Bio-Pharmaceuticals – A Pathway to Economic Growth?

Part I: Background and theory

Report to the Researched Medicines Industry

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Preface

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- by the interaction of team members on individual projects;
- by exposure of the team's work to the critical review of a broader range of Institute staff members at internal seminars;
- by providing for peer review at various stages through a project by a senior staff member otherwise disinterested in the project;
- and sometimes by external peer reviewers at the request of a client, although this usually entails additional cost.

Authorship

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1. INTRODUCTION

This is part one of a three part project that investigates possible knowledge based economy partners of a growing bio-pharmaceutical industry and the role pharmaceutical companies could play in its development.

The aim of part 1 is to:

- show the types of direct and indirect benefits generated by pharmaceutical companies investing in R&D in any particular country.
- describe, in general terms, the pharmaceutical industry using an approach which loosely follows the Structure, Conduct, and Performance (SCP) framework. The SCP approach acts as a "check list" so that we can describe how different economic factors impact on the pharmaceuticals industry (see Appendix A for an explanation of the SCP approach).
- demonstrate how knowledge based industries, such as the pharmaceuticals industry, can provide linkages to knowledge based economic growth.
- examine how other countries have removed impediments to pharmaceutical industries, demonstrating how pharmaceutical company R&D activities "spillover" into other research activities. These "spillover" effects have the potential to positively reinforce R&D activity and boost economic growth in other sectors.

Parts 2 and 3 examine the requirements for more investment by pharmaceutical companies in R&D in New Zealand and the components of those requirements. Part 3 briefly examines the clinical trials and fundamental research capabilities in New Zealand, the Factor f scheme in Australia, and the Canadian pharmaceutical industry regulatory regime.

1.1 Knowledge Vs commodities?

A lot has been said about how New Zealand might lessen its reliance on exported commodity products and transform its economy so that it depends more on knowledge based activities.

The problem for New Zealand, is that the sector in which its exports are concentrated is shrinking as a share of world trade while other areas are growing. Note, in Table 1, the decline of agriculture and of food within the merchandise sector.

Unfortunately, there is no magic formula that countries can follow to grow and prosper – a lot of features need to be brought together, right across the spectrum of economic activity. At the macro level, real income per capita growth requires an economic environment that fosters innovation. At a micro level, growth depends on entrepreneurial activity.

Wealth creation, within sustainable limits, is of benefit to New Zealanders and New Zealand. Commodity exports, foreign investment in New Zealand in productive activity, partnerships between foreign and domestic firms, production for domestic markets only, and efforts to foster "knowledge based" businesses – all are important if they generate wealth and activity. We see knowledge based growth as an adjunct to, not a substitute for, earnings from commodities.

Table 1 : Composition of World Trade, 1965-90

GATT breakdown (% shares of total world trade)	1970	1980	1990	1997
Merchandise				
Agriculture	16.5	12.5	10.0	9.0
Mining	12.0	22.0	11.5	9.0
Manufactures	50.0	45.5	57.0	61.0
Commercial Services	19.0	17.0	19.0	20.0
Capital Goods	29.5	26.5	37.0	Na
Other	2.5	3.0	2.5	1.0

World Bank breakdown (shares of total world merchandise imports	1965	1979	1985	1990
Food	18	12	10	9
Fuels	10	20	19	11
Other primary commodities	17	9	8	8
Manufactures	55	58	62	73
Machinery, transport	23	25	29	34

Source: Grant RJ, Papadakis MC and Richardson DJ (1993), WTO.

1.2 Why the interest in knowledge based industries?

Despite the upheavals in the 1980s and 1990s New Zealand's GDP growth rate has remained substantially lower than other OECD nations (see Figure 1).

Despite calls for New Zealand to reduce its dependence on traditional commodity exports, our reliance on commodities will remain for the foreseeable future.

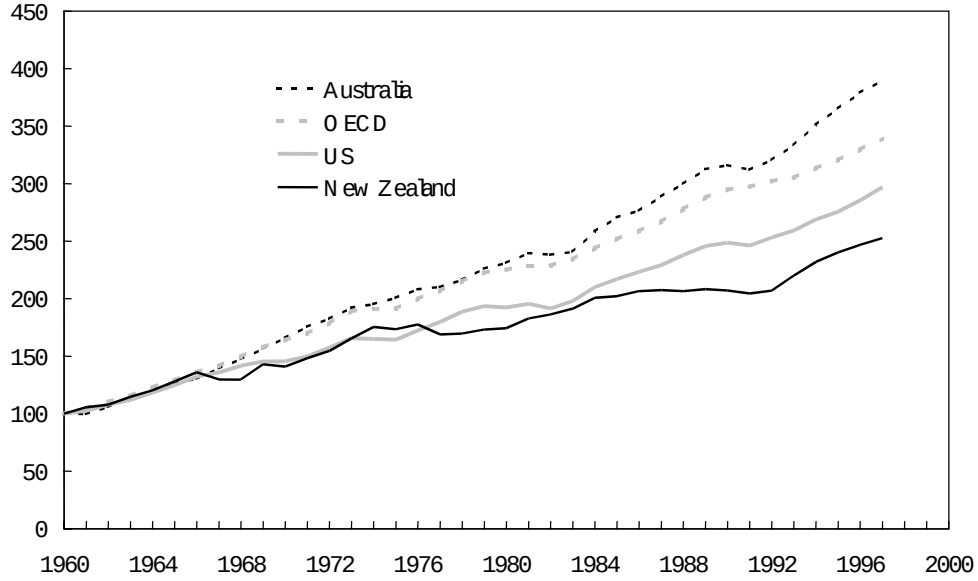
The attractions of knowledge based industries are:

- the potential to make more productive use of our generally well-educated workforce (with accordingly higher rates of pay); and
- their strong export potential (knowledge based goods typically facing low barriers in the consuming countries).

As shown in Table 2, the growth in world manufacturing exports is largest in high technology products. The OECD estimate that for 1994, 30% of all high technology products from member states were exported, compared with 12% and 10% for medium and low technology categories respectively. [1]

[1] OECD (1997)

Figure 1: Real GDP by country
1990 prices and 1990 exchange rates
Index, base 1960 =100



Source:OECD and NZIER

1.3 An opportunity for knowledge based growth on existing bio-pharmaceutical activity?

The motivation for this project is the possibility that New Zealand might build on existing bio-pharmaceutical businesses and related activities in public sector research organisations to develop a stronger pharmaceutical research sector.

- New Zealand has a comparative (or natural) advantage in growing grass (which is converted into meat, wool, and dairy products). Agricultural products provide a cheap source of raw materials for a bio-pharmaceutical industry.
- New Zealand has already built up a strong infrastructure of (mainly public) scientific institutions (universities, hospitals, and CRIs) that should have the capability, in partnership with the private sector, to expand the bio-pharmaceutical sector. There is also a strong relationship between pharmaceutical companies and the pharmacy and medical schools for phase II, III, and IV clinical trials.[2]
- the human and physical capital already developed in New Zealand is comparable with that of other developed nations, i.e. New Zealand has good education facilities and a well educated population, reliable communications systems, and a well developed transport infrastructure.
- some bio-pharmaceutical sector activities do not require large scale investment.

[2] The development, international standing, and financial viability of research units at these schools depends on access to pharmaceutical industry funded research. Without funding from pharmaceutical companies most researchers would rely on government (agencies such as FRST) for funding, or pursue work options over overseas.

Table 2: World manufacturing exports 1985-1993

Av. Ann. Growth (%)

Industry	Growth
High technology products	14.3
Medium – High technology products	9.9
Medium – Low technology products	8.0
Low technology products	9.4
Total Manufacturing	9.9

Source:Sheehan *et al* (1995) p5

2. PHARMACEUTICAL INDUSTRY FEATURES

2.1 Size, growth, market shares and major players

The pharmaceutical industry is one of the world's largest manufacturing industries and is now dominated by multinational firms. It is highly research intensive, is highly profitable, and has recorded above-average growth over recent years.

Pharmaceuticals have had a major impact on the quality of health care.[3] It has been estimated that for every extra $1 spent on pharmaceuticals in the US, $3.65 was on average saved in the costs of hospitalisation. Also, newer drugs have had a significant life enhancing and life extending impact.

The total world market for pharmaceuticals, including over-the-counter (OTC) and prescription products, was about US$300 billion in 1998.[4] Prescription products, which account for nearly 85% of sales, grew by nearly 10% per annum in the 1990s, although growth rates have been volatile.

The biggest pharmaceutical markets are North America, Japan, and the EU, (see Table 3) while the highest growth rates have been in the Americas and Europe.

Table 3: Market shares

Country/Region	Market Share
North America	33
Western Europe	27
Japan	17
Latin America/Caribbean	8
South East Asia and China	5
Middle East	2
Africa	2
Indian Sub-Continent	2
Eastern Europe	2
CIS	1
Australasia	1

Source: Scrip Yearbook 1998 p120

In New Zealand, the pharmaceutical industry obviously plays a critical role in the supply of medicines for the New Zealand population. While manufacturing and R&D has been significant in the past in New Zealand, relative to other knowledge based industries (see Appendix B), it now only plays a small role in the development of the economy.

[3] Lichtenberg (1998) in Scherer (2000)

[4] Scrip (1998), p29

2.2 Supply features

2.2.1 R&D investment and the importance of patents

R&D investment by pharmaceutical companies is very high;

> *"…expressed as discounted present value at the time of product launch, [then] R&D accounts for roughly 31% of total cost".*[5]

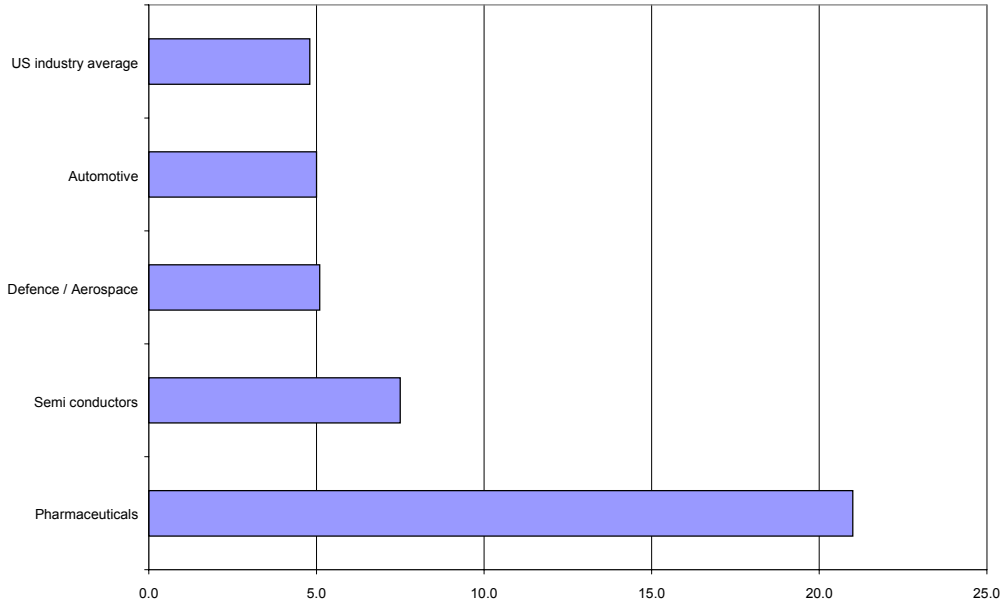
This is very high relative to other industries.

R&D programmes underpin the profitability of pharmaceutical companies.[6] Typically, for a large pharmaceutical company, sales revenues are dominated by their top three products.[7]

Figure 2 shows R&D costs – as proportions of sales revenues – without the present value effect.

Figure 2: R&D as a proportion of sales across selected US industries

Figures for 1994



Source: The Boston Consulting Group 1996, p22

The US pharmaceutical industry investment in R&D is twice as much in absolute terms as any other US industry.[8]

[5] Danzon (1997)

[6] Banks (1998), Balance et al (1992), and Bogner & Thomas (1996)

[7] Kane (1997)

[8] PhRMA (1996)

R&D is concentrated in the US, Sweden, UK, Germany, Switzerland, and Japan – this investment accounting for over 90% of all new products with innovative ingredients produced since 1960.

Because of this high R&D intensity, the pharmaceutical industry relies heavily on the protection of intellectual property provided by patents.[9] Patents are granted nationally but have international protection under the TRIPs Agreement of the Uruguay Round. Over the life of the patent, a pharmaceutical company has a state-sanctioned right to stop others from selling identical formulations. At the end of the patent life, the price commanded by the drug will drop markedly as it is exposed to additional competition. The role and importance of patents is looked at in more detail in section 3.24 and part 2.

It is expected, however, that pharmaceuticals product life span will become shorter over the next 5 to 25 years and new products supersede older less effective products. A patent may only be useful for 10 years, therefore an effective patent life (EPL) beyond 10 – 15 years will be irrelevant in respect to the return on investment for product specific companies.

2.2.2 Health and safety

Governments have a role in ensuring the safety, efficacy, and quality of pharmaceuticals. As the pharmaceutical industry has developed, governments have developed an extensive regulatory regime. In recognition of the costs of delay, governments, particularly in developed nations, have taken steps to improve the efficiency of regulatory processes so as not to hold back unduly the flow of pharmaceuticals on to the market.

2.3 Demand features

An individual's demand for pharmaceuticals is unpredictable and generally intermittent but often intensive when the need does arise. Because of the high costs of more sophisticated and innovative drugs, healthcare costs pose a significant risk for individuals. As is common in such circumstances, payment is often provided for by some sort of insurance mechanism. The mechanism might be actual private health insurance, or a socialised equivalent in the form of a public health system where premiums are paid through taxes, and health care is subsidised or publicly provided to some degree (instead of repaying expenses incurred privately).

Doctors have multiple and possibly conflicting roles. They are the agents of the patients (and accountable for their choice of treatment in this regard) but also control access to prescription pharmaceuticals and are influenced by the fact that patients do not generally have to pay the full costs of treatment (because of the insurance mechanisms).

Because appropriate levels of treatment are a subjective matter, the provider of the insurance needs to contain costs – but in a way consistent with honouring the insurance contract. Methods include pharmaceutical price controls, patient cost-sharing, generic substitution of generics for branded drugs, and attempts to modify the prescribing behaviour of physicians.[10] These approaches apply to both public and private health providers.

Governments are sole ("monopsony") buyers of pharmaceuticals for publicly funded medicines and use the power of this position to drive down the prices of even patented drugs and to confine "insurance cover" (the availability of the subsidy) to particular

[9] Howells & Neary (1995)

[10] Kane & Saltman (1997)

pharmaceuticals for each therapeutic purpose. The government Pharmaceutical Management Agency (PHARMAC) performs this role in New Zealand. Obviously there is a relationship between the sustainable tax paid "premiums" and the extent and quality of treatment provided. This is a controversial area since it involves judgements about the relative effectiveness of medicines – comparing newer innovative drugs with older technology drugs.[11]

[11] Emilien (1997) p82

3. PHARMACEUTICAL INDUSTRY TRENDS

3.1 Influences

3.1.1 Stronger competition from generics

In the 1970s, numerous pharmaceutical products were developed. The wave of new materials dried up somewhat in the early 1980s. As these products have come off patent, pharmaceutical company revenues have declined as generic drug companies (who do very little research) compete away profits. The response of the industry has been to try and improve their research performance, since this is the main competitive driver.[12]

3.1.2 The rise of biotechnology in the discovery process

There has been a major change in the industry in the way research is done, from traditional screening processes to biotechnology. The use of biotechnology, in particular genomics[13] and protenomics[14], has increased the number of candidate targets.

Combine this with the increasing costs of research and stagnant R&D productivity structural change is inevitable. Therefore, pharmaceutical companies are actively searching for new ways to reduce costs and increase productivity. An interesting feature of this shift is that the lowest development costs appear to be achieved by smaller specialist biotechnology companies, not by large multi-purpose laboratories run by the major pharmaceutical companies. Some believe that future R&D will be:

> *"... done by scores of small biotechnology companies that are either acquired or develop licensing agreements with the marketing giants"* [15]

How new research methods and new technologies change the pharmaceutical industry structure over the long-term is unclear.

3.1.3 Tightening safety standards

The trend internationally has been for governments to intervene more in the pharmaceutical industry. This includes developing purchasing environments that restrict the way pharmaceuticals companies can market products.[16] Government efforts to contain costs are made more difficult by the increase in consumer demand as the "baby boomers" age, overall production costs increase, and a broader range of drugs is introduced for a wider range of aliments.

Tightening safety standards have increased the time taken from initial development to market sales. For example, it is generally thought, within the industry, that a drug like penicillin would never pass current regulatory standards because of the risks it poses to some parts of the population. Figure 3 shows that time taken for medicines to reach the market has doubled since the 1960s.

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[12] Industries Commission (1996), Balance et al (1992)

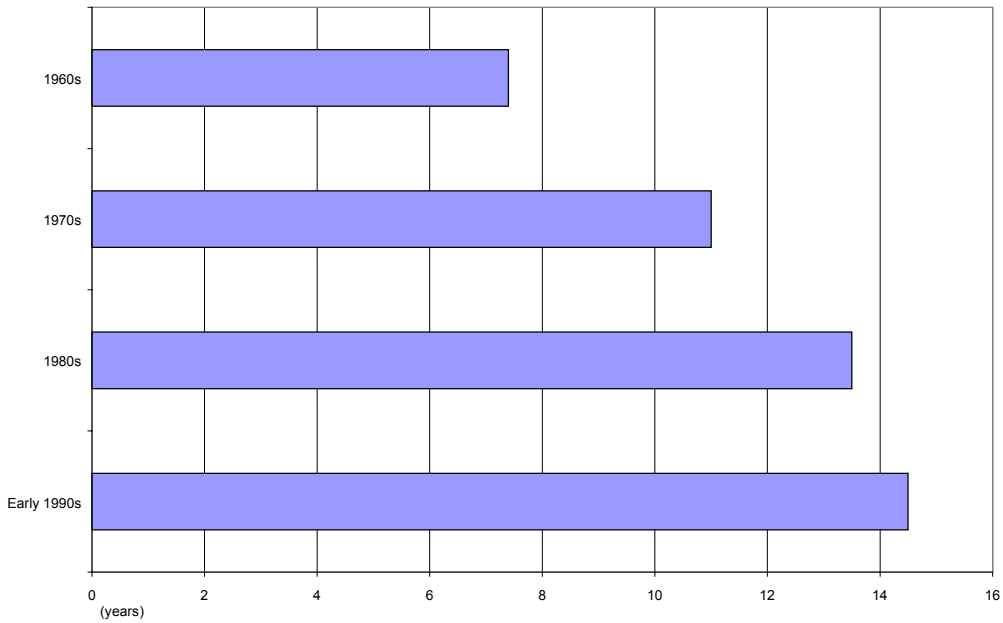
[13] Genomics refers to several technologies focused on characterising the genetic basis of diseases and using that information to identify promising drug targets.

[14] Protenomics is one of the genomic technologies that examines proteins produced by cells. It involves the identification of proteins in the body to determine their role. It is believed that through proteomics new disease markers and drug targets can be identified that will help design products to prevent, diagnose,and treat disease.

[15] Kane (1997) p79

[16] Vandergrift & Kanavos (1997) p256

Figure 3 The product pipeline: time from synthesis to market approval



Source: The Boston Consulting Group (1996) p39

3.2 Consequences

3.2.1 Mergers

The pharmaceutical industry has been undergoing a major restructuring process in response to the pressures outlined above. Mergers and partnerships are expected to:[17]

- reduce the disruption to earnings as pharmaceuticals come off-patent by joining with companies that have different products at different stages of development.
- produce scale advantages by
  - improving sales force productivity
  - minimising the unit costs of overheads, and
  - spreading R&D costs and risks, particularly when assets are complementary.
- speed up the closure of unproductive plants.

As mergers and acquisitions have occurred, the size and ranking of the major pharmaceutical companies has changed frequently.

Table 4 shows the top ten pharmaceutical companies (in terms of sales) between 1994 and 2000. Table 5 lists some of the major mergers.

[17] The Economist (1998) and Watanabe (1995)

Table 4 : Largest pharmaceutical companies

Various years

	1994	1996	2000
1	Glaxo Wellcome	Merck	Pfizer
2	Merck	Glaxo Wellcome	GlaxoSmithKline
3	Hoechst Marion Roussel	Novartis	Merck
4	American Home Products	Bristol-Myers Squibb	AstraZeneca
5	Bristol-Meyers Squibb	Hoechst Marion Roussel	Bristol-Myers Squibb
6	Roche	Pfizer	Novartis
7	Pfizer	American Home Products	Johnson & Johnson
8	SmithKline Beecham	Johnson & Johnson	Aventis
9	Pharmacia & Upjohn	SmithKline Beecham	American Home Products
10	Takeda	Roche	Pharmacia

Notes: (1) Based on world wide sales

Source:Wilson & Matthews (1997), APMA (1998), & InPharm.com (2000)

Table 5: Selected major mergers and acquisitions in the pharmaceutical industry

1989-2000

Beecham (UK) – SmithKline Beecham (US) (takeover)	1989
Bristol-Myers and Squibb (merger)	1989
Rhone-Poulenc (France) – Rorer (US) (takeover)	1990
Hoffmann La Roche (Switzerland) – Genentech (US) (takeover)	1990
Hoechst (Germany) – Copley (US) (takeover)	1993
Merck (US) – Medco (US) (takeover)	1993
Synergen (US) and Amgen (US) merged	1993
Hoffman La Roche (Switzerland) – Syntex (US) (takeover)	1994
Bayer (Germany) – Sterling Drug (US) (takeover)	1994
American Home Products (US) – American Cyanamid (US) (merger)	1994
Hoechst-Roussel (Germany) – Marion Merrell Dow (US) (takeover)	1995
Pharmacia (Sweden) – Upjohn (US) (takeover)	1995
Ciba-Geigy and Sandoz formed Novartis (merger)	1996
Glaxo – Burroughs Wellcome (takeover)	1996
Hoffman LaRoche (Switzerland) – Boehringer Mannheim (Germany) (takeover)	1997
Astra AB (Sweden) – Zeneca (UK) formed AstraZeneca (merger)	1999
Rhone Poulenc (France) – Hoechst AG (Germany) formed Aventis (merger)	1999
Glaxo Wellcome – Smith KlineBeechan formed GlaxoSmithKline (merger)	2000
Pfizer – Warner-Lambert (takeover)	2000

Source:Scherer (2000), Matraves (1999), and various websites.

While some commentators suggest that pharmaceutical industry restructuring will involve a reduction in overall R&D spending,[18] others believe that to achieve high rates of profit pharmaceutical companies will have to carve out niches that others can not duplicate. Doing that requires innovative products underpinned by a strong R&D sector.

3.2.2 Contracting for specialist inputs

Small specialist biotechnology companies appear to have become a cost effective source of new pharmaceutical candidates and technologies. Accordingly, there has been a trend over the past decade for the major pharmaceutical companies to form contractual relationships with these smaller firms.

The smaller firms have contributed to faster innovation thus enabling partner pharmaceutical companies to maintain a better flow of new drugs into their marketing businesses. This is a remarkable development. Given the importance of intellectual property (IP) protection in the sector, one would normally expect pharmaceutical businesses to remain vertically integrated. Clearly the cost effectiveness of the smaller firms and the strength of the patent (controlled by the pharmaceutical companies) more than compensates for any IP problems. Despite this, four fifths of pharmaceutical research activity is still carried out "in-house" by pharmaceutical companies.

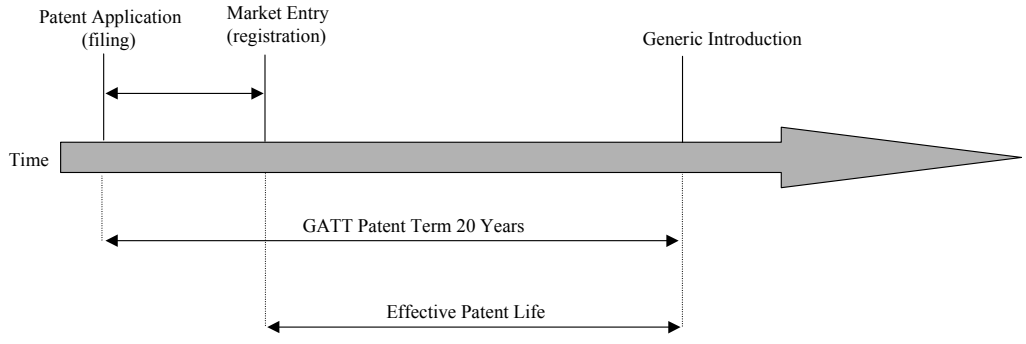
The shift in R&D sourcing is particularly important to small countries such as New Zealand since scale has become less important so long as the inherent risks of R&D are managed by contract with a larger sponsor or sponsors.

The strategy of large pharmaceutical companies has been to maintain their position by supporting "fast cycle" start-up companies that succeed or fail on specific new technology. This has been a successful strategy over the past twenty years since very few companies have moved from being a start-up to the status of a large pharmaceutical company.

3.2.3 Patent extensions

As a result of tightening safety standards, the time taken between the filing for a patent and market entry has increased. Thus the effective life of patents has been reduced and the incentive for developing new products weakened accordingly (see Figure 4).

Figure 4 : Effective Patent Life



Source:Hanson (1997) p20

Many governments have responded. Australia, the United States, Japan and the European Union have all amended their patent protection laws, with most establishing a minimum EPL of 15 years subject to a maximum extension of five years beyond the 20

[18] Friedhoff, quoted in Watanabe (1995)

year basic term. EPL is the time from when the patented medicine has received approval to market until the expiry of the patent term.

Patent extension has also been one way governments have sought to encourage pharmaceutical companies to:

- conduct research domestically by creating an environment where they can invest with confidence, i.e., there is transparent trading environment and assets invested to support that trade are secure, and
- it sends a signal showing that pharmaceutical companies are welcome and an important part of the countries economic activity.

4. THE NZ PHARMACEUTICAL INDUSTRY

New Zealand represents only 0.2% of global pharmaceutical sales. Nevertheless, the volume of sales is large enough for most major pharmaceutical companies to have maintained a marketing presence here. New Zealand consumption of pharmaceuticals is growing at 2% per annum, driven by an ageing population and free health care to children under six, amongst other things.[19]

85% of the pharmaceutical business is in prescription pharmaceuticals and the balance in OTC sales.[20] Pharmaceutical manufacture in New Zealand is mainly in generic drugs produced by New Zealand companies.

The majority of pharmaceutical products sold in New Zealand are sourced from pharmaceutical manufactures/suppliers outside New Zealand. The biggest multinational research based companies in New Zealand include GlaxoSmithKline, Pfizer, Merck Sharp and Dohme, AstraZeneca, Roche, Pharmacia, Janssen-Cilag, Eli Lilly, and Novartis.

Sales representatives, medical conferences, medical journals, continuing medical education meetings, and television advertising are all used to promote and market pharmaceutical products. There are four market segments in New Zealand for the major pharmaceutical companies:[21]

- ethical pharmaceuticals require a prescription and compete with generic drugs for PHARMAC subsidies.
- proprietary pharmaceuticals are brand named drugs sold OTC in competition with generics.[22]
- sales to private hospitals.
- sales to public hospitals.

Private and public hospitals purchase both ethical and proprietary pharmaceuticals.

4.1 Domestic Production

The number of pharmaceutical manufacturing facilities in New Zealand has declined. The biggest domestic pharmaceutical producer is Douglas Pharmaceuticals. It produces a range of solid dose pharmaceuticals, liquids, creams and ointments, both for its own brands and on behalf of the multi-nationals operating in New Zealand. It is actively involved in exporting in the Asia-Pacific region. Other New Zealand based pharmaceutical companies include Pacific Pharmaceuticals and PSM Healthcare Limited.

Table 6 shows that activity in the New Zealand pharmaceutical sector has declined substantially since 1997.

[19] PHARMAC Annual Report (2001).

[20] Commerce Commission (2001)

[21] Commerce Commission (2000)

[22] Some OTC products are “pharmacy only” medicines.

Table 6 : Medicinal and pharmaceutical product manufacturing

$ million

	1997	1998	1999
Total income	494	316	315
Percent change (%)		-37.9	-0.3

Notes: (1) This includes manufacturing drugs, medicines, medicinal chemicals or other pharmaceutical products for human or veterinary use.

Source:Statistics New Zealand

4.2 Investment

In parallel with reduced manufacturing in New Zealand, most major pharmaceutical companies appear to be redirecting their research efforts away from New Zealand. Many now have only a token presence in the local market.

Between 1988 and 1991, five plants with a total capital value of $NZ12.8 million, closed. Since 1991, three plants have closed with a total capital value of $NZ51 million. The most significant of these was the Glaxo plant in Palmerston North, which ended an association of 89 years and saw the loss of 120 jobs.[23]

While there could be many reasons for this behaviour by pharmaceutical companies (e.g. the small size of the New Zealand market, the restructuring amongst the major pharmaceutical companies, inadequate patent protection) some, for what ever reason, have blamed the actions of government procurement policies as the main reason for withdrawing from funding research in New Zealand.

The RMI (and surveys of RMI members) identify a number of disadvantages of undertaking R&D in New Zealand relative to other OECD nations:

- a limited venture capital base.
- a lack of science graduates in key positions.
- qualified international R&D management.
- low investment in R&D by the rest of the private sector; and
- PHARMAC's pricing policies.

PHARMAC's pricing and capped pharmaceutical budget is said to have an impact in that it lowers the profitability of marketing pharmaceuticals in New Zealand to the point where New Zealand sales are best abandoned or managed from further afield. Major pharmaceutical companies indicate that they would prefer to supervise clinical trials in regions where they have local marketing offices.

While Table 7 should be treated with care since R&D expenditure is only one component of the category "other purchases and operating expenses"[24], it does reflect the anecdotal evidence of a general decline in the pharmaceutical sector in New Zealand.

[23] RMI survey

[24] These categories are from Pharmaceutical ANZIC code collected by Statistics New Zealand

Table 7 : Pharmaceutical sector spending in New Zealand

$ million

	1997	1998	1999
Other purchases and operating expenses	297	159	152
Percent change (%)		-46.3	-4.7

Notes: (1) This includes manufacturing drugs, medicines, medicinal chemicals or other pharmaceutical products for human or veterinary use.

Source:Statistics New Zealand

Some efforts are under way to look at ways of increasing R&D expenditure in New Zealand. Two recently held Biomedical R&D showcases are among a number of initiatives that have been undertaken.

In the first event, sponsored by the Minister of Research, Science and Technology, New Zealand researchers (both from private and public institutions) and research directors from international pharmaceutical companies met for the first time. There was a recognition on both sides that New Zealand had areas of scientific research expertise required by pharmaceutical companies. Other matters to come out of the showcase included:

- a recognition that New Zealand companies needed the involvement of international pharmaceutical companies to commercialise discovery.
- a recognition that R&D expenditure by pharmaceutical companies had fallen over the past ten years in New Zealand.
- a commitment to an overseas visit by New Zealand R&D providers to pharmaceutical company R&D facilities.

The second event, sponsored by the pharmaceutical companies, addressed three critical areas:

- the new research paradigm in the pharmaceutical industry, where increased costs, lack of productivity, and the availability of new technologies that have dramatically increased the number of candidate targets, are transforming the structure of R&D.
- the importance of intellectual property rights (patents, copyright, and trademarks) to provide the necessary incentives to research and commercialise products; and
- that no single company is able to achieve its R&D objectives through traditional approaches to R&D. There is now much greater potential for relationships between pharmaceutical companies and external research agencies (i.e. academia, biotechnology companies, and government).

The recent Science and Innovation Advisory Council (SIAC) report highlighted issues that required action by business and government for the further encouragement of innovation. The report emphasised the importance of:

- **partnerships** – While government sector R&D spending is comparable with other OECD nations, private sector R&D is lagging. A more active partnership between business and government is required to capitalise on the ideas being created.[25]

[25] See Figure 6.

- **the efficient use of research and business networks and communications infrastructure** – Access to computers and to the internet is relatively high in New Zealand but this has not translated into the optimal use of e-commerce.
- **attitudes and culture in nurturing stronger economic performance** – Our current attitudes to business success may limit New Zealand's growth.

In February 2002, the Minister of Research, Science and Technology, Pete Hodgson, established a biotechnology sector taskforce to develop more effective links between government and the private sector. Priorities of the taskforce are:

- identifying international trends that the New Zealand's biotechnology sector might capitalise on.
- developing strategies for building an internationally competitive biotechnology sector in New Zealand.
- highlighting areas where government action might be appropriate for the development of the biotechnology sector; and
- acting as a focal point for a partnership between government and the industry.

4.3 Patents

Prior to January 1995, the New Zealand patent term for pharmaceuticals was 16 years with a possible 10 year extension. To conform with the TRIPS Agreement in the Uruguay Round, the regime has been altered to 20 years without extension. Parker (1997) argues that the present treatment of even the 20 year period does not meet the requirements for a dynamic and innovative pharmaceutical industry. As noted earlier, regulatory hold-ups have seen effective patent lives decline, reducing the profitability of new discoveries.

Parker (1997) has analysed 3 cases in New Zealand: 16 year patents, 20 year patents, and patent reform based on the European Union's supplementary protection certificate (SPC). Table 8 gives mean values of the EPL under the three patent regimes.

Table 8 Mean effective patent life

Years	
16 year patent regime[1]	7.63
20 year patent regime[2]	10.06
SPC year patent regime[3]	13.18

Notes: (1) Uses the whole sample with extensions included. (2) Applies a 20 year term to all patents not just those that qualified under the Uruguay Round Act. (3) Applies an SPC to all patents in the sample.
Source: Parker (1997) p 88

Parker recommends the SPC standard as the benchmark for international best practice. The SPC provides for the EPL described above, that is, a minimum of 15 years from approval to market subject, to a five year maximum beyond the normal 20 year term.

To encourage the availability of new medicines, European Union law makers have introduced a "diffusion incentive".[26] By stipulating that the registration period stops when the first marketing authorisation is issued anywhere within the EU,

[26] This is an industry generated strategy to resource compliance so that new technologies are rolled-out in all key international markets in approximately 2-3 years, rather than the traditional 'cascade' strategy of 0-10 years that rated markets on relative importance and size.

pharmaceutical companies are given an incentive to roll out the product as quickly as possible after registration.

The New Zealand position is the minimum agreed to under the Uruguay Round Agreement, i.e. twenty years from the time of filing the patent. This is at odds with most other industrialised nations which have taken steps to increase the EPL for pharmaceuticals.

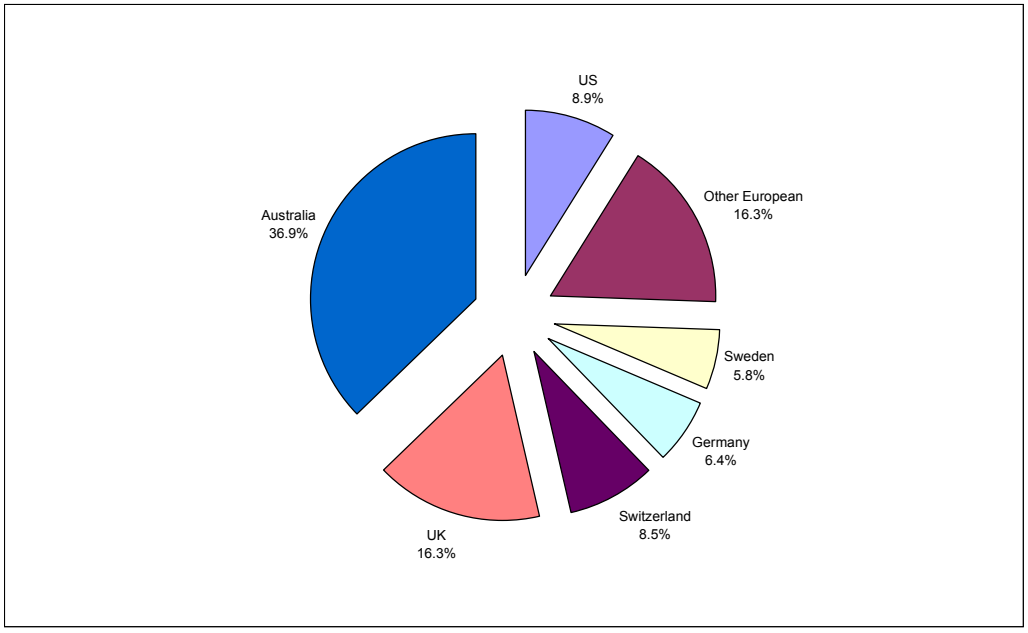
Patents are discussed in part 2 as one of the factors pharmaceutical companies look at when locating in any particular country.

4.4 Trade

4.4.1 Imports

Most of the pharmaceuticals sold in New Zealand are imported. A breakdown of the major sources is shown in Figure 5. The most important source is Australia.

Figure 5: Import market share



Note: Australian figures include a number of international pharmaceutical companies using their Australian manufacturing base to supply New Zealand.

Source:Statistics New Zealand

Pharmaceuticals manufactured in Australia and imported into New Zealand are typically from the large multinationals which have manufacturing plants in Australia.

4.4.2 Exports

Most New Zealand owned pharmaceutical companies supplying the domestic market are small, however Douglas Pharmaceuticals is involved in exporting pharmaceutical products to Australia and Asia. It should be noted that Douglas Pharmaceuticals have transferred some of their manufacturing facilities overseas to Fiji and Australia.

4.5 Employment, wages and profitability

While there is very little data specifically on the New Zealand pharmaceutical industry, Table 9 shows that the size of the New Zealand industry reflects the pattern of static or

declining investment that has taken place over the last ten years. The figures also show the consolidation, in percentage terms, of the number of companies has fallen by more than the drop in employment.

Table 9 : Numbers of employees and companies

Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
Employees	1038	1017	867	991	947	683	990	923	998	990	907
Companies	28	28	21	28	27	22	21	21	19	22	17

Source:RMI Survey

4.6 Trial phases: potential for research

The pharmaceutical pipeline is described in Table 10. Pharmaceutical R&D involves an important element of very general basic research, particularly in biotechnology. For example, in the discovery stage, studies of cloned animals as bio-pharmaceutical research "platforms" have wider research applications. This increases the likelihood of spillovers providing benefits elsewhere in our economy. With the spillovers from those flow-on applications, the chances of more rapid growth are improved. For further information on each phase see Appendix C.

Table 10 : Pharmaceutical pipeline

Stage:	Discovery	Pre Clinical	Phase I	**Phase II**	**Phase III**	**Phases IV**
Function:	Base IP/ Science	Preliminary Testing	Safety Toxicity	**Efficacy**	**Multi Trials**	**Product Marketing**

Source: NZIER

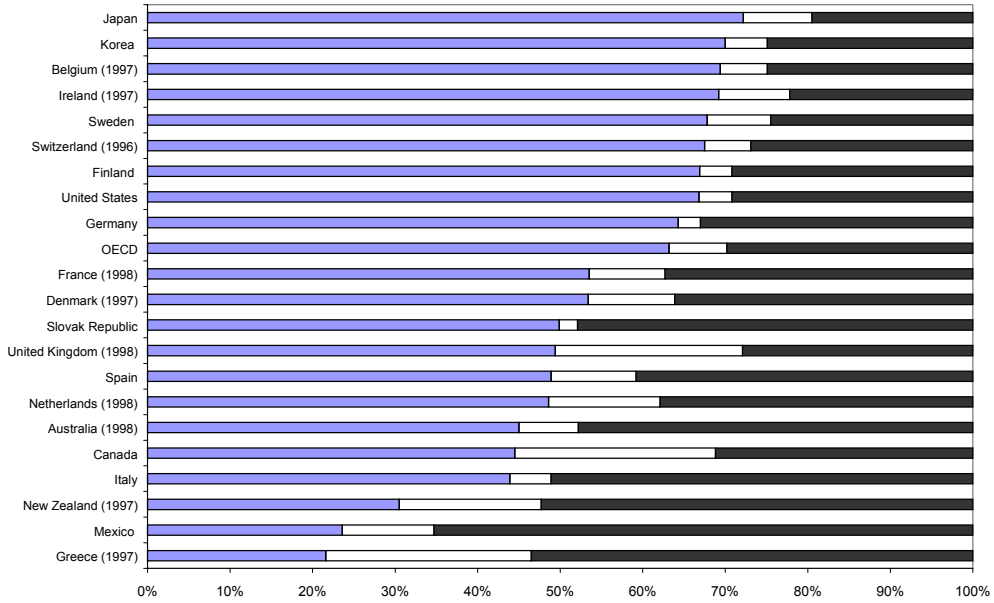
While all stages are important to the process, most pharmaceutical R&D money is spent on phases II, III and IV. Unless it is clear that discovery, pre clinical, and phase I produces stronger spillovers, it is reasonable to assume that under any R&D partnership with government the pharmaceutical industry would target this area first for funding.

Funding for phases II, III, and IV, the industry believe, would provide the infrastructure to develop the discovery, pre clinical, and phase I parts of the pharmaceutical pipeline. The illustration of these linkages will be further investigated in part 2 and 3 of this study.

4.7 Private research in New Zealand

Figure 6 shows that the mix of private, public, and other research in New Zealand differs from that in other OECD nations. While publicly funded research in New Zealand is close to OECD averages, in percentage of GDP terms, private research lags behind that of other OECD nations (see Figure 7).

Figure 6: Balance of public and private research
R&D in percentage terms (1999 unless otherwise stated)

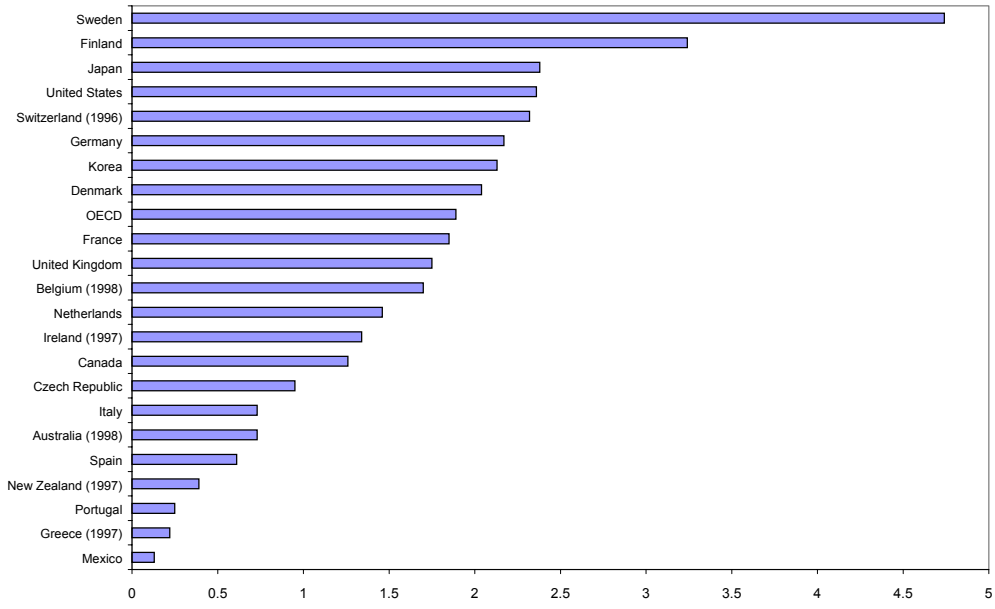


Notes: left hand side – business, middle – other research, and right hand side – government.

Source: OECD MSTI Database May 2001

Figure 7 illustrates the lack of private research, relative to other OECD nations. As a percentage of GDP New Zealand ranks at the lower end of the scale .

Figure 7: Private R&D
Percentage of GDP (1999 unless otherwise stated)



Source: OECD MSTI Database May 2001

The private sector R&D carried out in the pharmaceuticals industry in New Zealand mirrors this overall performance. The amount spent by pharmaceutical companies in New Zealand last year was approximately $18 million while the pharmaceutical

companies spent approximately 17 times that much in Australia on R&D. This suggests that more could be done to promote private sector R&D spending in New Zealand.

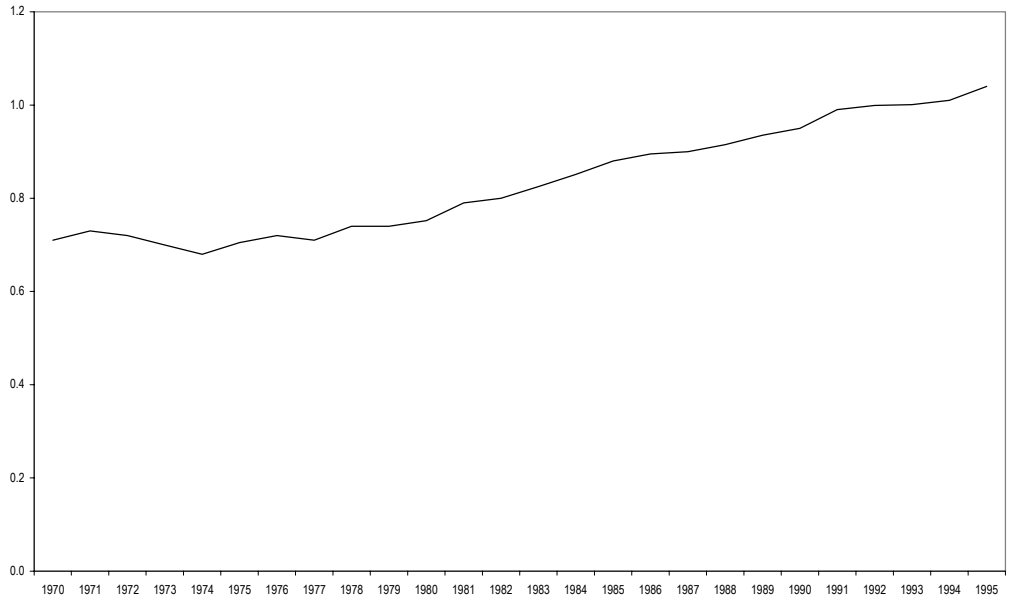
5. KNOWLEDGE BASED GROWTH

5.1 The emergence of the knowledge economy

As shown in Figure 8, there has been a rapid increase in the knowledge intensity of manufactured exports.[27]

Figure 8: The knowledge composition of manufactured exports

Index base year 1970



Note: Derived by weighting the exports by industry of a given country by the average knowledge intensity of that industry in the major OECD nations.

Source: Sheehan and Tikhomirova 1997a p16

Furthermore, the OECD (1998) point to the growth in importance of technology based manufacturing industries, particularly in G7 countries.[28] Despite the fact that manufacturing has declined in importance relative to services, the high technology sector accounts for between one quarter and one third of output growth in G7 countries.

This increased knowledge intensity has been underpinned by the immense improvements in generating, storing, and using information.

5.2 Theory

Discussion of the role of knowledge in economic growth is not new. Adam Smith (1723-1790) wrote about the issue and in the last sixty years, Schumpeter (1943) and Galbraith (1967) also made contributions. More recently, Romer (1986), Krugman (1986), Grossman (1986), Branstetter (1996), Freeman (1994), and Teubal et al (1996) have improved our understanding of the importance of knowledge in growth.

[27] OECD (1997, 1998, 1999); Tegart et al (1997); Sheehan et al (1995)

[28] see Appendix A for OECD R&D Intensity indicators

What is a "knowledge based economy"? The OECD have defined knowledge intensity as equivalent to R&D intensity. One way of measuring knowledge intensity is to identify:

- expenditure on "new products and processes which contribute to significant changes in products and processes",[29] (with quantitative information often obtainable from patent applications or actual R&D expenditure); and
- expenditure on non technological innovation, i.e. on significant management and/or organisational improvements.

The OECD has created a programme that seeks to measure technological and non-technological innovation and, in parallel, measure the *related* economic activity generated by linkages and networking between economic agents. Assessing the relationships includes analysis of:

- **clusters** – extent of formal and informal networks and how they translate into increased innovation through patenting and R&D expenditure.
- **adoption rates for new technologies**.
- **personnel mobility** – for highly skilled people between firms and countries.
- **spill-overs** – where possible, tracking advantages gained by firms through *proximity* to other firms' R&D efforts.

Two important streams of economic thought provide insights into how knowledge based industries impact on economic activity. These are New Growth Theory and Strategic Trade Theory. In broad terms, these theories confirm that knowledge production and distribution can be major sources of economic growth and higher living standards. They indicate that:[30]

- knowledge based growth is generated by spillovers from investment in physical capital, human capital, innovation, and R&D.[31]
- some development paths can be self-reinforcing, i.e. leading to rapid growth.
- certain industrial structures favour spillovers more than others; and
- government policy can assist, in a cost effective manner, by initiating a positive development path – beyond just the usual legal environment and macroeconomic settings.[32]

Schumpeter (1943) introduced the idea of linking innovation to growth. He emphasised that a firm could improve its competitive position by a variety of sorts of innovation – internal reorganisations, new processes, new marketing methods, and new products.

Grossman notes that the starting point of Strategic Trade Theory is the simple idea that:

> *"As soon as we leave the world of perfect competition where all resources earn their opportunity value ... we can no longer be indifferent to our country's industrial structure. There are some industries that provide greater national benefit than others, and all the countries in the industrialised world would prefer to be active and successful in these."*[33]

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[29] DIST (1996) p11

[30] see e.g. Marceau *et al.* (1997) p 1.9

[31] (Positive) spillovers arise where economic transactions produce benefits for third parties not involved in the transaction. In this setting, we envisage R&D in one firm providing insights for other firms, conveyed through industry meetings or personal contacts.

[32] Comparative advantage can lock a country into low growth if that country has few knowledge based industries.

[33] Krugman (1986) p66

Other research examined the spatial dimension. Dumais et al (1998) showed that when industry and R&D are clearly linked and in close proximity, the feedback between the two creates conditions for positive growth. Reductions in transport costs due to the proximity to markets leads to labour market pooling and specialisation, which leads to intellectual spillovers.

Encouragement given to knowledge intensive industries can support their clustering around specific physical locations. As documented by Porter in numerous publications,[34] clusters can create a virtuous circle of growth in skills and knowledge that would otherwise not develop.

Branstetter (1996) use examples to show that domestically conducted R&D is much more beneficial to the economy than importing R&D-intensive products and services. This is because, in the examples given, the domestic R&D generates spillovers in ways that imports do not.[35]

5.3 The policy prescription

The OECD has been at the forefront of attempts to understand how increases in knowledge-intensity impact on economic activity.[36] Their research has focused on "National Innovation Systems" in an attempt to illustrate the linkages between knowledge and economic growth – the commercialisation of R&D.

Data was collected on eight developed nations:[37]

- skill intensity in the production of goods and services – determined mainly through firm surveys.
- the re-orientating of research to blend pure and applied research activities on specific projects or processes – assessed by examining the number of joint research and technical activities between firms and university/research institutes.
- the growth of journals devoted to multi-disciplinary approaches to R&D.
- the increased diversity of public research institutions' activities.
- the lags between publication of ideas in journals and the registering of patents for commercial applications.
- the increasing number of alliances between companies leading to formal and informal clustering arrangements – from firm surveys.
- the increasing importance of co-operation in fostering innovation and its commercialisation – measured by the number of co-patents and co-publications developed by industry and university/research institutes.

The OECD studies identify a number of factors as important for successful commercialisation:

- **Commercialisation relies on joint and effective action by the scientific and business communities.** This means that the public sector science research agenda should be driven by problems identified within industry in the commercial development of a given technology.

[34] for New Zealand see Crocombe, Ewright, and Porter (1991)

[35] see also Dowrick (1995) p153

[36] OECD (1997) and (1999)

[37] These countries are Austria, Denmark, Italy, Finland, Norway, Netherlands, United Kingdom, and Sweden.

- **The main driving force behind innovation and diffusion of new technologies is small and medium sized business.** This is clearly an important conclusion for New Zealand since it suggests that our typically small scale of operation is not an impediment to participation. However, the OECD studies note that governments are often not doing enough to unlock the potential of small and medium sized businesses.
- **Networks are crucial to knowledge based growth** – not only collaboration between public agencies and private firms but more importantly, the informal links between researchers.
- **National innovation systems becoming more interdependent.** Cross border purchases of patents, international alliances, and foreign investment in R&D are all increasing. The ability to link into an international innovation network, regardless of the size of the business, is becoming an increasingly important part of a firm's competitive edge.[38]

5.3.1 Role of government

To meet the challenge of the new business opportunities, the OECD believe that individual governments need to ensure the overall framework of policies is consistent with enhancing an innovation based culture,[39] while facilitating links between private businesses and public learning institutions and removing impediments to innovation in the business sector.

In particular,

- to build an innovation culture, governments need to identify and overcome the problems associated with increasing technical progress at the firm level – poor management practices, inappropriate work organisation, and weak incentives for the uptake of new technology.
- to promote networking and clustering, a knowledge industry policy should not focus on a single firm but rather on how individual firms interact with other enterprises and organisations.
- to encourage public learning and research institutions to interact with businesses, governments could jointly fund projects and their commercialisation through patents, licences, and spin-off firms.
- to make the most of the opportunities provided by globalisation, governments should maintain an open economy. An improved ability to develop international R&D alliances enhances the capability of an economy to absorb new ideas.

5.4 Application to the pharmaceutical industry

As described above, R&D has a pivotal role in the global pharmaceutical industry. The scale of global R&D investment and the developments in biotechnology favouring smaller specialist R&D providers, suggest that New Zealand has an opportunity to build on its existing agriculturally based biotechnology sector and nascent bio-pharmaceutical industry to expand exports substantially.

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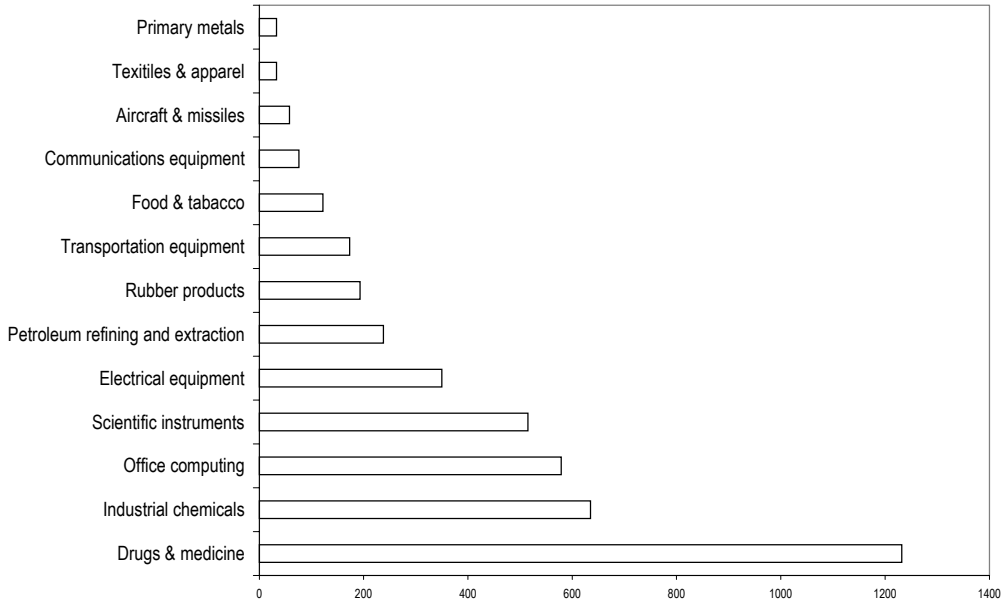
[38] This may disadvantage smaller companies that are further away from funders and markets. Smaller European or US companies have a major advantage over smaller New Zealand companies because of their proximity to the market.

[39] This includes having a stable macroeconomic environment, suitable tax and regulatory settings, and ensuring that infrastructure, education, and training policies are appropriate.

Figure 9 illustrates the importance of this basic level research relative to other industries in the United States.[40]

Figure 9: Basic research expenditures by industry
$USM, 1992



Source: US National Science Foundation, in PhRMA (1996) p11

There is a potential match between the infrastructure and capabilities of our publicly funded institutions – such as CRIs, hospitals and universities – and the basic research requirements of pharmaceutical companies.

This could be developed by government putting special emphasis on funding joint projects between CRIs, hospitals, and universities and the pharmaceutical companies.

[40] Basic research is defined as research which cannot be captured by an individual firm and whose uses extend to wider research activities.

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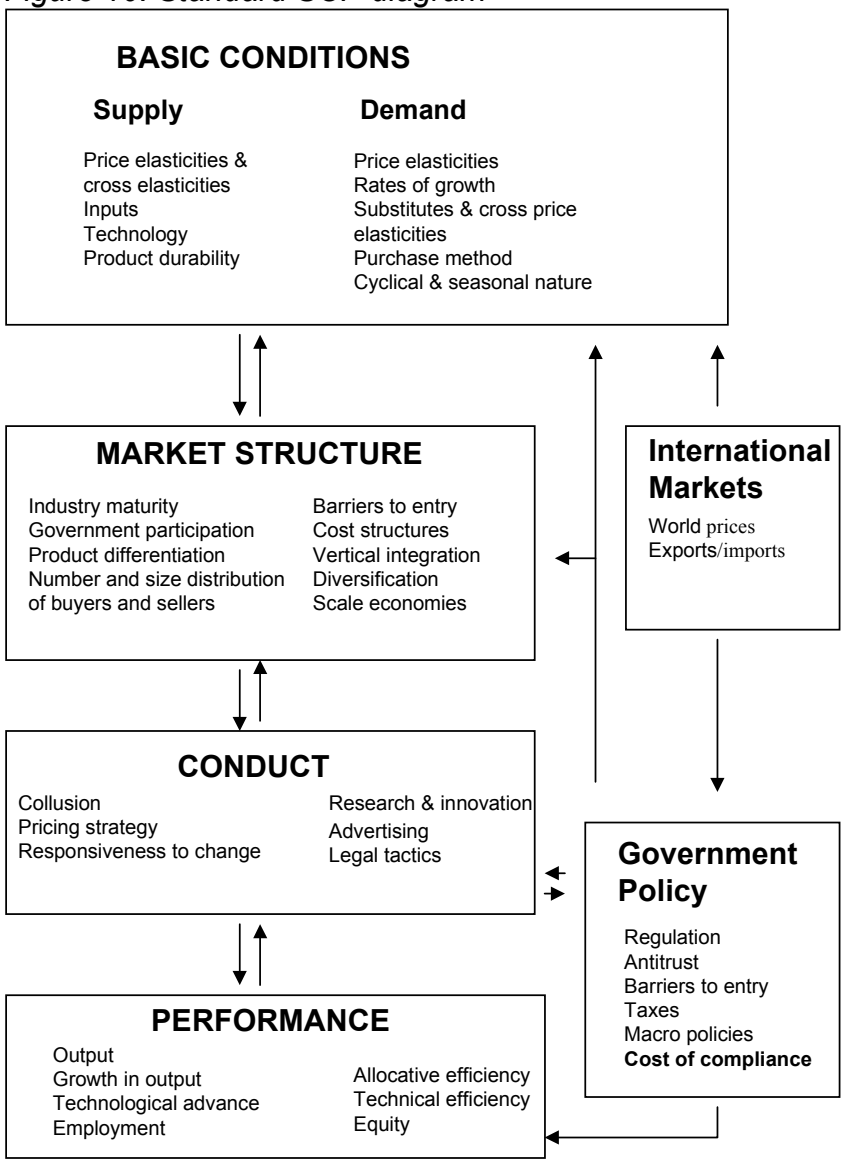
APPENDIX A: STRUCTURE, CONDUCT, AND PERFORMANCE

To better understand the workings of the pharmaceutical industry we have followed loosely the SCP framework. The SCP framework is used in the form of a "check list" (see Figure 10) so that we can describe how various parts of the industry (i.e. government regulation) can impact on how the industry operates.

Figure 10: Standard SCP diagram



Source: NZIER

The SCP framework has been widely used in economics (e.g. Schmalansee 1987, Scherer and Ross 1990) as an analytical tool. The basic assumption of the model is that the market structure determines, or at least has a strong influence on conduct, which in turn influences the performance of the industry.

The advantage of this approach is that very different industries can be evaluated by applying a general model. More importantly it also shows:

- how the unique and individual characteristics of the pharmaceuticals industry impact on economic behaviour in that industry (i.e. specifically on structure, conduct and performance).
- the interconnection between various parts of the industry (i.e. changes to one part of the industry will impact on structure, conduct, and performance).

The model has in the past been core to most studies of industry and was part of the so-called Harvard School (Grether, 1970). There are, however, a number of criticisms of the model:

- Posner (1979) believed that the SCP framework was over elaborate since the competitive market adequately explained most market behaviour and outcomes.
- others criticised the model for assuming causal linkages that might not always have been established empirically, and for being uni-directional in its focus.

In response to the latter criticism, the SCP model was modified to include feedback effects (included in Figure 10). These feedback effects have been added to recognise that the behaviour of firms and performance outcomes within industries can themselves alter market structure – whether it is because of mergers between rivals, statutory protection, or the increased costs of complying with government regulation. This recognises that all businesses operate in a dynamic setting and respond directly to changes in that setting. So when the cost imposed by government to do business increase – it will impact on the way businesses operates (see Figure 10).

The SCP framework is used here to describe the importance of the pharmaceutical's industry in a developed economy and illustrate the linkages between industry structure, conduct, and performance and how government can influence these linkages.

APPENDIX B: R&D INTENSITY INDICATORS

OECD R&D Intensity indicators

Percent

Industry	R&D Intensity (%)
High technology industries	*22.74*
Aircraft	32.05
Office & computing machinery	30.79
Drugs & medicines / pharmaceuticals	22.37
Radio, TV & communication equipment	16.95
Medium-high technology industries	*9.46*
Professional goods	14.82
Motor vehicles	13.18
Chemicals excluding drugs	9.27
Electrical apparatus	8.89
Machinery & equipment	5.23
Other transport equipment	4.24
Medium-low technology industries	*2.39*
Petroleum refineries & products	4.82
Non-ferrous metals	3.51
Shipbuilding & repairing	2.68
Rubber & plastic products	2.67
Iron & steel	2.58
Other manufacturing	2.21
Non-metallic mineral products	2.04
Metal products	1.37
Low technology industries	*0.88*
Food, beverages, & tobacco	1.09
Paper, paper products & printing	0.88
Textiles, apparel & leather	0.71
Wood products & furniture	0.49

Notes: (1)R&D Intensity is R&D as a share of value added. (2) the pharmaceutical industry is classified under drugs and medicines. (3) The petroleum industry is classified under medium-low technology despite its higher ratio of R&D as a share of value added.
Source: OECD 1997 Science, Industry, and Technology Scoreboard of Indicators: Paris.

APPENDIX C: PHASES OF PHARMACEUTICAL RESEARCH

During phases I to V, pharmaceutical companies typically spend US$ 800 million on pharmaceutical development over the course of 10-15 years.

Discovery	Promising compounds are nominated for testing.
Pre-clinical	Tests are conducted in the laboratory and on animals to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.
Phase I	Also called volunteer trials, phase I trials establish how the human body handles the new drug and what toxic effects, if any, are experienced. These trials are placebo-controlled and involve only very limited numbers of healthy volunteers (between 20 and 80). Phase I trials are monitored with extreme care throughout the trial.
Phase II	This phase describes the first patient trials; these will be very carefully controlled trials aiming to give an idea of efficacy, which dose is optimal and some preliminary information on safety. They are limited to a few hundred people, are likely to be placebo-controlled, and carried out mainly in hospitals.
Phase III	The major work on efficacy and safety are carried out in phase III. These trails simulate conditions that would prevail once the drug was marketed, but with close monitoring. These are usually conducted in general practice. They include comparative trials with marketed treatments and also placebo-controlled trials. These trials are necessary before a product licence can be submitted. Typically they involve between 1,000 and 3,000 people.
Phase IV	These trials are performed after a drug has been marketed. Many questions need to be answered, such as effectiveness and safety for children and or the elderly. They also are needed to identify cases where rare adverse events may occur. Phase IV trials also serve to establish the general usefulness of a new drug used in normal clinical practice in a significant number of patients.
Phase V	Another name for a Post Marketing Surveillance (PMS) study. These are studies to support the marketing of the drug.