traditional pharmaceutical companies.

  Another type of foreign R&D unit are those set up to **tap into a foreign country's scientific infrastructure**. Again, pharmaceuticals, biotechnology and electronics, are the most common examples, but such R&D units have also been formed in some engineering industries.

  Acquisitions of small technology-based U.S. firms by Japanese multinationals have elicited hostile press reaction, largely because reciprocal opportunities for U.S. acquisitions in Japan are much more restricted (Grandstrand et al., 1993, p. 427). Japanese companies have also attempted to compensate for the relative weakness of Japanese universities by "purchasing" endowed chairs at U.S. universities and thus tapping into their research potential. [The potential benefits and cost of making Canada a "host" country for such activities of foreign pharmaceutical multinationals need to be analyzed].

In order to obtain some measure of the strength of the relevant science base in Canada, Pazderka (1985) performed a survey of a small sample of the Deans of Faculties of Pharmacy at several Canadian universities. The respondents agreed that a number of scientific disciplines are relevant, among them Clinical Pharmacology, Medicinal Chemistry, Toxicology, Pharmacokinetics, including Drug Disposition and Metabolism, and Physical Pharmacy and Pharmaceutics. In addition, the strength of all basic science departments in the Faculties of Medicine, but especially Physiology, Biochemistry, and Microbiology was considered important.

The sample is too small and the results are a decade old to warrant a discussion here. However, a similar survey could be replicated on a larger scale to obtain an analogous assessment for 1994. Another quantitative perspective on the strength of the science base was obtained from data on citations of scientific articles. Based on the indicator "Canada as a percentage of the total of world citations", Canada appeared to be an attractive location of pharmaceutical R&D. Again, a more up-to-date figure would be useful.

- Some authors see a great deal of promise in **cross-border inter-firm R&D cooperation** as a method of creating and renewing technological capabilities of participating firms. [The current incidence and potential for such arrangements in the Canadian pharmaceutical industry should be the subject of future research]

- Both the **cost** and the **productivity of R&D** vary from country to country. Grandstrand et al. (1993, p. 417) note, as an example, that the availability of certain specialized biotechnology researchers in Bangalore, India is over one hundred times greater an in Sweden, a graduate researcher with a U.S. degree costs less than one-tenth of the cost in Stockholm, and one square meter of advanced biotechnology laboratory in Bangalore also costs about one-tenth of the costs in Stockholm. [For Canada, the comparisons of R&D costs with the U.S. are of special importance. Our literature search to date has not uncovered any systematic published study. A small-scale investigation of the relative costs of doing pharmaceutical R&D in Canada could be undertaken, with cooperation from pharmacologists and related disciplines at Queen's].

- **Government policies toward R&D** are one of the supply-oriented determinants of location. With respect to R&D **subsidies**, Grandstrand et al. (1993, p. 417) cite research showing that they may have some influence on firms already performing R&D in the country. However, given the political uncertainty (possibility of repeal) of such measures, firms may be reluctant to make their locational decision on this basis alone. **Patent protection** as a determinant of location of R&D has, of course, played a prominent role in the recent Canadian public discussion.

  It may be of interest to note that a 1972 submission by the Pharmaceutical Manufacturers Association to the U.S. Congress (PMA, 1972) listed as the most important determinants of location of production facilities the following characteristics of a country: tariff and trade restrictions, legal and other requirements for local production, better servicing of existing work. Tax benefits were important for only 33% of respondents and access to scientific research laboratories and other intangibles was judged as "inconsequential" or of no importance by 48%. The degree of patent protection in the host country was not explicitly mentioned, although it may well be a part of the "intangibles" which received a rather low priority rating. in [No similar recent rankings have been published. It may be useful to attempt to elicit an opinion from industry sources as to the reasons that the importance of patent protection should have changed over time].

  Recent research has established a trend toward increasing research intensity of foreign-based production among U.S. and European-based multinationals (Grandstrand et al., 1993, p. 424). Any observed recent increases in the R&D intensity of the foreign-owned segment of the Canadian pharmaceutical industry may therefore be simply a part of this general pattern, rather than the consequence of the tightening of Canadian patent protection for prescription drugs.

  The effectiveness of **tax concessions** for R&D has been analyzed in a number of studies, mostly covering a whole range of industries. McCutchen (1993, pp. 337-338) cites a study by the U.S. General Accounting Office which concluded that the U.S. R&D tax credit stimulated between 15 and 36 cents of additional R&D spending for each dollar of taxes forgone. Various studies by Mansfield and by Mansfield and Switzer estimated that the tax

credit stimulated much less increase in R&D than was the revenue loss to the Treasury. Some firms have also redefined expenses to take advantage of the credit. McCutchen's study focused explicitly on the U.S. pharmaceutical industry and concluded that 29.3 cents of additional R&D expenditure was generated for each dollar of tax credit between 1982 and 1985. Grandstrand et al. (1993, p. 427) concluded that tax concessions and similar measures usually have only a limited impact because they are launched on a small scale and are not tied into corporate decision-making regarding R&D.

- Some published research (summarized in Grandstrand et al., 1993, p. 418) suggests that the extent to which R&D is performed outside the home country varies with such factors as the **age and size of the firm**, and its stage of corporate development and rate of **growth**. Firms which employ a high **percentage of professional and technical employees** also tend to do a higher share of their R&D abroad, as do firms which **concentrate manufacturing in a few specialized factories** (rather than in many smaller factories dispersed over many countries). This last factor is of relevance in the context of the creation of free trade areas and assignment of world product mandates to selected firms.

  The length of **time for which the firm has operated abroad** is also important, since it takes time for a firm to appreciate the advantages of foreign R&D and to become informed on the host country R&D abilities. In this respect, given the geographic and cultural proximity, Canada has an advantage as a location for R&D facilities of U.S. multinational corporations. In the pharmaceutical industry, this apparent advantage tends to be offset by the typical firm's strategy of operating only one full-fledged R&D facility. Some large corporations have two such facilities, one in the U.S. and another in Europe (increasingly, Japan is ecoming a third location). The spreading use of electronic networks in R&D, alluded to above, makes smaller R&D units feasible. However, the uncodified nature of information that needs to be conveyed may favour face-to-face contact and thus geographic centralization of R&D. [Input from Canadian and U.S. industry executives is needed to assess the relative strengths of these two tendencies].

- The location of R&D both across countries and within a given country is increasingly subject to **clustering** (Piore and Sabel,1984; Porter, 1990).

4.3 PHARMACEUTICAL R&D IN CANADA

The determinants of location of R&D activity were discussed in a previous section. The literature review utilized theoretical models and empirical evidence from a wide range of industries and countries. References to the pharmaceutical industry and to Canada were made largely in the form of suggestions for further research to be pursued. The focus of this section is on R&D performance of the pharmaceutical industry in Canada. The discussion is somewhat rudimentary, both in the coverage of issues, and in the amount and type of statistical information gathered to date. One of the main objectives is to attempt an assessment of the impact of the recent modifications of the Patent Act on the volume of R&D performed in Canada.

A simple observation of time trends in such indicators as the dollar volume of Canadian pharmaceutical R&D expenditures, or the numbers of R&D personnel in the industry, or its R&D/sales ratio (R&D intensity), may lead to misleading conclusions, simply because these indicators are affected by many factors other than patent protection. The data gathered to date, and presented in Tables 4.1, 4.2, 4.3 and 4.4, helps make a step toward separating R&D trends in the Canadian pharmaceutical industry from R&D trends in its international counterpart, and from R&D spending trends in Canadian manufacturing industry as a whole.

The last column of Table 4.1 shows the R&D spending in Canada by member companies of the Pharmaceutical Manufacturers Association as a percentage of their total R&D spending abroad (outside the home country). The earliest available figure is for 1977; in that year Canada represented 5.8% of the member companies' R&D spending abroad. Canada's share reached a low of 4% in 1980, rose to a high of 10.4% in 1989 (two years after enactment of Bill C-22), but declined again to 7.4% in 1991 (the most recent data available), which is about the average for most of the 1980s. This information, based only on data for the multinational segment of the industry in Canada, would thus not suggest any sustained discernible impact of the tightening of patent protection on R&D in Canada.

Data in Tables 4.2-4.4 are taken from Statistics Canada sources and cover all companies operating in the industry. The last column in Table 4.2 shows total R&D expenditures in the pharmaceutical industry as a percentage of R&D expenditures in all manufacturing industries. The earliest available observation is for 1975, when pharmaceutical R&D represented 4.5% of total manufacturing spending. It subsequently declined, reaching the low of 2.8% in 1984, rose to 4.2% in 1988, 5.5% in 1989 proceded to rise rather sharply, with spending intentions for 1993 reaching 9.6% of manufacturing total. This trend may be interpreted as support for the hypothesis that the modification of patent legislation had the desired effect.

Table 4.2 Canada - Total R&D expenditures by industry (million $)

Year	Pharmaceutical and Medicine	Manufacturing	Total, all industries	Pharma as % of Manufact.
1993[i]	356	3,704	5,673	9.6
1992[p]	314	3,564	5,512	8.8
1991	263	3,525	5,391	7.5
1990	256	3,475	5,216	7.4
1989	177	3,225	4,783	5.5
1988	134	3,199	4,618	4.2

Year	Pharmaceutical and Medicine	Manufacturing	Total, all industries	Pharma as % of Manufact.
1987	107	2,932	4,312	3.6
1986	103	2,748	3,996	3.7
1985	81	2,601	3,605	3.1
1984	63	2,256	2,994	2.8
1983	66	2,021	2,585	3.3
1982	58	1,958	2,489	3.0
1981	52	1,700	2,124	3.1
1980	43	1,247	1,571	3.4
1979	33	1,000	1,266	3.3
1978	27	795	1,006	3.4
1977	25	669	857	3.7
1976	26	603	755	4.3
1975	25	561	700	4.5

Source: Statistics Canada, Industrial Research and Development, Catalogue No. 88-202

The R&D intensity of the pharmaceutical industry, reported in Table 4.3, increased only modestly, from 4.2% in 1973 to 5.3% in 1991, registering as low as 3.6% in 1986 and 1987. A significant increase did, however, take place between 1987, when the R&D intensity was 3.6% to 1991. The same measure for manufacturing as a whole, by contrast, rose steadily and doubled from 0.9% in 1973 to 1.8% in 1991.

Table 4.3 Canada - Current intramural R&D expenditures by industry as percentage of sales

Year	Pharmaceutical and Medicine	Manufacturing	Total, all industries
1991	5.3	1.8	1.7
1990	5.0	1.7	1.5
1989	4.3	1.5	1.4
1988	4.0	1.5	1.4
1987	3.6	1.5	1.4
1986	3.6	1.5	1.4
1985	3.7	1.4	1.3
1984	3.9	1.3	1.2
1983	4.7	1.3	1.2
1982	4.7	1.3	1.2
1981	4.3	1.1	1.0
1980	N.A.	N.A.	N.A.
1979	4.7	0.9	0.8
1978	N.A.	N.A.	N.A.
1977	4.6	0.8	0.8
1976	N.A.	N.A.	N.A.
1975	3.8	0.8	0.8
1974	N.A.	N.A.	N.A.
1973	4.2	0.9	0.9

Source: Statistics Canada, Industrial Research and Development, Catalogue No. 88-202.

Apart from the volume of R&D spending and R&D intensity, the composition of R&D expenditures (breakdown into basic and applied research and clinical testing) is of major interest. Published Statistics Canada documents do not provide this breakdown. However, a rough approximation, calculated in the last column of Table 4.4, is the percentage of professional occupational category in the total R&D personnel in the industry. This indicator shows a slow steady rise from 56.8% in 1982 to 60.3 percent in 1991.

Table 4.4 Canada - R&D personnel by occupational category: Pharmaceutical industry

Year	Professional	Technical	Other	Total	Professional as % of Total
1991	1,106	415	314	1,835	60.3
1990	905	370	305	1,580	57.3
1989	835	320	250	1,405	59.4
1988	665	295	180	1,145	58.1
1987	515	235	240	990	52.0
1986	485	215	230	930	52.1
1985	385	105	195	685	56.2
1984	330	120	165	620	53.2
1983	525	205	115	930	56.4
1982	520	190	210	915	56.8

Source: Statistics Canada, Industrial Research and Development, Catalogue Number 88-202

The Patented Medicine Prices Review Board (PMPRB) publishes detailed R&D statistics broken down by type of research. The data can be tabulated and trends analyzed in subsequent work on the pharmaceutical industry. The Board, however, covers only a segment of the industry, hence any inferences as to the impact of the patent legislation will have to be qualified.

Relatively little is known about the extent and composition of R&D conducted by member companies of the Canadian Drug Manufacturers Association (CDMA). Again, subsequent research can comment on the results of data gathering in this area.

The definition and measurement of R&D expenditures deserves a careful discussion of the differences between R&D as defined by Statistics Canada, by the Income Tax Act, by the OECD, by the PMPRB, by the PMAC and the CDMA.

4.4 PHARMACEUTICAL R&D IN EUROPE

As shown in Table 4.5, the sum of R&D expenditures in France, Italy, Germany and the UK represented over 90% of the European Union total in 1990. The R&D intensities in Table 4.5 are calculated as R&D spending divided by national sales excluding exports, and thus favour countries where exports are high relative to the size of the domestic market. These R&D intensities varied widely, from 40.8 percent in the U.K. to 2.8 percent in Spain. The European Union average R&D to sales ratio was very close to that of the United States.

Table 4.5 Selected data on the European, Japanese and American pharmaceutical industries, 1990

COUNTRY	NUMBER OF FIRMS[1]	OUTPUT[5] MILL. ECU	R&D[6] MILL. ECU	R&D AS % OF SALES[7]
Belgium	250[2]	1,589	141.9	13.8
Denmark	164[3]	1,053	125.7	35.8
France	362	12,446	1,426.2	17.6
Germany	1,009	12,512	2,008.8	25.9
Greece	54	404	N.A.	N.A.
Ireland	400[4]	662	N.A.	N.A.
Italy	303	10,271	1,426.2	11.2
Luxemburg	-	-	-	-
Netherlands	78	1,455	213.2	22.6
Portugal	706	581	N.A.	N.A.
Spain	351	4,881	83.6	2.8
United Kingdom	352	9,433	1,560.4	40.8
Total EC	3,629	55,287	6,986.0	20.0
Switzerland	387	N.A.	1,567.5	N.A.
Japan	1,315	N.A.	2,235.6	11.0
U.S.A.	790	N.A.	5,124.4	20.7

Source: Earl-Slater (1993, pp. 78-89)
Notes:
1) The firms are those engaged in the production of pharmaceuticals for human use. The data exclude wholesalers, retail or dispensing units and specialist, research-only companies.
2) 1989
3) 1988

4) 1987
5) Output is from industry located in the country, regardless of corporate nationality.
6) R&D expenditures include funding of projects to enhance quality, safety and efficacy of products, but excludes physical capital and staff training expenditure.
7) National sales exclude export sales.

Of the top 60 R&D performing firms in the world in 1989, 24 firms (40 percent) were European, 21 firms (35 percent) were U.S. and 15 firms (25 percent) were Japanese (Earl-Slater, 1993, p. 90).

The number of new chemical entities introduced to world health care markets is listed in Table 4.6 by nation of origin for three periods spanning 1941-1989. The periods are of uneven length and two of them (1941-63 and 1961-80) overlap. The figures are thus not strictly comparable, but it is evident that the number of new chemical entities peaked during the 1961-1980 period and sharply declined thereafter. A possible explanation is that the basic R&D results reached a plateau insufficient to produce a new generation of chemical entities. Another explanation might be increasing regulatory stringency and the resulting rise in R&D costs (Earl-Slater, 1993, p. 91).

Table 4.6 Number of new chemical entities introduced to world health care markets, 1941-1989

COUNTRY	1941-63	1961-80	1981-89
Belgium	3	36	6
France	21	272	31
Italy	1	112	42
Germany	32	191	37
Spain	N.A.	N.A.	10
Netherlands	6	N.A.	2
United Kingdom	27	73	21
Switzerland	44	106	34
U.S.A.	355	348	106
Japan	3	154	117
World Total	587	1,498	522

Source: Earl-Slater (1993, p. 91)
Notes:
1) The numbers are listed by nation of origin of the New Chemical Entity.
2) Two of the time periods overlap (1941-63 and 1961-80).

The Council of Ministers of the European Union agreed, effective in 1992, to extend the effective patent life for pharmaceuticals to a 15-year period. Earl-Slater (1993, p. 99) believes that even after this extension R&D efforts may be biased toward products that take a shorter time to test, and against products which need a longer time to test and evaluate, for example Alzheimer's, multiple sclerosis, motor neurone disease, and some cancers.

The economic strains and "image problems" of the industry has created tensions within the industry associations on both sides of the Atlantic. A group of subsidiaries of research-based multinational drug companies from Italy, Spain, France and Germany set up a new association to lobby for their interests both at the national and at European level, to enhance the "European" profile of the industry and its products. One of its immediate objectives would be to lobby for a speedy and efficient registration procedure within the European Union (Scrip, 5th Oct,1993: 10).

The German industry association, the BPI, broke up. In the U.S., a group of research-based companies formed Rx Partners to engage in more pro-active lobbying. The U.S. Pharmaceutical Manufacturers Association set up a committee to review its mission, structure, and functions. Abbott left the PMA; in the U.K. Syntex left the Association of the British Pharmaceutical Industry. In the Netherlands, the industry association split into two groups, one for producers of prescription drugs and one for over-the-counter drugs (Scrip Magazine, Jan,1994:4).

4.5 WORLD PHARMACEUTICAL R&D

This section first presents a possible classification of the various types of pharmaceutical companies according to the degree of their involvement in R&D. The geographic location of the various types of firms and its reflection in the strengths, weaknesses and potential of the pharmaceutical industry in each country and region of the world is discussed. The most important quantitative measure of such potential is the distribution of R&D spending and the number and type of new pharmaceuticals introduced to world health care markets.

4.5.1 Categorization of Countries according to Research Potential

Ballance et al. (1992, pp. 5-7) distinguish several types of pharmaceutical companies: The "integrated corporations" are multinationals engaged in all stages of the drug production and distribution, i.e. research, manufacture, and distribution. They are typically large (with sales exceeding $200 million), place a high priority on new product development and adhere to well-defined methods of operation, including reliance on patents and use of brand names.

The second category, the "innovative companies" are capable of developing new chemical entities, but typically produce drugs whose patents have expired, or under license. Their sales are less than $200 million; their operations in overseas markets are conducted either through own subsidiaries, or through collaborative ties with foreign producers.

The "reproductive firms" are either small, family-owned enterprises or publicly-owned

medium-size firms. They typically produce drugs which are off patent, purchase several of their inputs, and sell their products either under a brand name or as generics.

Another group are the "small, research-based drug firms". The most important of these engage in genetic engineering (e.g. Biogen, Biotech, Cetus, and Genentech). They typically incur operational losses at early stages, most become targets for acquisitions, and have become integrated with mainstream firms in the industry.

Finally, a small subset of firms specialize in the development of new therapeutic systems, synthesis of new compounds, in vivo studies, product registrations, etc., frequently under contract for other pharmaceutical firms (e.g. Alza, Elan, and KV Pharmaceuticals).

According to Howells (1990, pp. 497-498), the traditional categorization of international R&D activities of firms found in the literature derives from the geographic market scope of the firms' products. Some of the literature Howells reviewed treats these categories as stages in an evolutionary process, as firms move from domestic to more global orientation.

First, the "home market companies", with products oriented largely toward the home market, establish abroad only low-level technical support or test facilities, animals and farm facilities, frequently hiring local scientific staff. They conduct research necessary for technology transfer or narrowly specialized research in limited areas. The management of R&D units of this type is relatively decentralized and is characterized by "supervised freedom".

Second, research laboratories established abroad by the "host market companies", with products oriented at foreign markets, are likely to be capable of a full range of applied R&D activities and of developing and transmitting new technology to other affiliates. The management of these laboratories includes elements of centralized control and coordination.

Third, the "world market companies" are more likely to establish abroad not only low-level technical units, but also independent laboratories equipped to conduct long-term basic research, with a defined research mission and comprehensive research capacity. They tend to have centralized R&D management with product coordination on a global scale.

Recent developments introduced a number of other factors influencing the international location of R&D facilities. One of them is the rise of "pervasive enabling technologies", such as biotechnology, information and communications technologies, and advanced materials. Their development, among other things, has broken down the barriers between traditional scientific and technological disciplines. For example, in some areas of biotechnology, progress is impossible without breakthroughs in basic biology and biochemistry. In the pharmaceutical industry, medical research has to be directed to more complex and little understood systems in the physio-chemical processes of the human body (Howells, 1990, p. 499).

As a consequence, the length of time required to develop a new innovation and its costs have increased, and the rate of pharmaceutical innovation, as measured by the flow of new chemical entities, has decreased. The development costs have risen the fastest: while in 1970, about 50 percent of total R&D resources were spent on development, by 1983, this proportion has risen to 70 percent (Howells, 1990, p. 500).

To recoup the rising costs of R&D more rapidly, pharmaceutical companies have sought to launch their products in the largest possible geographic area, possibly on a global basis. In addition, the frequency of mergers and acquisitions has increased as firms attempt to strengthen their research base and develop international sales and marketing teams. Smaller firms, in turn, have engaged in R&D and marketing collaboration with large multinationals. This pattern is particularly characteristic of the new biotechnology firms.

Government policies have also influenced the location of R&D activities. For example, in France the prices foreign drug firms are allowed to charge depend on the amount of R&D done in the country. Empirical evidence on the effectiveness of other government tools, such as tax incentives and subsidies, in influencing the location of biotechnology R&D is contradictory (Howells, 1990, pp. 500-501).

Howells (1990, p. 504) gives a number of examples of the use of computer-communication networks in coordinating multinational research operations. As an illustration, Wellcome conducts its research on the anti-AIDS drug Retrovir on two main centres, one in the U.K. (Beckenham and Dartford), and one in the U.S. (Research Triangle Park in North Carolina). Smaller facilities are in Sophia Antipolis and Greenville in the U.S. and in Kobe High Tech Park in Japan, and related research activities are conducted in Rochester and in Vancouver. A computer communication network in Dartford links all of the company's research and manufacturing facilities. It helps avoid costly duplication, improves coordination of R&D projects and coordination among R&D and other corporate functions, and accelerates the flows of information.

Increasing global inter-firm research collaboration also influences the traditional patterns of location of R&D facilities. Howells (1990, p. 505-507) illustrates with the example of the largest Japanese pharmaceutical company, Takeda. It has a joint venture with Abbott in Tap Pharmaceuticals and research facilities located in Chicago, research and licensing links with Grunnenthal in Germany, and with Cyanamid, Roche, Ciba-Geigy, Glaxo, Bayer, Roussel Uclaf (Hoechst), and Yoshitomi. In 1988, it established a European R&D centre in Frankfurt.

4.5.2 Geographic Distribution

The large, integrated corporations are present only in countries listed in "Category A" in Table 4.7. Countries in "Category B" possess only innovative and reproductive firms. Some of them have significant export capabilities and countries such as Austria, China, Denmark, Hungary, Spain, and Yugoslavia are now among the world's largest exporters. Countries in "Category C" have only reproductive firms. (See also the classification map of these countries in Chapter 1.)

Table 4.7 Typology of countries according to the level of their pharmaceutical industries

Category A: Countries with a sophisticated pharmaceutical industry and a significant research base

Belgium, France, Germany, Italy, Japan, Netherlands, Sweden, Switzerland, United Kingdom, United States

Category B: Countries with innovative capacities (which discovered and marketed at least one new chemical entity between 1961 and 1990)

Argentina, Australia, Austria, Canada, China, Denmark, Finland, Hungary, India, Ireland, Israel, Mexico, Portugal, Republic of Korea, Spain, USSR, Yugoslavia

Category C1: Countries producing both therapeutic ingredients and finished products

Bahamas, Bolivia, Brazil, Bulgaria, Cuba, Czechoslovakia, Egypt, Indonesia, Macau, Norway, Poland, Puerto Rico, Romania, Turkey

Category C2: Countries producing only finished products

Afghanistan, Albania, Algeria, Angola, Bangladesh, Barbados, Belize, Benin, Brunei, Cambodia, Cameroon, Cape Verde, Chile, Colombia, Costa Rica, Côte d'Ivoire, Cyprus, Democratic People's Republic of Korea, Dominican Republic, Ecuador, El Salvador, Ethiopia, Fiji, Gambia, Ghana, Greece, Guatemala, Guyana, Haiti, Honduras, Hong Kong, Iran, Iraq, Jamaica, Jordan, Kenya, Kiribati, Kuwait, Lebanon, Lesotho, Liberia, Madagascar, Malawi, Malaysia, Mali, Malta, Mauritius, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nepal, New Zealand, Nicaragua, Niger, Nigeria, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Saudi Arabia, Seychelles, Sierra Leone, Singapore, Solomon Islands, Somalia, South Africa, Sri Lanka, Sudan, Syrian Arab Republic, Taiwan, Thailand, Tonga, Trinidad and Tobago, Tunisia, Uganda, United Arab Emirates, Tanzania, Uruguay, Venezuela, Vietnam, Yemen, Zaire, Zambia, Zanzibar, Zimbabwe

Category D: Countries without a pharmaceutical industry

[All other countries]

Source: Ballance et al. (1992), pp. 8-9.

The geographic allocation of R&D funds by major multinational corporations is both a cause and a consequence of the industry strength in a particular region or country. Table 4.8 illustrates this relationship with data on R&D spending of member companies of the U.S. Pharmaceutical Manufacturers Association over the last decade. The continuing strength of the West European industry is reflected in the fact that almost 75% of all overseas R&D spending of PMA member companies goes to Europe. The share of Latin America, on the other hand, has declined sharply, from 5.5% in 1982 to only 1.2% in 1991. This is paralleled by the rise of importance of Japan, which is largely the reason for an increase in the share of "Japan, Australia and New Zealand" from 13.3% in 1982 to 19.2% in 1989 and 17.6% in 1991. (A separate figure for Japan is available from the PMA Annual Survey Report only for 1991; it shows that the PMA member companies spent 16.4% of their overseas R&D in Japan and 1.2% in Australia and New Zealand).

Table 4.8 Trends in international distribution of R&D expenditures ofAmerican PMA member companies, selected years: percentage of all research performed abroad

Year	Canada	Latin America	Western Europe	Japan, Australia and N.Z.
1991	7.4	1.2	72.4	17.6
1989	10.4	1.6	67.7	19.2
1987	7.6	2.0	69.8	19.4
1986	7.5	2.1	71.1	17.6
1985	7.3	3.0	67.3	19.4
1983	7.0	4.1	71.8	14.1
1982	6.1	5.5	72.7	13.3

Source: Pharmaceutical Manufacturers Association, Annual Survey Reports, various years.

4.5.3 Trends in Product Innovation

The distribution of introductions of new chemical entities presented in Table 4.6 illustrated the decline in innovative productivity of the industry in the 1980. Table 4.9 reports introductions of new molecular entities both by time period and by major regions of the world. Western European firms have been leaders in innovation, followed by the U.S. Japanese firms increased their output of new entities from eight per year during 1961-80 to 13 during the 1980s. The research productivity of firms in Eastern Europe dropped sharply in the 1980s.

Table 4.9 New molecular entities marketed world-wide, by country of discovery, 1961-1990 (number and percentage of total)

Period	Total	U.S.	West Europe	Japan	East Europe	Other
1961-70	844	201	509	80	49	5
1971-80	665	152	375	75	58	5
1981-90	506	117	243	126	10	10
Total	2,015	470	1,127	281	117	20
Percent	100	23.3	55.9	13.9	5.8	1.0

Source: Ballance et al. (1992, p. 86).

Table 4.10 focuses on new molecular entities classified by the corporate nationality of firms which introduced them. In this context, the U.S.-owned laboratories, regardless of their location, account for about 40% of new molecular entities introduced in 1989, almost twice the share of Japanese-owned laboratories, but they have the second-largest number of self-originated drugs under development.

Table 4.10 Self-originated drugs under development by corporate nationality for the top hundred ranked firms in 1989

COUNTRY	Number of firms	Drugs under development	Percentage of total
United States	34	1,190	40.0
Japan	28	623	20.9
Germany	8	250	8.4
United Kingdom	7	185	6.2
France	6	183	6.1
Switzerland	3	168	5.6
Italy	4	88	3.0
Others	10	289	9.7

Source: Ballance et al. (1992), p. 87.

Simple counts of new molecular entities are not an adequate measure of research productivity in that some new products ("breakthroughs") are more significant than others. No precise evaluation of significance is possible; one approach is to account for the rate of adoption of the new product, on the assumption that the more important the innovation, the faster it will diffused. Table 4.11 defines a "consensus new molecular entity" as new drugs introduced in six of the world's eleven major markets during the relevant period. According to this measure, U.S.-owned firms developed 42% of all consensus products during the period 1970-83, while the Japanese-owned firms only developed 4%, possibly because they concentrated on imitative rather than innovative research. The Japanese share, however, began to rise during the 1980s (Ballance et al, 1992, pp. 85-88).

Table 4.11 Distribution of "Consensus New Molecular Entities" by nationality of originating firm, 1970-83

COUNTRY	Number	Percent
United States	71	41.7
Switzerland	22	12.9
Germany	17	10.0
United Kingdom	17	10.0
Sweden	12	7.1
Italy	8	4.7
Japan	7	4.1
France	4	2.4
Others	12	7.4
Total	170	100.0

Source: Ballance et al. (1992), p. 88.

4.5.4 New Trends in R&D

The head of R&D at Hoffmann-La Roche, Jürgen Drews, estimated that the global pharmaceutical industry in 1993 spent around $30 billion on R&D. He described this level of spending as excessive - if this amount was invested at 10%, it would yield about $70 billion in ten years. However, to generate the $70 billion in profits (assuming 25% profit margin), the worldwide pharmaceutical industry would have to achieve around $250-300 billion in sales, which is highly unlikely. Roche-Genentech has one of the largest research budgets in the industry and spends 24% of sales revenues on R&D (Roche itself spends around 20%, while Genetech spends 50%). Drews announced that the R&D/sales ratio for Roche-Genetech will be reduced to 17-18% over the next few years (Scrip, 5th Oct,1993:10).

The "excessive" levels of pharmaceutical R&D spending in the U.S. drug industry came under attack in a report prepared by the US Office of Technology Assessment (OTA), released in early 1993. It estimated that the average compounded cost of bringing a new drug to the market in the 1980s was about $194 million, in 1990 dollars. This includes the opportunity cost of capital imputed at 14% during the early stages of R&D and 10% at the final stages. The after-tax R&D cash outlay was about $65 million.

The average net revenues for new chemical entities introduced in the U.S. between 1981 and 1983 are estimated at about $230 million. Each new drug thus earns some $36 million in excess of the amount needed to attract R&D investment, i.e. about 4.3% of the drug's sales revenue. The OTA report attributes these excess profits to the market power of the drug companies. It results in average annual economic returns in the U.S. pharmaceutical industry about 2-3% higher than in other industries, over the period 1976-1987, after the differences in risk among industries are taken into account.

The marketing costs in the U.S. pharmaceutical industry represent about 22% of sales, or about $10 billion annually, compared with some $8 billion spent on R&D. The authors of the report argue that the nature of rivalry in the industry "can lead to wasteful and duplicative R&D efforts". Thus, if increased price competition in the industry drives down R&D spending, this "might not be a bad thing".

Representatives of the American Pharmaceutical Manufacturers Association (PMA) argue that the industry is very different in the 1990s. In particular, generic drugs reach the market more quickly, and the proposed Clinton health care reform measures might further intensify competition. Next, the PMA challenged the calculation of the 4.3% excess profit, arguing that it incorporates R&D tax credits at 46% corporate tax rate prevalent in the 1970s, while the rate introduced in 1986 is only 32%. Finally, the PMA disputed the OTA estimate of the costs of development of a new drug. According to its own calculation, the more correct after-tax figure is $231 million, and the fully capitalized cost of R&D before tax savings is around $359 million per new chemical entity (Scrip, 5th March,1993:18-19).

The global R&D spending by the pharmaceutical industry rose steadily, from $8 billion in 1980, to $22 billion in 1990, $24.2 billion in 1991 and $26.5 billion in 1992. Yet over the same period, the number of new chemical entitis marketed annually remained constant within the 35 to 45 range. As a result, the cost per new chemical entity rose from $82 million in 1980 to $136 million in 1985, $230 million in 1990, and an estimated $270 million in 1993.

Across the entire range of 200 therapeutic areas, research is being conducted on some 6,000 potential new drugs. Based on past experience, only about 700 of these will be marketed. Horst Meyer, Head of Bayer's Business Group Pharmaceuticals Worldwide, argues that it is economically futile to attempt to launch "me-too" products, especially if they are the fourth or subsequent compounds in a class. Evidence shows that doctors are unwilling to prescribe them, and various national health insurance schemes are unwilling to reimburse them, even if they are competitively priced, unless they provide some quantifiable therapeutical benefits.

In some areas in particular, there are already more than enough low-priced standard medicines, and chances of achieving a significant cost-effective breakthrough are remote. According to Meyer, these include hypertension, gastric ulcer, mycoses, coronary heart disease, asthma, and diabetes. By contrast, in a number of areas, there are either inadequate or no standard therapies. These include arrhythmias, osteoporosis, lipid metabolism, rheumatic disease, schizophrenia, hepatitis, cancer, AIDS, dementia, and multiple sclerosis.

In this environment, pharmaceutical companies have started reducing the range of research projects and have intensified the formation of strategic alliances with entrepreneurial, start-up high-technology and biotechnology companies, as well as with universities and research institutes. It is necessary for each company to establish a rigorous on-going project review system which includes hands-on researchers together with those responsible for clinical testing and marketing (Scrip Magazine, June 1993:14-16).

A ranking of international pharmaceutical companies shows that as of December 1993, Ciba-Geigy had the largest number of products in R&D (116), followed by Bristol-Myers Squibb (110), Merck & Co and Lilly (both with 104), the U.S. National Institute of Health (101), etc. This ranking is, however, only an imperfect measure of the research effort, since it is influenced by the way in which the company classifies the compounds initially evaluated for therapeutical activity. In addition, a substantial proportion (on average almost a third) of the compounds in R&D are licensed-in from other companies (Scrip Magazine, Jan,1994:45).

In addition to reducing the number of research directions pursued, R&D costs can be cut by reducing the number of patients used in clinical trials needed for submission to regulatory authorities. Former Director of R&D at SmithKline Beecham, Keith Mansford, believes that the 10-12 thousand patients in the database of some companies could be reduced to 3-4 thousand, provided the studies are well controlled with a common protocol. Worldwide regulatory harmonization would also contribute to reducing R&D costs (Scrip Magazine, March,1992:28).

The main type of pharmacological action investigated by pharmaceutical companies in 1993 was protein synthesis antagonism, with 83 compounds under development. A cardiovascular-related research on platelet aggregation antagonists registered 72 compounds another cardiovascular area, calcium channel antagonists, had 70 compounds under development. The fourth major area of research were antiinfectives.

The leading therapeutical research categories were anti-cancers, anti-inflammatories, anti-asthmatics, and anti-HIV agents. For example, there were 231 anti-AIDS drug under development worldwide, including 175 in preclinical research and over 40 in clinical trials (Scrip Magazine, January 1994, p. 47).

Some 15 years ago, the first pharmaceutical companies adopted the project team approach to R&D management; it is now the standard for most. It incorporates a "matrix management" relationship between line managers of particular servicing departments such as toxicology, pharmacokinetics, and formulation, and the multidisciplinary project teams. Bayer's experience, for example, shows that its adoption reduced the time needed to launch new products, accelerated the initiation of studies of new products in humans, and reduced the time needed to complete Phase II clinical studies.

A number of companies are decentralizing (globalizing) their R&D activities. For example, Boehringer Ingelheim reduced the share of its R&D spending in Germany from 73.3% of the total in 1978 to 52.6% in 1992. The share of other European countries increased slightly, from 13.4% to 13.9%, while spending in the Americas rose from 7.7% to 27.1% and in Southeast Asia from 5.6% to 6.3%. Such decentralization is seen to have a number of benefits, among them better access to technology and knowhow, easier affiliation with universities and easier recruitment of scientists, better ability to monitor technological development, easier technology transfer, faster development times, better access to the registration authorities, and proximity to the market.

Decentralization also makes it possible to take advantage of international variations in R&D personnel costs. Boehringer Ingelheim's data, adjusted for actual working time, absence from work and social costs, show the following R&D personnel costs "normalized per person-year": Europe - DM 124,000; North America -DM 90,000; and Japan - DM 92,000. The nominal cost of DM 106,000 in Japan is reduced by the willingness to work longer hours (19% more than in Germany), and a lower rate of absenteeism (7.5% in Japan compared with 18.5% in Germany).

Sandoz opened a new research institute in Tsukuba, Japan, in October 1993, "completing a worldwide triad of R&D bases with existing sites in Europe and the U.S.". The facility will employ 120 researchers and is the first to combine biological and physicochemical research within the same complex (Scrip, 5th Oct,1993:11).

Otsuka Pharmaceutical has adopted a "satellite" system of decentralization of its basic R&D. It operates 11 domestic and two overseas laboratories. The various disciplines are split between a number of sites, each of which is run independently to take advantage of local expertise and foster creativity. There exists a centre for gathering and exchange of information at the Tokushima research institute, which also organizes annual congresses for the presentation and discussion of corporate research findings. After the basic safety of new drugs is assessed and its administration routes and dosage forms are determined in Tokushima, subsequent clinical studies are performed either in Japan or through satellite facilities in Maryland, San Francisco, London, and Frankfurt (Scrip, 8th Oct,1993:15).

Widespread use of information technology (IT) is a necessary prerequisite for effective decentralization. For example, around 6% of the staff at Pfizer laboratories work in computing and IT support. The IT staff must be fully integrated in all aspects of R&D; training and services are provided by IT managers, project managers, project teams and user support groups across discovery, development, and clinical and regulatory functions (Scrip Magazine, June 1993:14-16).

Other companies, by contrast, find it is necessary to close laboratories located in other countries, because of recession, currency instability, and price cuts and delistings of products. For example, Elf Sanofi which operates seven research centres in four countries, announced the closing of its research facilities in Brussels and in Manchester by the end of 1994. Their activities are transferred to France, to reduce cost and the "fragmentation of the company's research base" (Scrip,14th Dec,1993:8).

After the merger of SmithKline and Beecham, the group's R&D operation was rationalized. It employs some 5,000 people, of which 60% are in development, 25% in discovery, and 15% in administration. The 13 locations existing prior to the merger have been reduced to seven. The company has established six core therapeutic areas, and some centres became specialized. However, serendipity is considered important, and individuals and teams are expected to spend only 80% of their time on highly-focused research, while 20% can be spent exploring the periphery (Scrip Magazine, March 1992:30).

In yet another type of restructuring of R&D operations, some pharmaceutical companies are dividing their R&D departments into two units. For example, Glaxo reorganized its UK-based research and its international development and commercial functions. Two new divisions were created: the Research Division and the Group Development and Product Strategy Division. This reorganization was described as a "formal recognition of the new realities of R&D, in which product strategy and marketing considerations are becoming a more integral part of the development process". Creation of the Research Division, in turn, is a response to the developments in cellular and molecular biology, which are dramatically changing the approach to drug discovery (Scrip, 1st Oct,1993:6).

Sandoz formed a stand-alone "research department", charged with the responsibility for finding new therapies and meeting the challenge of biotechnology, and a "development department", responsible for clinical research and project management. The separation is expected to decrease the time needed to bring new drugs to the market and strengthen the influence of marketing considerations in the drug development stage (Scrip,17th Dec,1993:7).

Grabowski (1990, pp. 171-174) presents data on the shifting patterns of international competitiveness in the drug industry, as measured by new product introductions. As shown in the first column of the following table, U.S.-owned firms were the source of more new drugs than any other country during the two decades between 1961 and 1980, France was second, Germany third, and Japan fourth. In the following decade, the U.S. was overtaken by Japan and the rankings of other countries also significantly changed, as is evident from the third column of the table.

These numbers do not, however, reflect the commercial and medical significance of the various new products. This type of information is incorporated in the measure of "consensus" new products, defined as those which are marketed in the majority of important world markets. This data, reported in the fourth column of the table, shows the U.S. again in the lead and Japan only in seventh place. This relatively low rank of Japan would suggest that its pharmaceutical industry produces imitative compounds rather than more fundamental advances. Grabowski (1990, p. 174) cautions, however, that the Japanese industry has been evolving rapidly from a generic-oriented and imitative type to innovative research. The results of this re-orientation, as measured by the number of "consensus" new products, will become evident over time.

Table 4.12 New Drug Introductions by Nationality of the Originating Firm

COUNTRY	% SHARE OF NEW DRUG INTRODUCTIONS AND COUNTRY RANK		% SHARE OF "CONSENSUS" NEW DRUGS AND COUNTRY RANK 1970-1985
	1961-1980	1981-1987	
United States	23.6 (1)	23.1 (2)	43.4 (1)
France	18.1 (2)	7.8 (5)	2.5 (8)
West Germany	13.4 (3)	10.5 (4)	8.7 (3)
Japan	10.3 (4)	27.9 (1)	4.1 (7)
Italy	7.9 (5)	9.0 (4)	4.6 (6)
Switzerland	7.3 (6)	7.2 (6)	13.8 (2)
United Kingdom	4.9 (7)	4.5 (7)	9.7 (3)
Sweden	N.A.	N.A.	5.1 (5)
Others	14.4	9.9	8.1
Total	99.9	99.9	100.0

Source: Grabowski (1990, pp. 172-173).

Notes:
1) Substances developed simultaneously in two countries are included in each country's total.
2) "Consensus" new drugs are defined as those approved for marketing in at least six of eleven major world markets over the period 1970-85.

In a 1992 study, the U.K. Centre for Medicines Research surveyed 49 leading pharmaceutical companies representing 70% of worldwide R&D spending in 1989. One finding was that Japanese companies had a lower attrition rate of synthesized compounds than the U.S. and European companies. Over the past 20 years, they succeeded in marketing one new chemical entity for every 2,276 compounds synthesized. The ratio for European companies was 4,317 to one, and for the U.S. companies 6,155 to one. Japanese companies allocated 84% of R&D spending to research into new chemical entities (pre-marketing development) as opposed to post-marketing development (such as new indications, new formulations, etc.). European companies allocated 76% and U.S. companies 74% to pre-marketing development. Japanese companies had the highest R&D cost per staff member, at $150,000, compared with $140,000 in the U.S. and $112,000 in Europe.

U.S. companies in the sample spent 72% of their R&D funds in the U.S., 22% in Europe and 7% in Japan. European companies spent 72% in Europe, 22% in the U.S. and 4% in Japan. Japanese companies spent 90% in Japan and less than 5% in Europe and the U.S. However, Japanese pharmaceutical investment in Europe showed a 100% increase between 1988 and 1990 (Scrip, 9th Sept,1992:11).

4.5.5 The Role of Government R&D Spending and Regulation

Private sector R&D has been rising systematically over the past two decades, as detailed in Table 4.1, for member companies of the American Pharmaceutical Manufacturers Association, and in Tables 4.2-4.4 for Canada. Government spending on biomedical research has also been growing and in almost all industrialized countries exceeds the private sector R&D spending. For example, the U.S. government spent $7.7 billion on biomedical research in 1988, which exceeds the private R&D spending by a wide margin (Ballance et al., 1993, p. 90).

The government regulation of the pharmaceutical industry and its impact on R&D has already been discussed in earlier chapters. A quantitative perspective on one aspect of the costs of government regulations is offered in Table 4.13, which gives a breakdown of the R&D costs of an average pharmaceutical company by type of research activity.

Table 4.13 Approximate breakdown of R&D costs of a typical new molecular entity (percentages)

Activities	Purpose	Percent
Synthesis and extraction from natural substances	Search for lead compounds	11-19
Biological screening		8-12
Animal pharmacology	Verification of basic effects; determination of specific pharmacological properties	8-12

Activities	Purpose	Percent
Toxicology and safety	Verification of basic effects; determination of specific pharmacological properties	9-10
Metabolism and pharmacokinetics		6-7
Analysis research		5-6
Clinical trials	Efficacy, safety	16-28
Chemical process	Standard quality	10-12
Pharmaceutical technology	Optimum dosage form	7-10
Documentation for regulatory authorities	Registration	3-4

Source: Ballance et al. (1992), p. 97, based on annual reports of various national pharmaceutical manufacturers associations.

Between 20 and 30% of the total R&D costs of a typical successfully marketed new molecular entity is applied to the search for new biologically active compounds. Tests for pharmacology, toxicology, and pharmacokinetics account for between 23 and 35% of the total. In the U.S., about 10 years typically elapse before a new drug is approved for marketing. The pre-clinical stage (screening of synthetic chemicals for potential use, pre-clinical studies in test tubes and animals, and filing of Investigational New Drug Application with the Food and Drug Administration) takes about 2 years. The clinical stage (clinical studies in healthy humans, in patients, large clinical studies, and filing of New Drug Application for review by the Food and Drug Administration) takes on average another 6 years, and the approval process adds 2 more years (Ballance et al., 1992, p. 93).

4.6 R&D IN BIOTECHNOLOGY

Biotechnology is narrowly defined as the "application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services". It employs genetic engineering techniques to transfer genes which exhibit a desirable feature between different living species or organisms (e.g. plants, animals, and micro-organisms). For industrial applications of biotechnology, a broader definition is more applicable. It includes, in addition, the use of tissue culture techniques to reproduce organisms in controlled settings and the use of micro-organisms to produce chemicals of commercial interest.

Until recently, biotechnology resulted largely in the development of more efficient procedures for conducting research into potentially useful products and processes. In the future, genetic engineering techniques are expected to yield new products (e.g. new pharmaceuticals or new forms of animals and plants) (Marks, 1993, p. 101).

Historically, biotechnology has been characterized by three stages of development. The first generation employed fermentation techniques to produce drinks, food and fuel; large-scale fermentation techniques were used around the time of the First World War to manufacture solvents. The second-generation technology emerged after the Second World War from the integration of microbiology, biochemistry, and chemical engineering. They were employed in large-scale fermentation for brewing, sewage treatment, and in the chemical and pharmaceutical industries. The third-generation technology grew out of advances genetic engineering developments resulting largely from medical research conducted in university laboratories that were, or are, sponsored by governments (Marks, 1993, pp. 102-104).

Genetic engineering has already had a significant impact on the pharmaceutical industry. Genetic engineering transfers genetic information from one living cell to another or from one species to another. Bacteria can be programmed to produce proteins which have potential applications in treating many conditions, including cancer, viral infections, heart attacks and anemia. Recombinant DNA (rDNA) or genetic engineering techniques have been used to produce human insulin, human growth hormone, alpha interferon, tissue plasminogen activator (tPA), and interleukin-2 (IL-2).

Another development of relevance to the pharmaceutical industry is the monoclonal antibody technology which allows firms to produce large quantities of specific antibodies used as diagnostics (Marks, 1993, p. 109). Monoclonal antibodies are created by the fusion of white blood cells with cancer or other cells that reproduce uncontrollably. They can be used to produce protein for use as therapeutic and diagnostic agents.

The biotechnology industry does not fall into the Standard Industrial Classification of industries; instead, biotechnology firms operate in many different industries and are linked by the use of a common technique or process technology. There are two types of firms: The "new biotechnology firms" (NBFs) pioneered R&D in new areas, market their own products, or provide technical and R&D services to other firms. The "large established firms" (LEFs) may be conducting their own research into biotechnology or contracting research services from the NBFs and public research institutes (Marks, 1993, p. 102). Due to the high cost of R&D, the NBFs are unlikely to compete with established pharmaceutical companies. Some of these companies (e.g. Bristol-Myers and Eli Lilly) have recently acquired NBFs. Following a different strategy, Eastman Kodak has acquired Stirling Drug and simultaneously helped establish a biotechnology institute at Cornell University (Marks, 1993, p. 112). Apart from large firms taking equity stakes in NBFs, other forms of collaboration include joint ventures and licensing.

The large companies (LEFs) have an advantage in their ability to finance large-scale biotechnology R&D, patenting and marketing. The smaller start-up firms (NBFs), however, have greater flexibility and faster response time in developing biotechnology products and/or research niches. In the U.S., many of the NBFs were established by university researchers, backed by venture capitalists. The best-known of these companies is Genentech, recently acquired by the European multinational Hoffmann-La Roche. During the period 1970-1980, some 600 biotechnology companies were established worldwide, almost all of them in the U.S. In Britain, 43 NBFs were established during the period 1976-86. According to a 1991 estimate of the European Commission, there were some 1,000 biotechnology firms active in the U.S., about 800 in Europe, and 300 in Japan (Marks, 1993, p. 114).

Since 1982, the European Commission has initiated a number of programs in support of biotechnology industries. The most recent such program is called BRIDGE (Biotechnology Research for Innovation, Growth and Development in Europe). At least 10% of funds are allocated to basic research and 5 to 7% for the training of researchers. So far, however, the European R&D spending has been much more fragmented than in the U.S. or Japan.

Many of the large pharmaceutical companies have also launched important programs in biotechnology. For example, ICI, Sandoz, and Ciba-Geigy were spending up to one-third of their research budgets on biotechnology in 1988. These ratios are characteristic of the pharmaceutical industry as a whole and the research spending by the private sector exceeds that of the governments. Most of the biotechnology companies launched since the 1970s have been making losses ever since (Marks, 1993, pp. 115-116).

Patent statistics show a high degree of international cooperation between biotechnology companies in countries of the European Union and those of Switzerland, the former East Germany, Austria and Canada. It usually takes the form of mixed inventor teams and some cooperation between companies and public institution. This suggests some role for government coordination and public policy intervention in facilitating collaborative research. A particular area of weakness in the countries of European Union is bio-informatics. The U.S. has the best developed biotechnology information infrastructure, including both databases and software and thus has the potential of controlling the sources and flow of information. Researchers from countries of the European Union, for example, rely on the U.S. for much of their information (Marks, 1993, pp. 119-123).

Biotechnology has enabled scientists to develop new biopharmaceuticals based on naturally occurring substances. These include tissue plasminogen activator, erythropoietin, and various growth factors. Their number will increase as traditional extraction processes are replaced by recombinant methods of production. According to one estimate, the worldwide 1992 sales of biotechnology-derived pharmaceutical products reached $20 billion and are expected to reach $60 billion by the year 2000.

Biopharmaceuticals are unlikely to replace chemically derived pharmaceuticals, but will be used mainly in niche therapeutic applications. Of particular significance are vaccines, where already almost 100% of sales are products using biotechnology. Another important niche is diagnostics through the use of tissue/cell specific agents such as monoclonal antibodies, enzymes, and nucleic acid probes. Some 60-70% of sales of diagnostic products are already based on biotechnology. By far the most important impact of biotechnology on the pharmaceutical industry is expected in the drug discovery process. Traditional random approaches, largely dependent on serendipity, will be increasingly replaced by rational drug design, made possible by the cloning of the appropriate drug receptors (Scrip Magazine, Dec/Jan 1993:14).

Lansing and Gabriella (1991) argue that while the U.S. still has technological leadership in both genetic engineering and monoclonal antibody research, Japan can be expected to gain ground. One reason is the existence of industry consortia in Japan which concentrate on basic R&D, making it possible for pharmaceutical companies to concentrate on applications and process technology development. Second, the Japanese government can be expected to contribute capital and facilitation skills. Third, as a result of developments in biotechnology, the basis of process technology in pharmaceuticals will change from chemical production of drugs to dependency on production by living organisms. According to Lansing and Gabriella, Japanese companies have an advantage in process technology improvements and will be able to compete on the basis of price.

The Chairman and CEO of Amgen, Gordon Binder, noted that 99% of biotechnology companies have yet to sell their first product, and almost all of them are completely dependent on outside financing for survival. Fear of government drug price controls, as a part of the U.S. health care reform has made it difficult for these companies to raise equity capital. The value of stock offerings completed by biotechnology companies in the U.S. during the first six months of 1993 was only $759 million compared with $3.3 billion for all of 1992 and $4.2 billion for 1991. In order to survive, biotechnology companies must either sell licenses or merge with large (cash rich) pharmaceutical companies (Scrip, 28th Sept,1993:15).

While mergers, research alliances and licensing arrangements are methods of financing for the biotechnology companies, they are also a potential source of new product ideas for the pharmaceutical companies. In some cases, biotechnology companies are prepared to swap the development and marketing rights to their research drugs for the right to market an established revenue-generating product. For example, Aetna Neuroscience swapped its cell-trafficking technology with Wyeth-Ayerst in return for marketing rights to an established drug for treatment of epilepsy. Similarly, Isis gave Ciba-Geigy the development and marketing rights to four research drugs in exchange for cash payments for R&D costs.

ImmuLogic developed an allergy vaccine, but realized that a successful marketing effort would be extremely costly, since it has to be directed at allergists and general practitioners. It therefore entered into an "asset-sharing deal" with Marion Merrell Dow in which the large-corporate partner obtained the marketing rights in exchange for 50% of the profits and $ 40 mill. in licensing and support payments. Biotechnology company Chiron has about 200 similar arrangements with universities. Immunex signed an alliance agreement with American Healthcare Systems, one of the largest U.S. hospital purchasing groups (Scrip Magazine, Dec/Jan 1993:21-22).

The U.S. biotechnology industry spent 81% of sales revenues on R&D in 1992, compared with 16% for the pharmaceutical industry. Chiron had the highest R&D/sales ratio (128%), followed by Genentech (71%), Immunex (60%), Genzyme (51%), Biogen (49%) and Amgen (17%). Stock market financing has become increasingly more difficult. In 1992-93, for example, the average number of public offerings per month was between four and five, while in the previous year there were eight public offerings on average per month. To compensate for the diminished access to stock markets, biotechnology companies have employed new financing mechanisms, including stock index reset rights, convertible securites, stock warrants, and asset and risk redeployment option with warrants.

In the year ending June 30, 1993, biotechnology companies completed 196 alliances worth $2.9 billion (i.e. 44% more than the year before). Some biotechnology companies are moving away from the traditional vertical integration characteristic of pharmaceutical companies. Instead, they are choosing "virtual integration" (or quasi-vertical integration), by divesting divisions and product groups and out-sourcing some functions. This provides more flexibility than they would have if they remained fully integrated, or if they were dependent on royalties and a strategic partner (Scrip, 28th Sept,1993:17).

4.7 A POLICY PERSPECTIVE

The partial review of the literature presented above makes clear that corporate decisions on the location of R&D activities usually consider a whole range of factors, including marketing, production, acquisition targets, etc. The literature review also demonstrates a wide variety of differences among countries, firms, industry sectors, and technologies and, above all, reveals that the understanding of these problems and processes is rather incomplete. As a consequence, **general** policy measures aiming at influencing the R&D location decisions of multinational corporations cannot be devised with sufficient precision.

Grandstrand et al. (1993, p. 426) conclude that a rationale for government intervention in the home country may exist when the interaction of foreign R&D with the host country's economy generates positive externalities. They tentatively describe this as a case for infant industry protection, or, more precisely, "infant innovation system" protection. And they endorse the broad consensus in the literature that the interaction between foreign R&D and the domestic economy can be beneficial only if "the national science and technology infrastructure and the whole national system of innovation have a sufficient degree of development and strength". Specific policies include building up the "capabilities to scan, acquire, absorb, refine and exploit foreign R&D and technology, to sustain frontier research capabilities in some areas ... to provide effective mechanisms for domestic technology transfer and to provide an environment conducive to technology-based innovation and entrepreneurship" (p. 427).

Similarly, the key policy recommendation of Porter's (1990) massive study of ten major trading nations is to encourage R&D efforts by business firms which are characterized as "by far the most important influence on innovation". The emphasis should be on stimulation of rivalry and sophistication in the domestic market. Other key characteristics of "innovative economies" include the following: preference for research universities, rather than government laboratories (this is a strength of the U.S. and a weakness of Japan; strong links between

research establishments and the universities; emphasis on commercially relevant technologies, rather than on defence research; preference for faster diffusion of innovation, rather than long-lived patent protection; and limited role for cooperative research (in Japan, research consortia are used primarily as a signalling device to indicate emerging technologies and to compensate for weakness of research in Japanese universities).

According to Porter (1990, p. 4), "... a decisive role for government policy in competitiveness is not confirmed by a broader study of experience ... significant government policy intervention has occurred in only a subset of industries, and it is far from universally successful, even in Japan and Korea".

4.8 DEFINITIONS OF (PHARMACEUTICAL) R&D EXPENDITURES

4.8.1 Statistics Canada definitions[4]

Research and development (R&D) is a systematic investigation carried out in the natural and engineering sciences by means of experiment or analysis to achieve a scientific or commercial advance.

Research is original investigation undertaken on a systematic basis to gain new knowledge.

Development is the application of research findings or other scientific knowledge for the creation of new or significantly improved products or processes. If successful, development will usually result in devices or processes which represent an improvement in the "state of the art" and are likely to be patentable.

Scientific research and experimental development (R&D) in natural sciences and engineering is creative work undertaken on a systematic basis in order to increase the stock of scientific and technical knowledge. The central characteristic of R&D is an appreciable element of novelty and of uncertainty. The work is normally performed by, or under the supervision of, persons with postgraduate degrees in the natural sciences and engineering.

Data on R&D in the business enterprise sector covers commercially oriented enterprises (privately or publically owned), industrial research institutes and trade associations. The reporting unit is generally the company or enterprise. In the case of a company with decentralized research units, the reporting unit may be the division, if the accounting system enables divisions to supply the required data. A company can only be assigned to one industry, although it may have establishments in several industries. The assignment is based on the activity from which the firm derived the greatest portion of its income.

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[4] Source: Statistics Canada, Industrial Research and Development, Catalogue No. 88-202, and Federal Scientific Activities, Catalogue No. 88-204.

4.8.2 The Canadian Income Tax Act definition[5]

The definition of "Scientific Research and Experimental Development" in Section 37, Regulation 2900 of the Income Tax Act explicitly excludes the following: (i) market research, sales promotion; (ii) quality control or routine analysis and testing of materials, devices or products; (iii) research in the social sciences or the humanities; (iv) prospecting, exploring or drilling for or producing minerals, petroleum or natural gas; (v) the commercial production of a new or improved material, device or product or the commercial use of a new or improved process; (vi) style changes, or routine data collection.

Certain expenditures for scientific research cannot be claimed for income tax purposes (e.g. land, buildings). All such expenditures attributable to R&D are, however, included in Statistics Canada R&D data.

4.8.3 Canadian Pharmaceutical R&D Data[6]

Companies with active Canadian patents pertaining to a medicine sold in Canada are required by the Patent Act to report R&D expenditures on medicines to the Patented Medicine Prices Review Board (PMPRB). They report only those expenditures that would have been eligible for an Investment Tax Credit in respect of scientific research and experimental development as allowed under the provisions of the Income Tax Act in effect as of December 1, 1987, plus an allowance for depreciation of new (post 1987) capital expenditures.

The PMPRB has its own unique definition of the Canadian pharmaceutical industry and its R&D data are not comparable with other domestic manufacturing sectors, or with data reported by Statistics Canada. The PMPRB does not include firms without active Canadian pharmaceutical patents in its definition of the "drug industry". The PMPRB, unlike Statistics Canada, includes extramural research (funds expended by one statistical unit for R&D performed by another unit) as part of the total R&D expenditures for this industry.

"Basic research" consists of scientific investigations for which no immediate practical applications are envisaged.

"Applied research" is directed towards some practical application and in most instances represents clinical trials.

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[5] Source: Statistics Canada, Industrial Research and Development, Catalogue No. 88-202.

[6] Source: Ross Duncan and Dave Blaker, R&D Expenditures in Canada and Other Countries, Consumer and Corporate Affairs Canada, 1992.

4.8.4 The PMA Definition[7]

R&D expenditures are the total cost incurred for all pharmaceutical research and development activity, including cost of salaries, other direct costs, service, routine supplies and supporting costs, plus a fair share of overhead (administration, depreciations, space charges, rent, etc.). Costs of drugs of medical research and development conducted on grant or contract for other companies are excluded. Conversely, total outlays for all research and development work contracted to others (manufacturers, independent research laboratories, academic institutions, etc.) are included. R&D figures presented in the PMA Annual Survey Reports include both human-use and veterinary-use pharmaceuticals. Veterinary-use pharmaceuticals comprise less than 3 percent of R&D.

Data supplied directly by corporate respondents account for about 90% of the reported aggregate industry totals. For non-respondents, the PMA makes estimates, based on publicly available data from the Securities and Exchange Commission, proprietary market research data, and historical trends.

Biotechnology companies without launched products are classified as PMA Research Affiliates, not full PMA members. R&D carried out by PMA Research Affiliates is captured to the extent that full PMA member companies fund biotechnology research through collaborative arrangements or ownership. Biotechnology R&D funded through other sources is not captured by the survey.

4.8.5 International Comparisons of Pharmaceutical R&D Expenditures[8]

The Patented Medicine Prices Review Board conducted, in 1992, a preliminary analysis of the level of R&D in countries listed in the regulations implementing the 1987 Patent Act Amendments (France, Germany, Italy, Sweden, Switzerland, the U.K. and the U.S.). It concluded that differences in definitions of R&D, methodology, and the definitions of the universe used between the various international data sources prohibit any statistically meaningful direct comparisons of figures to either Statistics Canada or Board data. Any comparisons should be restricted to examining the changes in each country's R&D over time, and comparisons of Canadian data with foreign data for any given year should be avoided.

In any comparison of international data, Statistics Canada definitions of R&D are more pertinent. They are based on the OECD "Frascati Manual", which serves as a basis for data collection for all OECD member countries. In contrast, the PMPRB data are based on the Revenue Canada definition of R&D expenses.

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[7] Source: PMA, Backgrounder: U.S. Pharmaceutical R&D and Sales, February 1994.

[8] Source: Ross Duncan and Dave Blaker, R&D Expenditures in Canada and Other Countries, Consumer and Corporate Affairs Canada, 1992.

4.8.6 OECD R&D Data and Definitions[9]

Most R&D data for OECD countries is derived from retrospective surveys of the units carrying out ("performing") R&D projects on the national territory (i.e. excluding payments to international organizations or other performers abroad). Typically the publication of such survey data lags 2-3 years behind the year in which the spending occurred. Information on government support for R&D is more up-to-date, since it can be derived from budgetary information. However, the specifications of the budgetary data vary from those of the retrospective surveys. In general, the methodology of data collection is guided by the OECD publication The Measurement of Scientific and Technical Activities: Proposed Standard Practice for Surveys of Research and Experimental Development - Frascati Manual 1980.

Data on R&D in the business enterprise sector covers private and public enterprises and institutes serving such enterprises. Most countries categorize multi-product enterprises according to the "primary" activity at the level of the enterprise, although some countries are able to break down the R&D data for multi-product enterprises according to the line of business. Pharmaceutical R&D spending by business enterprises is classified as "Drug industry", ISIC 3522.

Government appropriations for R&D usually cover central or federal governments only, and are classified by "socio-economic objectives", rather than by industries. Government spending on pharmaceutical R&D can thus conceivably be included under any one of several socio-economic objectives, among them "economic" (which includes "R&D programs financed for the purpose of the advancement of ... industry ..."), "health and environment", "non-oriented research" (i.e. programs directed at advancement of knowledge, rather than commercially-oriented R&D), and "general university funds".

Data for R&D expenditures in the U.S. as reported in the OECD statistics underestimate the true level for several reasons. First, in the Business Enterprise Sector, depreciation is reported instead of capital expenditures. Second, the government sector covers only federal government. Third, the Higher Education Sector R&D does not include the part of General University Funds which is devoted to R&D (although capital expenditure covers total General University Funds, i.e. both for R&D and for teaching). Fourth, R&D in private non-profit sector covers only current expenditures (not capital expenditures).

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[9] Source: OECD, Main Science and Technology Indicators, Semiannual.

4.9 SUMMARY

Research and development is central to the success of pharmaceutical firms. An understanding of that component is equally critical to governments and policy-makers as they attempt to unravel the business strategies of the major corporations. As this chapter has suggested, governments play an important role in providing an environment conducive to research. This may be through human resource development, investment incentives and the encouragement and fostering of collaborative linkages amongst firms, research institutions and universities.

At the same time, the present structure of R&D in the global industry is very much a product of the historical context in which the industry has emerged. This chapter, and indeed earlier chapters, have suggested that R&D can be stimulated given the appropriate mix and development of an integrated industrial strategy that is focused on the long term regardless of the short term political dimension. Such an approach has proved to be effective in other national contexts - in particular the commitment to long term strategy in Japan. For Canada then, the critical question is how can such a long term policy be developed and what will be the fundamental goals and objectives that it will be based upon? The growth of a conducive research and development environment will be central to any long term industrial strategy.

CHAPTER 5: SUMMARY

This report has come full circle. It began with a general overview of the industry and then focused on specific and current issues related to the regulatory environment and corporate strategy. The report then returned to the more general considerations that are essential to understanding the role of "R&D" as a driver of competitiveness in the industry.

As chapter four suggests, emphasis for a viable, competitive industry should be placed on mechanisms which support innovativeness. These, however, must be balanced with the interests of the consumer. The "consumer" is at one end of the pharmaceutical continuum but is likely to play a more important role in the future as governments (both federal and provincial), and physicians, absorb the pressures of cost containment in the health care system. There is a trickle-down effect which ultimately impacts upon the profitability of firms in the pharmaceutical industry. It is a direct response to the threat of profitability that brand-name manufacturers are pursuing the strategies outlined in this study.

The industry is undergoing considerable restructuring at present in a variety of different ways. This restructuring is a function of the following broad trends:

- increasing levels of harmonization of patent terms and regulatory controls
- potential erosion of profitability
- continual pressure from healthcare reforms
- increased globalization of the industry

Throughout this study we have identified many questions that should be addressed in subsequent studies of the industry. For example:

1) With harmonized patent protection spreading how can Canada take advantage of a more level playing field to attract pharmaceutical investment?

2) How are newly industrializing countries developing their domestic pharmaceutical industries?

3) Will growing markets in these countries be a "competitive threat" to the Canadian industry?

4) What strategies can Canadian-owned companies develop to increase their presence in developing markets?

5) What are the strategic directions companies operating in Canada are pursuing with regard to NAFTA?

6) What are the implications of US healthcare reforms for Canadian and foreign-owned companies operating in Canada?

7) How will Europe's price controls and cost containment policies affect investment in Canada?

8) What factors would contribute to European firms locating in the US as opposed to Canada?

9) How does "location" and agglomeration tendencies of firms at the regional and sub-regional levels influence the competitiveness of the industry in other markets? What can Canada learn from examining the spatial dimension of industrial activity?

10) How critical is a centralized location to conducting effective R&D?

11) To what extent are firms embracing notions of specialization as part of corporate strategy?

12) Are there specific niche markets in pharmaceuticals in which Canada could develop a critical mass?

13) How can industrial policy accommodate the complexity of inter-regional collaborative integration?

14) Are companies using collaborative ties as part of long term corporate strategies or are they seen as "quick fixes"? What are the implications?

15) Given the observed trend towards the distribution of pharmaceuticals and the OTC market what are the implications for employment in the industry?

16) To what extent will new manufacturing technologies confer a competitive advantage to firms in the industry?

17) To what extent will new manufacturing technologies be integrated into the broader business strategies of companies?

18) What will be the impact of brand-name manufacturers entering more competitively into generic drug production?

19) If consumers and gatekeepers are to have more say in the consumption patterns of drugs what will be the impact for brand-name and generic drug manufacturers?

20) What will it mean for the consumer if there is consolidation of the US generic drug industry?

21) If brand-name manufacturers begin to dominate the generic drug sector, what will be the effect on prices and what will be the response of governments?

22) What are the key determinants of foreign locational strategy for the major pharmaceutical firms?

23) Is there a global generic drug industry, or are there a series of national generic drug industries? What would be the implications of greater global consolidation of this sector?

24) To what extent, and how, do subsidiaries operating in Canada compete with other sites within their corporate organization? In other words, what is the level of internal competition within the global operations of the large multinationals?

It is hoped that this current report has provided a foundation for addressing these questions.

There is a need for further research which examines the interactions of the major stakeholders in the pharmaceutical industry (figure 1.1). It is difficult to fully understand the industry without an appreciation of how the players relate to one another, and how these relationships are changing in the new industrial environment of the 1990s.

Canada, like many other industrialized countries, represents an economic landscape upon which multinational companies attempt to maintain and enhance their global market presence. When we consider the question 'how competitive is the Canadian pharmaceutical industry' we first need to define just what is meant by competitiveness? This is essential given the dominance of the Canadian industry by foreign multinationals.

What is equally important is an understanding of the strategies these companies employ on a global scale to maintain their profitability. To a certain degree we can see patterns and processes from a review of the business literature, but it necessary to discuss these issues directly with the decision-makers of the major players at the corporate headquarter level.

- How can we hope to understand the industry if we do not fully understand the processes and factors involved in strategic decision-making?

- How can industrial policy-makers articulate a coherent industrial strategy without first understanding how a specific region or country is perceived by corporate decision-makers who are relatively unconstrained by national boundaries?

Finally, as the Mercks and the Glaxo's compete and collaborate with one another, and as smaller research intensive and technically specialized firms develop strategies to conduct business in a fiercely competitive global environment, it is important to remember the final consumer.

With healthcare costs being contained, and profit margins for firms decreasing along the value chain, what will the changing corporate strategies and the industrial policies of governments mean for the provision of pharmaceutical products to individuals?

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APPENDIX : COUNTRY PROFILES - based on Spivey et al (1992).

AUSTRALIA

DENMARK

FRANCE

GERMANY

ITALY

JAPAN

NETHERLANDS

SWEDEN

UNITED KINGDOM

UNITED STATES

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
AUSTRALIA	. Over 150 firms manufacture and/or supply Australian market	. Australian R&D currently $25 million per annum (mainly clinical testing).	. Most manufacturers are multinational subsidiaries that formulate and package imported supplies.	. Generic products have never had a large market share.	. Lengthy approval time of new product - 91 to 115 weeks.
	. Total cost for pharmaceuticals to Australia has been falling as a % of GNP. Now accounts for 8% of the total health expenditures.		. Less than 15% of pharmaceuticals are manufactured using ingredients produced locally.	. Pharmacists prevented by law from substituting unless with prescribing physician's permission.	. Variety of advertising and promotion regulations.
	. Skill transfer to Australia in engineering, quality control & analytical chemistry	. Little incentive for R&D but prices among the lowest in the world.	. Decline in the 1970's and 1980's in local manufacturing activity attributed to the Pharmaceutical Benefits Scheme (PBS).	. Branded products with generic equivalents must be priced within 20 cents of the generic product to remain listed on the PBS.	. Almost 90% of prescribed drugs have prices determined by the PBS.
	. 7000 employed directly in the industry (16% graduates)		. Substantial balance of payments deficit in medical and pharmaceutical products.	. Export markets are NZ, Hong Kong, UK, US and Japan.	. Prices set by the Pharmaceutical Benefits Pricing Authority (PBPA).
	. Proportion of health expenditures spent on pharmaceuticals has fallen from 22.5% (1960-61) to 7.8% (1984-85).				. Monopoly control over drug prices and listing of products.

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
DENMARK	. 29% of Danish market sales is by local manufacturers; 57% by foreign multinationals; 13% by the Danish Pharmaceutical Assoc. (DAK Laboratories). . 50 firms	. The 7 danish companies spend 13% of sales on R&D.	. Production mainly insulins, vitamins, antibiotics, psychotropics, diuretics and sulfonamides. . Danish firms small when compared to multinationals; but very specialized. . Companies in Denmark differ considerably in size. . 90% production is exported; 90% of imports come from Germany, U.K., Switzerland, France & Sweden.	. Pharmacists prevented from choosing substitutes unless with permission from prescribing physician. . Highly competitive market. . About 60% of all original products have a copy on the market. . Generic market approx. 50% in volume. . Free price setting.	. Industry has set up its own regulatory body, The Danish Board of Drug Advertising to ensure information given is objective & correct. . Price levels set by government . drug retail prices uniform across country. . Drug approval based on EC and Nordic Council regulations. . Patients are reimbursed with between 50-75% of expenditure on drugs.

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
FRANCE	. Approx. 350 drug companies	. Low profitability cited as preventing firms from making necessary R & D investments.	. Trend to reduce # of production workers through automation.	. Pharmacists cannot substitute.	. Price of reimbursable drugs strictly controlled - among the lowest in Europe.
	. Low levels of concentration.	. # of research employees doubled over the 1980's.	. Rise in # of employees in medical information R &D.		. French drug prices have not kept pace with inflation.
	. Top 12 companies account for only 30% of production.	. In 1986, gov't financed only 0.31% of pharm. R&D (cf 47% for aerospace & 36% for electronics).	. France is the 4th largest exporting country.		. Over the last 10-15 years, there has been a set annual price increase.
	. Only 11 companies employ over 1000 people.	. 11.9% of sales spent on R&D.	. Sizeable trading surplus of exports over imports.		. Drug reimbursement by the Securite Sociale.
	. Substantial foreign share of French market.	. Fewer new drug innovations than in the past.			
	. Foreign firms approx. 45% of sales.				

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
GERMANY	. 95% of production comes from the 480 member BPI (pharmaceutical industry assoc.).	. Approx. 15% of sales put into R&D.	. 78.6% of production is for human pharmaceuticals.	. Market share of generics has expanded considerably over the 1980's.	. Advertising of drugs strongly regulated.
	. Drug sales not expected to increase because of fixed pricing regulations.	. 35 managers conduct their own research.	. Top 10 companies account for 1/3 of all sales.	. On average, generics are 1/3 less expensive than original products.	. No gov't. restrictions on pricing for manufacturers.
			. Highest export rate in the world.	. Recent intro. of fixed prices for reimbursable drugs will effect competitive position of generic manufacturer.	. Reimbursements for drugs through social sickness fund.
				. Physician can allow pharmacist to select drug.	. Fixed prices intro. in 1989. Has had effect of lowering brand-name drug prices.

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
ITALY	. Approx. 310 drug firms.	. 10% of employees engaged in research.	. Increasing share of market for products on the following areas:	. Generics allowed on the market 10 yrs. from when the original product was registered.	. Can be a block on price of medicines for a de fined length of time - but this has contributed to shift in new products.
	. Almost 60% of market based on foreign control.	. Patent protection unheard of prior to 1978.	. - cardiovascular, dermatological, antibiotics, psycholeptics, antacids, antiulcerants & ophthalmics.	. Generic market almost non-existent.	. Reimbursement for drugs between 20% and 40%.
	. Increasing trend towards greater levels of concentration.		. Deficit in balance of trade of drugs.	. Prior to 1989, generics were not avail. under the NHS grogram (Nat'l Halth Service).	. Gov't. instituting computerized system for control of medical prescriptions.
	. Top 25 firms account for almost 50% of market.		. Exports to 175 countries & imports from 66.	. No incentive for generics to be prescribed as an alternative.	
	. 65,000 employed in industry.				
	. Consumption has shifted towards new (but not necessarily innovative) products.				

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
JAPAN	. 2nd largest drug-maker in the world. . Stimulated by promotion of high-tech. industries in general. . Largest consumer of drugs per capita in the world.	. Rapidly developing R&D expertise but require substantial growth of basic research. . Joint research activities between U.S. and Japan in cancer research.	. Main products: antibiotics, cardiovascular, agents affecting CNS. . Exports 2.9% of total pharmaceutical output. . 27% of exports to U.S. . Other major exporting to Germany, Italy, Taiwan & France. . Imports 1½ times greater than exports. . 32% of imports from the U.S., followed by Germany, Switzerland, UK and France.		. Pharmaceuticals regulated mainly from the Pharmaceutical Affairs Law.

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
NETHERLANDS	. Approx. 100 drug firms - mostly subsidiaries of multinationals..	. Little R & D	. Major areas of production area.	. Growing # of generic firms (concern of innovative firms).	. Advertising for prescription-only and pharmacy-only drugs to general public.
	. Employs 12,600 people	. Concentrated in the 3 innovative firms:	sex hormones, antibiotics and raw products for fermentation industry.	. Approx. ⅛ of products on market are generic.	. GVS reimbursement system.
	. Industry belongs to the top 10 drug manufacturers in the global industry.	Organon (subsid of AKZO); Duphar (subsid. of Slavay) & Gist-Brocades.	. Major growth areas in sales: anticancer, respiratory, gyn/urological & gastro.	. Growing political pressure to control costs.	. Have tried negative lists, co-payment, generic substitutions, reduced pharm. fees-None effective!
	. Drug prices among highest in Western Europe.	. Organon expanding into psychotropic drugs, cardiovascular & immunomodulators.	. About 90% of drugs on Dutch market imported.	. Lack of competition.	. Stakeholders (excl. Ministry of Health) have initiated cost-cutting measures themselves.
	. Drug utilization lower than in most other countries (reluctance of patients to use drugs).	. Duphar focusing on gastro & neurological diseases.	. Export of drugs produced in Netherlands directed to EC countries.	. Absence of incentives for generic substitution (although endorsed by gov't)	. Drug approval regulations amont strictest in Western Europe.
		. Gist-Brocades moving into biotechnology.		. All major wholesalers have generic production divisions.	. Drug approval regulations amont strictest in Western Europe.
					. General failure to control drug costs.

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
SWEDEN	. employs over 18,000	. High level of research medicine chemistry in Sweden.	. 80% of production sold out of Sweden.	. Only a few firms in Sweden are strictly generic.	. Effective period of patent protection has been reduced as approval times have become longer.
	. 2 major Swedish firms: Kabi Pharmacia & Astra.	. Long history of cooperation between universities and industry.		. Generic market small but growing.	. Price control agency and company agree on reasonable price for drug products.
	. Strong global focus of firms.	. Both Kabi & Astra have strong research programs in Sweden.		. Generics have approx. 10-15% of the market.	. Some cost-containment through local formularies.
	. Drug costs as % of total health care costs fell between 1970 & 1985.				
	. Together with autos, the most prosperous industry in Sweden.				

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
UNITED KINGDOM	. In 1987, 3rd largest drug-exporting country.	. In 1987-88, of the top 20 selling drugs worldwide - 5 discovered in the UK.	. Large proportion of very small firms are generic, OTC manufacturers, and foreign subsids.	. 80% of generic market supplied from 30 firms.	. Pharmaceutical Price Regulation Scheme (PPRS) for top companies - 1st version intro. in 1957.
	. 2nd largest contributor to balance of payments from manufactured goods in the UK.	. 18% of workforce in R & D.	. UK has 12% world trade in pharmaceuticals.	. Generic substitution is the norm in hospitals.	. Limit on promotional spending.
	. Employs about 87,000 people.	. Similar $$ spent as in aerospace industry.	. 40% of production is exported (mainly to Europe).	. 80% of NHS demand met by generic firms with remaining 20% by brand-name manufacturers.	. Price controls at pharmacist level through reimbursement scheme.
	. U.K's fastest growing manufacturing sector betwen 1977-87.	. Major therapeutic classes for research: cardiovascular, anti-infectives & CNS.	. Imports are 16% of home market.		. In 1988, all NHS hospitals instructed to introduce formularies.
	. Market-share evenly split between UK, US and European firms.				
	. Approx. 300 firms in industry.				
	. Five firms account for ½ of output.				

	INDUSTRY CHARACTERISTICS	RESEARCH & DEVELOPMENT	MANUFACTURING	COMPETITION	REGULATION
UNITED STATES	. Over 600 companies involved in manufacture & sales of drugs.	. $4.7 billion spent by PMA members on R & D in 1986.	. Concentrated in 9 states: New Jersey, N.Y., Penn., Indiana, Illinois, Michigan, Missouri, Ohio, California.	. Brand name manufacturers highly critical of generic industry expansion.	. Strict controls on advertising & promotion.
	. Over 150 conduct R&D.	. Less than 1% of research financed through US gov't.	. Largest importer & exporter of drug products.		. No uniform price regulations - but many payers introducing programs to limit or control costs.
	. Largest pharmaceutical industry in the world.	. in 1986, 72% of R & D focused on cardiovascular, infections, neoplasms and CNS.	. Japan receives 20% of US exports.		. Lengthy and highly regulated approval process (much longer than most foreign markets).
	. 1771 new drugs introduced to US market between 1961-1987. (only 24% from US firms).	. 18% of company R&D is conducted abroad.	. Recent trend toward distribution through wholesalers and decreased manufacturer direct sales.		. Most states have generic substitution laws (without permission from physician required).