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List of Abbreviations

AACR	American Association for Cancer Research
ACSRC	Auckland Cancer Society Research Centre
AEGIS	Australian Expert Group in Industry Studies
AIDS	Acquired Immune Deficiency Syndrome
API	Active Pharmaceutical Ingredient
A*STAR	Agency for Science, Technology and Research (Singapore)
AUD	Australian Dollars
GBP	Great Britain Pounds
CEO	Chief Executive Officer
CRA	Clinical Research Associate
CRF	Case Report Form
CRI	Crown Research Institute
CRO/s	Contract Research Organisation/s
EU	European Union
FDA	Food Drug Administration
GBAORD	Government Budget Appropriations or Outlays on R&D
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GLP	Good Laboratory Practice
GM	General Manager
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HRC	Health Research Council (New Zealand)
ICH	International Committee for Harmonisation
IIB	Institute for Innovation in Biotechnology (University of Auckland)
IND	Investigational New Drug
IP	Intellectual Property
IRB	Institution Review Board
MED	Ministry of Economic Development (New Zealand)
MoE	Ministry of Education (New Zealand)
MoH	Ministry of Health (New Zealand)
MoRST	Ministry of Research, Science and Technology (New Zealand)
MSI	Ministry of Science and Innovation (New Zealand)
N	Number
NCE	New Chemical Entity
NDA	New Drug Application
NERF	New Economy Research Fund
NICE	National Institute for Health and Clinical Excellence (UK)
NIH	National Institutes of Health (USA)
NIHR	National Institute for Health Research (UK)
NMA	New Medicine Application
NME	New Molecular Entity
NMP	National Medicines Policy (Australia)
NZACReS	New Zealand Association of Clinical Research
NZ	New Zealand
NZD	New Zealand Dollars
NZIC	New Zealand Institute of Chemistry
NZSO	New Zealand Society of Oncology
OECD	Organisation for Economic Co-operation and Development
PBS	Pharmaceutical Benefits Schedule
PHARMAC	Pharmaceuticals Management Agency (New Zealand)

PhD	Doctor of Philosophy
PIAA	Pharmaceuticals Industry Action Agenda (Australia)
PIS	Participant Information Sheet
RS&T / RST	Research, Science and Technology
RSNZ	Royal Society of New Zealand
SCOTT	Standing Committee on Therapeutic Trials
SD	Standard Deviation
TGA	Therapeutic Goods Agency (Australia)
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UAHPEC	University of Auckland Human Participants Ethics Committee
UK	United Kingdom
USA	United States of America
USD	United States Dollars
WHO	World Health Organization
WTO	World Trade Organization

Introduction

1 Introduction

1.1 Background

The pharmaceutical industry is undergoing considerable change as it seeks to address its declining profitability caused primarily by declining research and development (R&D) productivity and increasing R&D costs. Its challenge is to find alternative sources of innovative compounds and more efficient mechanisms of managing them through the high-risk drug development process. As a result the industry is moving away from its traditional in-house or closed method of drug development (1-5). The new, more open approach to drug development involves the industry forming alliances and partnerships with smaller companies and academic groups to gain access to innovative compounds and complementary expertise (1, 6). The industry is also outsourcing parts of the R&D process in an attempt to reduce the extraordinary expense of drug development.

The industry's rapid expansion in their outsourcing of drug discovery and development projects has created significant opportunities and there is increasing competition from countries wanting to capitalise on these (1). A policy to support its drug development industry is attractive to governments because of the potential benefits of wealth creation, employment, international trade and the desired development of high technology industries (7). In addition, a viable pharmaceutical industry could reduce a country's dependency on expensive imported medicines, or provide treatments for their population's specific medical needs (6-9).

The barriers to a successful drug development industry include the high R&D costs, knowledge capital required, price competition from emerging economies and unpredictable potential economic benefits (10, 11). The risks of drug development, both technical and financial, are well-known but often underestimated, and the return-on-investment horizon can be more than 20 years (12). These factors make the development of a local industry a high risk proposition, however this risk may be mitigated by the increasing opportunity created by the pharmaceutical industry outsourcing drug development projects (10).

1.2 Rationale

New Zealand (NZ) has the advantages of a strong biomedical research basis for drug discovery innovations, a resourceful and entrepreneurial society that encourages innovation (13), and a western culture and is conveniently located in the Asia–Pacific region. The NZ government has invested in science, research and technology as a mechanism to increase the knowledge economy, encourage innovation and support NZ's best biomedical and drug development research (14, 15). However, many developed and developing countries have also implemented policies to promote local

innovation and increase capability in drug development. Therefore, NZ's challenge is to understand where to position itself in the global drug development industry.

An assessment of existing expertise would allow NZ to define its strengths in drug development and allow it to differentiate itself from competitor countries. There is also a need to understand the enablers and barriers that have influenced the growth of the NZ drug development industry so far and to identify those that could provide support for further industry development. Finally, calculations of the potential economic value that could accrue to NZ from its drug development industry do not appear to have been conducted and an estimation of this value is an important component of an assessment of the viability of this industry. The results of this research into NZ's drug development industry would assist NZ in maximising the opportunities presented by the current changes in the pharmaceutical industry, as it faces the challenges of finding new sources of innovative compounds and more cost-efficient drug development processes.

1.3 Objectives

The objectives of the research were:

1. To develop a theoretical framework for evaluating the drug development industry in NZ
2. To critically evaluate the expertise of this industry in NZ
3. To identify the enablers and barriers to the use and/or development of NZ expertise and the factors that have allowed this industry to arise
4. To assess the potential economic benefits to NZ of policies supporting the drug discovery and development industry

This research was conducted in a manner that involved as much of NZ's drug development industry as was possible, rather than using an in-depth case study approach of a few selected organisations. The three topic strands of expertise, enablers and barriers, and economic benefits are not mutually exclusive and therefore have the potential to produce complementary findings.

1.4 Organisation of the Thesis

The remainder of this thesis is organised as follows:

- Section 2 is a **literature review** encompassing:
  - A description of process, risks and costs of developing a new medicine, the changes in the drug development process that the pharmaceutical industry is undertaking, and a summary of NZ's drug development compounds and companies
  - The assessment of expertise including knowledge management and innovative behaviours

- The policies and factors affecting a country's industry development, including summaries of countries with significant industry. On the basis of the policy approaches used to support a drug development industry six distinct categories were defined and countries allocated to these as appropriate
- The actual and potential economic benefits from a drug development industry

- The third section presents the **theoretical frameworks and methods** (quantitative and qualitative) used for this research
- Section 4 presents the research **results**, by objective
- Section 5 **discusses the results** in the context of the relevant literature. The **limitations** of this research are also presented
- Section 6 provides the **conclusions** of this research and potential areas for **further research**

These sections are followed by Appendices I to V that contain the questionnaires administered to the research participants, Appendices VI to X that contain the publications that have been generated by this research and Appendix XI that contains a manuscript which is under review for publication.

Literature Review

2 Literature Review

2.1 Drug Development

2.1.1 The Drug Development Process

Pharmaceutical research and development is a lengthy, expensive and risky process that is based on the expectations that the successful drug innovation will provide premium returns once it receives marketing approvals (16). While the outcome of the process of discovering and developing new medicines is very uncertain, the regulatory requirements and the approval procedures are highly structured and follow a linear pipeline process (17).

During the 1990s the process from identification and screening of a potential compound until regulatory approval to market the product, required an average of 10 years (18, 19). However, for products marketed from 2000 onwards, this time increased to 13.9 years (20). The drug development process generally follows the stages described in Table 1.

The factors that influence how quickly a compound moves through the drug development process include the priority that the company gives to the project, the resources applied, having a sound development plan, monitoring the progress of the compound and effective management to make decisions and keep the project on track (17). Companies continuously evaluate the progress of their drug development projects in order to reduce risks, minimise costs and adhere to budgets and timelines (21). Companies also set strict criteria for progressing compounds through the development pathway with a clear 'go' or 'no-go' decision point for each compound as it completes each development phase. A no-go decision on progressing compounds can be based on an unacceptable clinical safety profile, low bioavailability, manufacturing and formulation issues, unpromising results from preclinical studies, and unsatisfactory pharmacoeconomic projections. The main reason that potential medicines are abandoned in phase III is economic rather than safety or efficacy concerns (22).

Table 1 – Summary of the Drug Development Process

Stage	Description	Phase transition probability
Drug discovery	Identifying potential new pharmaceuticals either by testing compounds chemically similar to known products, those hypothesised to have a certain biological activity, or by random screening of large numbers of known substances for therapeutic activity (23). A lead candidate is identified to undergo further development (17, 24).	Of 10,000 compounds screened, only 250 will be issued an IND[1] (25)
Phase I	Studies conducted in 20–80 healthy volunteers administered single or multiple doses of the compound, usually in ascending doses per group (19). The aim is to evaluate the safety and pharmacokinetics of the compound, plus evidence of activity where possible (26). In some instances, patients are the only suitable population (e.g., an anti-cancer compound), however it is not expected that they will derive any benefit (27).	71% of phase I compounds enter Phase II[2]
Phase II	These studies evaluate the efficacy and safety of the compound in a targeted disease or condition. Two or three different doses are studied, and compared with placebo using a randomised, double-blind study design involving 100–300 participants (19). These studies provide the dose-response efficacy and short-term safety data, and guide the phase III programme (23).	45% of phase II compounds enter Phase III[2]
Phase III	Phase III usually includes two large confirmatory, pivotal studies involving 1,000–5,000 participants to confirm efficacy of the selected dose on the endpoints chosen (23) and data for pharmacoeconomic arguments (28). Other studies include pharmacokinetic studies in special populations (e.g., elderly, those with renal or hepatic impairment) and drug interaction studies (19).	64% of phase III compounds have a New Drug Application (NDA) submitted for registration of the product[2]
Registration	The required information is compiled into an NDA and submitted to regulatory authorities (e.g., FDA) for approval to market the product.	93% of NDAs are approved[2]

[1] IND = Investigational New Drug application, which allows a clinical trial to proceed in the USA

[2] Phase transition probabilities are for the 1999–2004 period and include both self-originated and licensed-in compounds (29)

The phase transition and clinical approval probabilities in Table 1 are from research by DiMasi and Feldman (29) which used data from the top 50 pharmaceutical firms to estimate that only 19% of drugs entering phase I trials eventually gain marketing approval (29) agrees with the FDA's statistics (30). A publication summarising the literature reported a wide range of drug development success rates from 7% to 78%, with the extremely high success provided by hormone therapies (31). Another analysis based on data from 14 companies suggested that the chance of market launch for a product in phase I dropped from 10% in 2002-2004 to 5% in 2006-2008 (32). It is difficult to compare the rates reported due to the use of different data sources, compound types and/or therapeutic areas and there is also data that is available only to the pharmaceutical industry. The probabilities suggested by DiMasi and Feldman (29) appear to be based on the largest, and one of the most recent, datasets and

are the most widely cited. It has been suggested that the increase in attrition rates of drug development candidates has contributed to the decline in pharmaceutical R&D productivity (20).

A new drug's probability for successful completion of phase III is associated with firms that have a narrower focus in their development programmes rather than a broad focus (33). The therapeutic class of the new drug can affect its probability of getting to phase III; DiMasi et al. (29) reported a range from anti-infective drugs with the highest rate of success of approximately 24% through to central nervous system and cardiovascular drugs with low rates of 8–9%. This may be related to the ability to define and measure clinically relevant efficacy endpoints; for example, the endpoint for an anti-infective is reasonably well defined and easy to assess compared with that for a psychotropic compound. Unfortunately, some of the indications that have poor success rates in clinical research are also those of unmet medical need (29).

Biotechnology in the drug development industry describes any compound or technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. Therefore, biotechnology is defined by the methods used for manufacture rather than the products themselves (23). In practice biotechnology and pharmaceutical firms are indistinguishable because they use the same development milestones and R&D practices and methods (17, 34), and since virtually all drug discovery organisations use forms of biotechnology in their research, Hopkins, Martin et al. (34) suggest that biotechnology firms should be considered as a specialty subset of pharmaceutical companies.

2.1.2 The Cost of Drug Development

The cost of drug development covers the process from drug discovery through to the submission of a New Drug Application, including preclinical testing, formulation and manufacturing evaluations, and the extensive clinical programme. The estimated cost of drug development has been rising steadily from the 1970s estimate of USD137 million to USD803 million in 2000 (both in the value of 2000 dollars). This rise was much more than could be accounted for by inflation alone and the cost increases are mainly attributed to increased regulatory requirements for increased numbers of study participants, additional procedures, increasing complexity of trials and a shift to more expensive chronic and degenerative diseases (18, 35). Others, replicating the methodology of DiMasi et al., estimated the costs to be between USD500 and USD2,000 million depending on the therapy or organisation developing the compound (36, 37). A more recent estimate of the average capitalised cost to develop a pharmaceutical rose to USD1.24 billion in 2005 dollars (38) and the estimated total capitalised cost for biopharmaceutical companies is nearly the same as for traditional pharmaceutical companies (39).

This methodology employed by DiMasi et al. whereby the time cost of the funds invested contributed more than half the total cost, has been criticised (40). If the time cost of the funds invested is not included, the mean total cost is reduced from USD804 million to USD226 million in 2005 dollars (23). Other economists argue that the inclusion of financial costs is valid because the investment horizon for drug development is 12–15 years and investment returns may take more than 20 years (12). Other criticisms of the calculations by DiMasi et al. are that they were based on a highly selected sample of drugs that tended to be for chronic diseases, and the drug development was predominantly conducted in the USA and Europe and made no allowance for tax rebates (41). Critics also argue that even though the costs of drug development are high (up to about 13% of income), pharmaceutical companies spend very large amounts on advertising and promotion, with marketing and administration budgets up to 32% of income (41). A review of all research articles on the cost of drug development published from 1980 to 2009 found that cost estimates ranged more than ninefold due to differences in data and methodologies and DiMasi's data produced relatively high results (40). However, it is evident that the costs of drug development have been increasing and that there has been a decline in R&D productivity (20, 34, 40).

The development costs for an existing medicine for a new indication is less expensive than developing a completely new compound because previously collected information (e.g., formulation and preclinical testing) is usually applicable to the product's new indication. This has resulted in companies specialising in repositioning: developing known medicines for new indications or reformulations to gain improved pharmacokinetic or safety profiles (42).

There is no average cost for any phase clinical trial that can be generally applied (43) because there are too many variables that influence the costs including the type of compound, number of participants, duration of the study, type and number of test procedures required, number of sites and countries involved and the indication being studied. The cost of studies with oncology compounds, for example, can vary widely depending on whether the sponsor is a private company or a government/publicly funded cancer research organisation (41). In 2003, the cost of phase I alone was estimated at USD15.2 million and phase II at USD16.7 million (35) while DiMasi et al. (44) estimated costs of USD15 million for phase I, USD24 million for phase II and USD86 million for phase III. Costs were least variable for phase II trials and most variable for phase III. This is due to the more standardised format of phase II trials, while phase III trials are dependent on the indication being studied. A more recent analysis has found that expenditure on phase I and II may be higher than the calculation by DiMasi et al. while phase III may be lower (45).

There is considerable interest in methods that reduce the extraordinary costs of drug development, especially as the payers increasingly need to contain the costs of healthcare. Cost-saving approaches

are of particular interest in the expensive clinical phase of drug development and include conducting clinical trials in different locations, the use of information technology, adaptive study designs and outsourcing components of R&D projects (4).

2.1.3 The Changing Model of Drug Development

There continues to be a global demand for new medicines, both to treat conditions for which there are currently no effective drug therapies, and to improve the management of diseases for which medicines are available but have limited efficacy and/or cause unwanted side effects. There is also a global imbalance in medical and drug development research—approximately 90% of the global health research resources are spent in the diseases (such as cardiovascular and obesity-related) that affect only 10% of the world's population (46).

Traditionally the majority of new medicines were discovered and developed by pharmaceutical companies based in the USA and Western Europe that had the in-house expertise and financial resources from their products already on the market (6, 47). Since the 1970s, the 'holy grail' of pharmaceutical companies has been the identification of a blockbuster drug, defined as a medicine that can achieve peak global sales over USD1,000 million (48). However, the value of returns from new pharmaceuticals is highly skewed and only a third generate sufficient revenue to recoup the average industry R&D costs (49).

Despite the rapid rise in R&D spend over recent years many pharmaceutical companies are not enjoying high earnings (4) and there are indications that industry returns have decreased (5). This decline is primarily due to failure to continue to discover successful new medicines, pricing pressures including increasing generic competition and rising R&D costs (3, 4, 50). It has been suggested (51) that the more disciplined and analytical approach to R&D, which included companies benchmarking their outputs with others in the industry, stifled innovation and resulted in drug companies becoming more similar to each other instead of capitalising on their unique skills and expertise. This more regimented approach has not been successful and a return to the industry investing in the higher risk research that produced innovative drugs is required (52). Companies with unique products have achieved higher company valuations than those marketing blockbuster 'me-too' drugs, underlining the value of innovative medicines (3).

It is widely accepted that the traditional international model of drug development is undergoing rapid change in an attempt to turnaround recent declining profitability. The industry is moving from its traditional closed approach to a more open model, becoming more fragmented with a wider range of contributing organisations in an attempt to increase innovation and control the rising costs of drug

development (6, 47, 53, 54). In addition, the geographic base of the industry is broadening with Asia–Pacific developing an emerging industry from generic manufacture to drug innovation (55).

Company mergers have been undertaken to realise synergies, gain access to innovative compounds and specialised drug development services, improve R&D efficiency and to increase speed to market and sales results (1, 56). The pharmaceutical industry is attempting to procure inventiveness by forming alliances and partnerships with innovative academic researchers (2, 51), especially those that can offer expertise in designing molecules of the desired therapeutic class or specific drug candidates (23). It has been calculated that for the industry to maintain its historic double-digit growth and rates of return it will need to significantly increase its discovery output. The current industry average of five new lead compounds per year per 1,000 discovery employees needs to be increased to 14 and have a greater focus on novel R&D (57).

The advantages that academia can offer the pharmaceutical industry include having a creative and innovative culture, being a source of intellectual capital, being less expensive due to lower overheads, having a broad range of expertise allowing multi-disciplinary collaborations, and being able to take risks and approaches not possible within the constraints of a pharmaceutical company (58). The industry is expanding past the blockbuster approach to developing niche innovative medicines. These may not provide a high volume of sales but which can still be highly profitable with lower R&D costs, high prices and targeted marketing efforts. In addition, medicines for orphan drug indications may benefit from incentives such as market exclusivity, regulatory assistance and reduced fees (6, 38).

The pharmaceutical industry can work with other organisations to gain access to the knowledge sources to complement their internal R&D expertise and to build the capabilities required. These relationships can include partnerships, alliances, collaborations and virtual networks with the external organisations. The knowledge sharing that occurs may result in the sum of the organisation's knowledge being greater than that of its individual components (59). A study of the top 10 global pharmaceutical companies found that their rate of alliance formation increased from an average of 6.3 per company in 1990 to 13.2 in 2005 (23).

There are many economic, organisational, cultural, ethical and political issues associated with forming and maintaining partnering and alliance relationships that need to be appreciated by all parties (60). An effective relationship depends on each party understanding the needs and culture of the other party, respecting the unique expertise that each contributes, and agreement to meet the common expectations and goals set (61). They must invest time to understand each other's knowledge so that they can recognise its potential use. The sharing of complementary knowledge can provide access to missing competencies and enhance the performance of both organisations (23, 62).

Small drug development companies, universities and other public research institutions usually do not have the infrastructure, expertise or financial reserves to complete the development of their compounds. Therefore, forming an alliance with a multinational pharmaceutical company can be an attractive option (6, 54, 62). There are successful scientist-entrepreneurs who can bring benefits to both parties by being allowed to pursue their private commercial interests while keeping their faculty appointments (53).

2.1.4 New Zealand's Drug Development Industry

New Zealand is a small country in the South Pacific, some distance from the twin hubs of the global pharmaceutical industry, located in Europe and the USA. It is of similar geographical size to the United Kingdom (UK) and Japan but with a population of only 4.3 million, and its drug development industry is limited compared with other developed countries. In 2007, there were 12 NZ-discovered compounds in clinical development, which was an increase from two compounds in 2001. This rise is considered to be at least partly due to the increase in government research funding for drug discovery and development from NZD16.3 million in 2000/2001 to NZD46.1 million in 2006/2007 (63). In 2009, the NZ drug development sector employed almost 900 people and generated revenues of NZD200 million, providing a positive return on investment for government funding (64). Further support has come from NZ's Ministry of Research, Science and Technology (MoRST), which specified that 'the government will continue to support best biomedical and drug development research' (14). In early 2011, MoRST was restructured to provide a new Ministry of Science and Innovation (MSI) as part of a government focus on the economic growth potential of these two areas.

Despite this support, NZ's levels of both government and business investment in R&D are low compared with Organization for Economic Co-operation and Development (OECD) averages. In the 2005/6 financial year, government-financed gross expenditure on R&D as a percentage of GDP was 0.50% compared with the total OECD average of 0.67% (65), while business enterprise R&D investment at 0.49% in 2002 was approximately a third of the OECD average of 1.6% (66). While NZ faces additional challenges due to its remoteness from major markets and knowledge centres, its society values resourcefulness and creativity. This has allowed it to develop a culture for innovation and niche areas of research excellence (13, 67). Furthermore, NZ's small pharmaceutical market size may not make it an attractive destination for pharmaceutical companies considering locations for R&D investments.

New Zealand's drug development industry is mostly founded on its academic research in science and medicine. This research has lead to a number of spin-out NZ drug development companies, that obtained funding from government, private and public investors (63). Some of these companies (e.g., Antipodean, Neuren, CoDa, Proacta, Genesis and Living Cell Technologies) have undertaken preclinical

and clinical development with varying success. Table 2 summarises the status of compounds that have originated from NZ research and the companies that have been involved in their development. The data in this table have been obtained from NZBio's SIGHT Report (63) and supplemented with searches of the USA clinical trials registry (68) and company websites as indicated in the References column of the table. Note that information on the earlier compounds in development is limited due to websites no longer being available, or companies merging or taken over by others, or being unwilling to publicise negative results.

The Auckland Cancer Society Research Centre (ACSRC) has produced at least six cancer drugs that have reached clinical trials. One of these, DMXAA/ASA404, was out-licensed at the preclinical stage to Antisoma, a British biotechnology company, and has earned the University of Auckland NZD10 million to date. It was sub-licensed from Antisoma to Novartis in 2008 for USD800 million and attainment of development milestones would have produced further payments to NZ (63). However, the large phase III trial failed its primary endpoint and Novartis discontinued its development in 2010 (3, 69). DMXAA/ASA404 is now being investigated as part of combination therapy, sponsored by The Swiss Group for Clinical Cancer Research (68). Industrial Research LTD (IRL), a NZ Crown Research Institute (CRI), has earned a similar amount to that generated by DMXAA/ASA404 from Fosodine and BCX-4208 through its licensing deals with BioCryst, a USA company (63).

As well as the innovative compounds listed in Table 2, two other NZ entities are developing known medicines in novel formulations. Although the product is marketed through retail pharmacy, AFT Pharmaceuticals is conducting clinical trials on its paracetamol plus ibuprofen tablet to obtain data on its use for pain management (63, 70). The University of Auckland's Clinical Trials Research Unit (CTRU), with support from the Wellcome Trust and Dr Reddy's, an Indian pharmaceutical company, is conducting a clinical trial on a polypill. This is a unique formulation that contains aspirin and agents to lower blood pressure and cholesterol in one tablet (71).

Table 2 – New Zealand Drug Development Compounds and Companies

NZ company or originator	Compound	Indication	00	01	02	03	04	05	06	07	08	09	10	11	Status	Other reference
Antipodean Pharma-ceuticals Ltd	Mito-quinone (MitoQ)	Liver disease						Ph I	Ph II	Ph II					Positive Ph IIa; Ph IIb study terminated. Topical product in development.	(72)
Anzamune NZ Ltd (CMP Therapeutics UK Ltd)	Chitin micro-particles	Allergic disorders								Ph II	Ph II				No clinical results or updates available.	(73)
CoDa Therapeutics Inc	Nexagon	Wound healing (eye and ulcers)									Ph I	Ph IIa	Ph IIa	Ph IIb	In Ph IIb for venous leg ulcers; Further Ph II studies planned for eye wounds and diabetic foot ulcers.	(74)
Genesis R&D	AVAC	Eczema, asthma			Ph I	Ph II	Ph II								Both compounds failed Ph II; Genesis suspended operations in May 2010.	(75)
	PVAC	Psoriasis	Ph I	Ph II	Ph II											

Table 2 – New Zealand Drug Development Compounds and Companies *(continued)*

NZ company or originator	Compound	Indication	00	01	02	03	04	05	06	07	08	09	10	11	Status	Other reference
Innate Therapeutics (previously Virionyx Corporation)	PEHRG-214	AIDS			Ph I	Ph I	Ph I	Ph I	Ph I	Ph II	Ph II	Ph II			Study discontinued due to poor recruitment.	(76)
	MIS416	Multiple Sclerosis											Ph IIa	Ph IIa	Due for completion 2012.	
Industrial Research Ltd (IRL)	Fodosine	Lymph-oma and leuk-aemia							Ph I	Ph I	Ph II	Ph II	Ph II	Ph II	Licensed to BioCryst and Mundipharma. Ph II trial ongoing but not recruiting.	(77, 78)
	BCX-4208	Psoriasis, trans-plant rejection						Ph I	Ph II	Ph II	Ph II	Ph II	Ph II	Ph II	Licensed to BioCryst; Failed Ph II in psoriasis. In Ph II for gout.	
Living Cell Technologies (previously Diatranz)	DiabeCell	Diabetes Type 1								Ph I/II	Ph I/II	Ph I/II; Ph IIb	Ph I/II; Ph IIb	Ph IIb	First study in Russia completed 2010; NZ study Ph IIb started 2009.	(79)
Migco	MGX-008	Migraine													Completed some clinical trials but no information available.	(80)

Table 2 – New Zealand Drug Development Compounds and Companies *(continued)*

NZ company or originator	Compound	Indication	00	01	02	03	04	05	06	07	08	09	10	11	Status	Other reference
Neuren Pharma-ceuticals Ltd	Gly-promate	Stroke					Ph I	Ph II	Ph II	Ph III	Ph III				Programme has stalled, no data available.	(81)
	NNZ-2566	Neuro-protect-ion								Ph I	Ph I	Ph II	Ph II	Ph II	In FDA fast track programme.	
Pathway Therapeutics	PWT-33597	Cancer												Ph I	Phase I study started in the USA.	(82)
Proacta Inc	PR-104	Cancer - Acute Leuka-emia							Ph I	Ph I	Ph I	Ph I/II	Ph I/II	Ph I/II	Phase I/II studies ongoing.	(83, 84)
Protemix	Laszarin	Diabetes					Ph I	Ph II	Ph II	Ph II	Ph II				Company was placed in liquidation in 2010.	(85)
University of Auckland	Amsacrine	Leuk-aemia													Marketed as second line therapy by Parke Davis. No longer available in USA but is in Canada.	

Table 2 – New Zealand Drug Development Compounds and Companies *(continued)*

NZ company or originator	Compound	Indication	00	01	02	03	04	05	06	07	08	09	10	11	Status	Other reference
University of Auckland (ACSRC)	DMXAA (ASA404, Vadimezan)	Non-small cell lung cancer	Ph I			Ph I	Ph I and Ph II	Ph II	Ph II	Ph II	Ph I/II	Ph I/II	Ph III	Ph I/II	Out-licensed to Antisoma; and then to Novartis. Ph III trial failed its primary endpoint.	(69);(68)
	DACA (XR-5000)	Cancer	Ph I												No information available.	(86)
	XR-11576	Cancer			Ph I	Ph I	Ph I								Licensed to Xenova. Ph I trial found unacceptable toxicity.	(86, 87)
	MLN-944 (XR-5944)	Cancer					Ph I	Ph I	Ph I						Licensed to Millenium and Xenova. Ph I showed unpredictable pharmacokinetics.	(88)
	CI-1033 (caner-tinib)	Cancer			Ph I/II	Ph I/II	Ph I/II	Ph I/II	Ph I/II	Ph I/II					Licensed to Pfizer; discontinued after Ph II.	
Total number of development compounds each year			**3**	**2**	**6**	**5**	**8**	**8**	**10**	**12**	**11**	**8**	**8**	**9**		

2.2 Evaluation of Expertise

2.2.1 Introduction

The process of developing a new medicine requires a vast amount of expertise (89, 90), which is generally held in a distributed knowledge system that spans across departments, companies and even countries (33). This dispersed state of knowledge means that knowledge sharing is imperative so that key members of the development team can understand the major problems encountered by others and that co-ordination of activities is achieved (90). More specialised knowledge may need to be imported by the group, and innovation can occur when different combinations of experts examine data or have a problem to solve (89) or knowledge is acquired from novel sources (91).

2.2.2 Expertise

Expertise is the skills and knowledge that a person has that distinguishes them from less experienced people. There are several methods of assessing expertise, or whether someone is an expert in their field. The number of years of job-related experience can be a surrogate for expertise based on the premise that a person could not function as an expert if they were incompetent (92). It has been suggested that because of the complications of drug development and low chances of success, people working in the pharmaceutical/biotechnology industry need at least 10,000 hours (i.e., 5 years) in order to become competent in their area of expertise (93).

However, not everyone who has years of experience and holds a senior position becomes an expert. Expertise requires more than knowledge and experience, it includes applying the facts to a particular situation. Other markers of expertise are recognition by certification from their professional organisation and identification of experts by asking a group of their peers (92).

Other skills an expert should have include intra-person reliability so that their decisions are internally consistent; agreement between experts in the same field; and the ability to make fine discrimination between similar cases. Behavioural characteristics of experts have also been studied, however the required characteristics are dependent on the type of expert being assessed and may also be characteristics of some non-experts.

Some researchers have developed a case-study based test for expertise using a ratio of discrimination to inconsistency, however this test needs to be adapted to the individual's specific area of expertise (92). Even experts are not always accurate when asked to make judgements outside their knowledge domain. Complex problems can be addressed by a team of people with expertise in different areas using their combined expertise, which may be supplemented by expertise from other sources (e.g., academic literature) (94).

2.2.3 Knowledge Management

Knowledge management encompasses the knowledge generated and shared by an organisation's employees. It focuses on using knowledge assets to meet the organisation's goals and objectives (95-98). The uniqueness of a firm's knowledge is important for developing and maintaining its competitive advantage (97). External knowledge is usually more novel than that from inside an organisation, and R&D professionals need to constantly update their knowledge in order to be able to facilitate innovation (90, 99-101).

A successful organisation builds its expertise by obtaining knowledge and skills through collaborations, partnerships and alliances (61). These are integrated into the organisation, and then employed to assist the organisation to respond quickly and innovatively to the changing environment (102). The decision to build a new capability is often due to individuals recognising and responding to a change in the organisation's environment (103). Knowledge sharing may result in an immediate benefit due to use of new knowledge, or the knowledge may be accumulated and used in the future (99). However to maintain a competitive edge, organisations must effectively manage their knowledge and leverage it for success (95).

The focus of knowledge management has evolved from an organisation just concentrating on its internal resources and information to also integrating externally with partners, regulators, customers, investors, analysts and any other entities that can influence the environment in which the organisation operates. This has meant that an organisation must support and encourage a collaborative culture in order to share knowledge and work with external agencies in a productive fashion. Employees in an organisation may work more closely with those in another organisation than within their own (104). Since knowledge workers own their means of production using acquired information, they are therefore mobile, and an organisation should actively seek to retain its intellectual assets (95, 105).

Knowledge can be classified as explicit or tacit. Explicit knowledge can be written down and therefore codified and is available from books, journals, conferences, manuals and so forth. Tacit, or non-codified information, includes personal know-how that is not available in a formal way. It is not observable, and is available through person-to-person communication (90). There needs to be connection between those who need to acquire knowledge and those who posses it, as well as active participation in the knowledge sharing process (89, 106). Knowledge sharing can be initiated by the person who desires the knowledge seeking it out, or by the person with the knowledge, or it may occur by information pooling. Knowledge transfer or transactions can occur in a structured setting (e.g., project group meetings, conferences, telephone/email conversations, electronic or verbal discussion forums) but can also happen on an informal basis or even unintentionally (e.g., chance

meetings, fortuitous introductions) (89). Effective knowledge sharing requires the person to identify the knowledge that they lack and who to approach to find the information; or for the person with the information to provide new ideas and knowledge to someone who may benefit from it. Those who receive the information can choose to analyse it and apply it to their own situation or problem that they are attempting to solve (98). This application of knowledge to new circumstances does not hinder its original use, but is a spillover benefit of the information (107).

Organisations must actively seek information that may be valuable to their development projects including utilising non-traditional sources (108) and may include both local and more distant searches for the information (91). An organisation's ability to innovate therefore depends on effective, efficient and fast accumulation of useful knowledge, which may require searching outside pre-existing experiences if the desired information is not found (91). Systematic knowledge sharing is more effective than traditional knowledge sharing that could depend more on random luck in finding the right person to ask, a tendency to search only in the local environment and could be fragmented (109).

Knowledge sharing can lead to increased employee satisfaction, motivation and performance (106). Knowledge transfer that provides an innovative or interesting result leads to higher levels of satisfaction and greater readiness for further knowledge sharing (110). Organisations with a culture that encourages open communication, a high level of trust amongst its individuals and promotes innovation and decision-making also have high knowledge transfer environments (111, 112). Other factors that influence the culture of sharing knowledge in an organisation are communication channels providing mechanisms for sharing knowledge, management support and a reward system linked to the sharing of knowledge (106, 113). Employee identification with and attachment to the organisation can affect their knowledge sharing behaviours and therefore the quality of the employment relationship is critical (113). An employee should be encouraged to transfer their personal knowledge into the organisation's knowledge so that others and therefore the organisation as a whole can benefit from it (98).

Once new knowledge is acquired by someone in an organisation it needs to be transferred to others in the organisation in order to maximise the potential benefit of the knowledge. Organisations can use a variety of mechanisms to disseminate knowledge: formal documents, training programmes, group meetings and company publications. In larger organisations this wider sharing of information may require more effort and it may be time-consuming to find the right person who has the knowledge desired. In smaller organisations it is easier to identify the person likely to hold the knowledge and to obtain it; this is due to the closer personal ties between the individuals and more frequent interactions between the transmitter and receiver of the information (90). Knowledge

sharing is becoming easier and more feasible as communication technologies advance (95). Therefore, the apparent preference for geographical proximity of organisations sharing knowledge may become less important in the future and this may have implications for cluster development (114).

Barriers to knowledge sharing include the parties being geographically dispersed, culturally different, educationally diverse, concerned that their knowledge is inaccurate or substandard, and having time constraints and competing deadlines. Therefore, a person with potentially useful knowledge may not have the time to invest in knowledge sharing, and fear that others may not reciprocate and share their knowledge as well. These barriers can lead to knowledge, either intentionally or accidentally, not being shared effectively (106).

2.2.4 Innovative Behaviours

Innovation depends on interactive relationships and active knowledge transfer between different knowledge sources (100). Innovation rarely occurs in isolation and the most influential high-value inventions have been produced by at least two people (3). Innovation has been described as "re-creating the world according to a particular vision or ideal" (98) and as "a new match between and a need and a solution" (3). There are two types of pharmaceutical innovation —incremental innovation, which can be defined as an innovation that adds new features to an existing product or class (e.g., as once-a-day administration or fewer adverse effects compared with other medicines of the same therapeutic class); and radical innovation that is a result of new technology and may result in a new market opportunity (90, 112).

Measuring innovative performance objectively is very difficult. Measures such as the number of patents registered or scientific papers published can be affected by the type of organisation or industry concerned, which makes comparing results problematic. An assessment of two medical biotechnology areas, Brisbane in Australia and Gothenburg in Sweden, collected the number of published papers, patents and firm start-ups as measurable outcomes of expertise (115).

Thompson and Heron (113) used the 'innovator' subscale from a longer 34-item instrument that covered innovator attitudes and behaviours that was validated by Ettlie and O'Keefe (116). The questions on the innovator subscale are a measure of innovative behaviour in organisations and cover the following aspects: having new ideas, developing contacts with external experts, making time to work on ideas and projects, solving problems that caused others difficulty, project planning, innovative output, teamwork and communication.

Analysts of the pharmaceutical industry have been extensively debating whether the level of innovation seen until the mid-1990s has been maintained (117, 118). One of the problems with this

analysis is how to measure innovation because there is no universally accepted definition of drug innovation. Pharmaceutical innovation is also difficult to quantify because its price is not dictated purely by how much the consumer is willing to pay, therefore sales and profit are not good indicators (119). The analysis is further complicated because the time from a discovery innovation until marketing may be more than 10 years (118). Caprino and Russo (120) proposed three main factors that determine the innovative value of a drug: its potential to decrease mortality/morbidity/disability; its capacity to reduce the social cost of the disease; and its ability to enhance social and economic progress. Morgan (121) suggested that a drug could be considered a pharmaceutical innovation only if it meets "otherwise unmet or inadequately met healthcare needs" (p. E5). Other direct measures consider the novelty of the compound (e.g., of its molecular structure, biological target or pharmacological action) or its additional health value to cost ratio compared with current therapies. Indirect measures of pharmaceutical innovation include number of scientists employed, the levels of public and private funding and number of patents filed (119).

Other researchers have suggested that pharmaceutical innovation for a given disease can be measured by the number of distinct drug treatment options available and the number of related articles published in relevant scientific journals (122). Most pharmaceutical companies take a more pragmatic approach and consider a medicine to be innovative if it is successful in the marketplace (50). Pharmaceutical innovation is time-dependent because a new medicine may be innovative when first available however this could decrease if further advances are made in the same therapeutic area (120, 121). Therefore, there is reduced scope for innovation in therapeutic areas where existing treatments already provide good levels of efficacy and safety (121).

The incentive to innovate is driven by the high expected profits from an innovative medicine (123). A 2001 study (48) analysed the factors driving technical innovation in the pharmaceutical industry and found that they included: external science/technology 'push' and market 'pull'; luck/serendipity plus systematic development; organisational expertise and corporate technology traditions; companies that already have shown innovation; and even geography (the majority of innovations have been from the USA, Germany, Switzerland, the UK and France). Innovation depends on interactive relationships between different sources of knowledge, such as universities and the pharmaceutical industry, and intense knowledge transfer in both directions (60). The factors that influence the innovation process in drug development include the science base, government policies, funding, universities, intellectual property rights, regulatory systems, industry culture, and linkages and clustering of the various organisations (46). Because the pharmaceutical industry is global, reduced spending on innovation and so fewer innovative medicines will affect industry profitability but also may result in harm to patients (123).

The industry also faces other factors such as pricing, increasing competition, market fragmentation, and loss of revenue as products come off-patent, that limit its profit and therefore its spend on R&D. Companies may also be less interested in developing innovative products because of the higher hurdles to overcome in terms of investment and increased risk (118). Some companies have found that incremental innovations such as exploring the use of an existing product in a new indication (i.e., repositioning), improved formulations and alternative delivery methods are a better investment strategy and can result in substantial health benefits (42, 117, 118).

A major market failure for the pharmaceutical industry is the absence of incentives to develop some medicines that would have important health and social benefits, especially for developing nations (124). The USA and European Union (EU) have introduced incentives, such as protocol assistance, market exclusivity and fee waivers, to encourage R&D into uncommon diseases (125). This has resulted in new medicines for unusual diseases, however there is a tendency to focus on diseases that are more likely to afflict developed countries and require long-term treatment, rather than diseases of developing nations (6).

2.2.5 Linking Expertise, Knowledge and Innovation: Cluster Development

Expertise is the skills and knowledge a person or organisation has attained (92). The network of people working together on a drug development project exchange information with each other and obtain external knowledge through collaborations and alliances (61). This knowledge transfer and sharing is positively associated with innovative performance (113). Other factors, such as strong links between academia and industry, supportive infrastructure and availability of venture capital, may promote the development of an industry spark into a high technology cluster (126).

Figure 1 illustrates these links between expertise, knowledge sharing and innovation in a network of people collaborating on a drug development project. External knowledge is acquired by the network, shared between the network organisations and can result in innovation outputs.

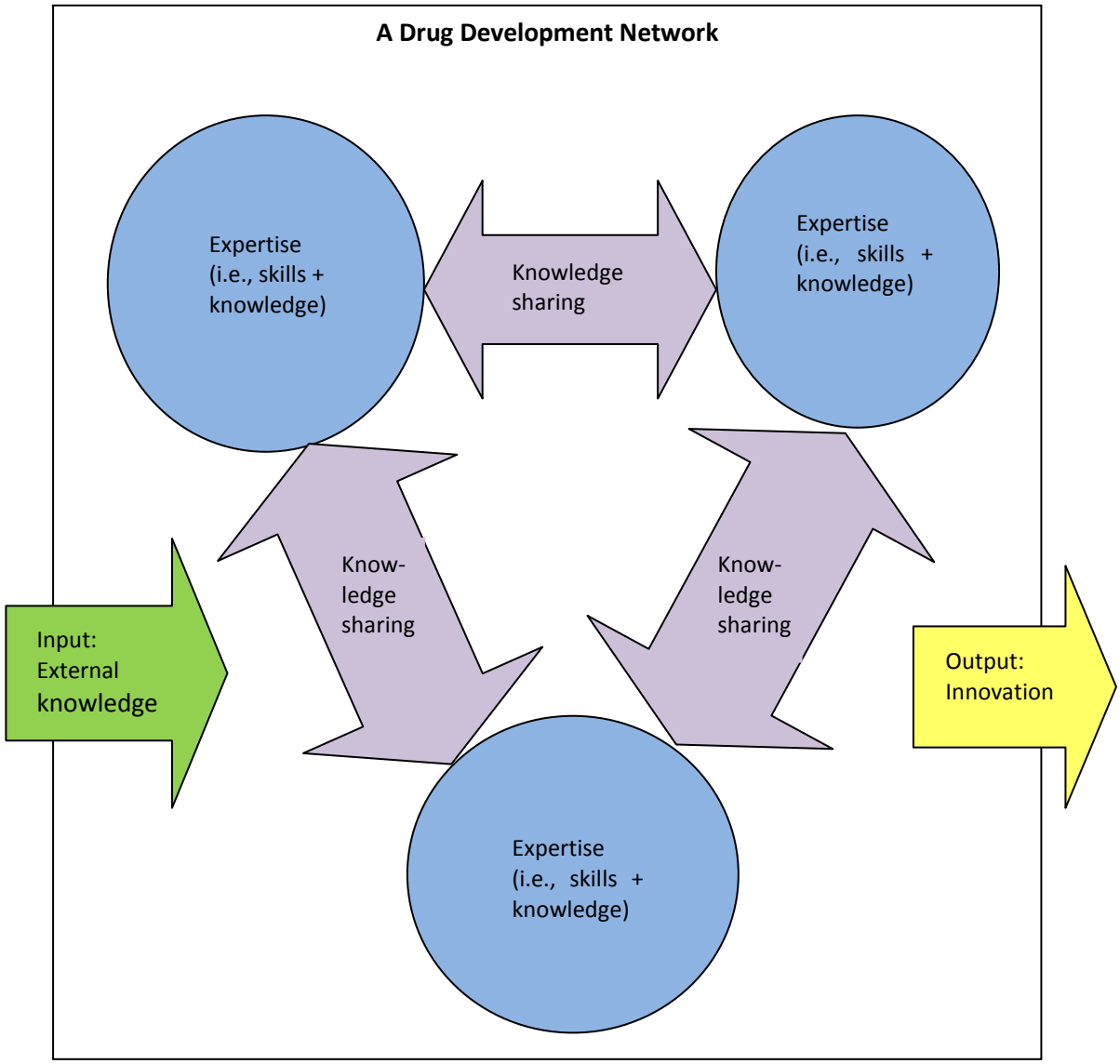

Figure 1 – Relationship between Expertise, Knowledge Sharing and Innovation in a Drug Development Network

There is increasing interest in creating clusters (also known as hubs or hotspots) as the basis of a knowledge-based industry and a potential mechanism for economic growth of their region or country (127). Industry clusters can be described as "geographical concentrations of interrelated individuals, firms and institutions that are both competing and collaborating by accumulating know how and intellectual capital" (128) (p.24). The group of organisations in a cluster have diverse and dense ties with each other, and are open to new ideas (129). Therefore, several of the drug development networks as illustrated in Figure 1 would constitute a cluster.

A successful cluster is a well-functioning community with shared perceptions, and a united purpose and understanding (129). There are proposed benefits from industry and universities being located close to each such as cross-fertilisation of knowledge whereby academics can gain industry experience and industry gains access to university researchers (130). Linkages between firms and universities allow greater knowledge spillovers and a higher net social benefit due to less duplication of effort, leveraging of specific expertise and more efficient use of assets (131). Universities, government laboratories and technology transfer offices are common features of life science industry clusters of all sizes (114), however most policy initiatives to create biotechnology hotspots have been ineffective (127). The difficulties in starting a cluster from the initial spark and then successfully growing it stem from the unique characteristics of each area and the array of factors that influence it (127).

It has been proposed that successful regional cluster development requires effective co-operation between universities, industry and government and the interrelationships between these three organisations have been described as a Triple Helix (126). The characteristics of a given region, including any dominance of one or two of the three actors at a given time, may influence the profile of the triple helix model in operation. A university's contribution to a regional triple helix is its provision of 'star scientists' and as a source of skilled labour, while its significance as a source of new technology has been debated. Research in Oxfordshire in the UK showed that the industry viewed the universities as being only of medium importance as a source of information and provided conferences, competitors, collaborators and the internet as more highly rated sources. The same research suggested that while the triple helix of university, industry and local government is important, national government support and the availability of funding sources play a very important role (126).

The tripod model for innovation (127) suggests that three critical factors are essential for a region to successfully grow a technology-based industry: knowledge creation, commercialisation and retention. The presence of knowledge creators such as universities and research institutes are mandatory but in themselves will be insufficient to the development of a biotechnology cluster or hotspot if commercialisation and retention of knowledge are not available in the region. The features of innovative research, entrepreneurship, venture capital, skilled labour and access to related industries are required to support these key factors. Significant long-term government financial input and leadership is required from the early stages of a spark, which can take more than a decade to develop into a cluster or hotspot. To facilitate communication and develop closer relationships with entrepreneurs, venture capitalists may prefer to invest locally. Experienced people joining the cluster from related industries can be an important source of knowledge, entrepreneurship and managerial

skills. An entrepreneurial culture that encourages innovation, is open to new ideas and is tolerant of business failure is an asset to cluster development (127).

Many factors influence whether and how a high technology sector develops from an initial spark. The well-known USA biotechnology centres (e.g., San Francisco and Boston) have arisen in locations that have leading academic institutions and the early companies were typically founded by their scientists; therefore a close association between the industry and academia was unavoidable. The development of the pharmaceutical industry of Basel in Switzerland includes several very successful companies (e.g., Roche and Novartis) and was based on technology from a pre-existing chemical industry (127). In Scotland, the biotechnology clusters in Dundee and Edinburgh are a result of formal knowledge transfer between industry and academia, whereby industry can acquire and exploit university patents. However, in the Scandinavian clusters such as Stockholm and Medicon Valley, the existence of supportive infrastructure provided by public research organisations was a dominant factor in the location of their development. The high employee turnover associated with the USA clusters, which contributes to knowledge transfer between organisations, is not generally seen in Europe (130).

Research into the life sciences cluster development in Canada's three largest and three smaller city regions provided evidence that while public sector research institutes are an essential component of a knowledge-based life science cluster they are not always enough to catalyse the cluster's development. The other factors that were instrumental in the development cluster varied but included a local lead or anchor firm, availability of venture capital and the presence of an established pharmaceutical company. In addition, each region had at least one representative organisation to promote the industry on a local and national level, provide information to its members and to facilitate networking between industry, research institutions and government (114).

There are early stage biotechnology centres in Shanghai (China) and Bangalore (India) that are based on their local expertise for low cost manufacturing and information technology. However, their development so far has been hampered by a lack of connections between research institutes and firms, and by insufficient venture capital and ability to commercialise their research (107).

2.3 Enablers and Barriers of a Drug Development Industry

2.3.1 Introduction

The enablers and barriers to the development of an industry are, generally, the government policies employed and the effects of those policies. Other factors that may affect industry development are country specific issues, regional-level policies and the activities of multinational organisations. Organisations, such as the World Health Organization (WHO), have policies to encourage the global

industry to develop pharmaceuticals to treat diseases that are predominantly a concern of developing countries (6).

The literature review focussed on identifying publications relevant to the government policies that countries employ to support their drug development industry. From this review, a framework was developed to categorise the various policies of different countries. The framework encompasses the range of different national policy components that could be used to support a drug development industry. The selection and mix of these policy components varies by country and the policy options that each country considers while developing its overall policy are discussed in the next section. The countries included in this research were developed countries with an established drug development industry and developing countries, mainly in the Asia–Pacific region.

The framework includes the range of policies and strategies available to influence a country's drug development industry. These include government investment policies; pharmaceutical price control policies; legal policies; policies to encourage foreign and private investment; and policies to support expertise, knowledge management and innovation (6, 132-135).

These are summarised in Table 3 and discussed in the next sub-sections.

Table 3 – Summary of Policy Types

Policy type	Details	Examples
Government investment	Widespread throughout the developed world, and especially effective in industry development in the USA and Western Europe.	- Medical research in academic and research institutes - Funding specific programmes - Subsidising non-commercially viable research
Pharmaceutical price control	Conflicting data on whether price control policies affect the pharmaceutical industry R&D investment in that country. Some countries allow premium prices for innovative products and have cost-containment measures on older medicines.	Options include: - price-setting, - reference pricing, - limiting a prescriber's budget, - profit controls - encouragement of generic prescribing and substitution
Legal policies	Stronger regulatory and patent protection may encourage pharmaceutical companies to invest in a country's manufacturing capability and the expertise gained may stimulate local R&D.	- Allowing manufacture of medicines still under patent - Encourage the manufacture of generic medicines for export and own use - Regulation of new medicines and clinical research
Foreign and private investment	Needed where there is insufficient local capital or when foreign investment may also result in the acquisition of new knowledge.	- To obtain funding for specific drug development projects or build manufacturing facilities - Encourage increased business investment in R&D
Expertise, knowledge management and innovation	Support knowledge sharing between organisations and to encourage knowledge transfer, especially from academia to industry. Promotion of a country's specific expertise to obtain contracts from the pharmaceutical industry. Policies to encourage or reward pharmaceutical innovation	- Education: encourage higher education and encourage the return of skilled expatriates - Networking: to promote knowledge sharing and take advantage of knowledge spillovers - Country promotion: to showcase specific drug development expertise - Innovation: encourage research into orphan drug indications, extension of patent protection to compensate for development and regulatory assessment times

Government support of industry has become more business orientated, especially in the provision of regulatory services and economy policy objectives that may conflict with public policy. Government—industry relationships are becoming more complex and span three major sectors: regulatory and health activities covering safety and efficacy controls; social policy activities including pricing and

reimbursement issues; and economic development policy influencing R&D activities (136). Governments can try and subtly influence the industry through tax incentives on R&D and policies on the approval process, patents and pricing (41).

There is a tension between the pharmaceutical industry's requirement to maximise its profit and society's requirement to maximise the health of its members, and policy-makers need to balance these competing needs (137). Through its innovations, the industry has contributed to decreased mortality and increased quality of life, while also experiencing some outstanding commercial successes (12, 138). The pharmaceutical industry is unique because the products can save or improve the quality of people's lives, giving an ethical dimension to any policy debate, and because the end-user (i.e., the patient) often does not select the product that they use (138). Most countries struggle to balance supporting R&D, while meeting the healthcare demands of its citizens within the budgetary constraints imposed. This dichotomy of health and economic policy objectives has not been resolved and each country attempts to reconcile these objectives in its own way (139). Therefore, the policy mix employed by each country is influenced by its individual responsibilities (e.g., specific health issues), characteristics (e.g., population demographics), public expectations, funding availability and even the activities of stakeholder organisations (140, 141).

For many countries, supporting a drug development industry is under the jurisdiction of a different ministry from that responsible for health policy, and so there is no coherence of policies that could affect the industry (142). However, the health policies of some countries (e.g., Australia) have included a pharmaceutical policy supporting the research and development of medicines and including economic objectives (136).

2.3.2 Government Investment Policies

Direct government funding of drug development through public funding, support of universities and research institutes, and grants are important policies to support the industry. However, engaging the private sector may bring additional advantages in terms of efficiency, innovation and competitiveness (119). Originally R&D tax credits and incentives were placed in this category because they are a form of government investment policy but they fit better into the foreign and private investment policy.

2.3.3 Pharmaceutical Price Control Policies

Pharmaceutical price control policies include global budgets that cap a country's spending, prescriber's budgets, profit controls, reference pricing and encouragement of generic prescribing and substitution and these may restrict access to certain medicines (143). However, countries without price controls may also have reduced access to pharmaceuticals due to lack of affordability or availability (132, 133). A study evaluated the pharmaceutical regulations from 1999–2004 in 19 OECD

countries—Australia, Canada, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Japan, the Netherlands, NZ, Norway, Portugal, Spain, Sweden, Turkey, the UK and the USA. Direct price controls were the most common and most effective mechanism of regulation, with policies supporting increased generic use becoming popular during the study period. At the start of the study, only NZ had global budgets as a policy for controlling pharmaceutical costs, however five more countries—France, Hungary, Italy, Spain and the UK—adopted this mechanism during the study (143).

There is evidence that reducing prices for pharmaceuticals reduces the strength and innovation of the country's pharmaceutical industry (53, 143, 144). Vernon (145) suggests that there appears to be a direct relationship between a country's pharmaceutical prices and pharmaceutical industry R&D investment in that country. The reasons for this include lower profitability, especially from newer products, and lagged cash-flow resulting in reduced investment in R&D (145). Civan and Malhoney (122) found that the number of medicines in the development pipeline for a given disease is strongly and positively related to the price of existing pharmaceuticals for treating that disease. Critics of price control systems that exist in countries such as Canada and Australia, argue that they stifle investment and innovation and may lead to multinational companies preferring to locate R&D and other services in other countries. The UK appears to be an exception because it has pharmaceutical price controls but continues to be competitive in pharmaceutical innovation (54). The pharmaceutical industry is global and if price controls were introduced in the USA it is anticipated that innovations may be reduced and so adversely affect both USA as well as European citizens (123). It has been calculated that pharmaceutical price controls in the EU from 1986 to 2004 resulted in USD5 billion (1985 values) lower spending on R&D, 1,680 fewer research jobs and 46 forgone new medicines. The researchers suggested that if the same restrictions had been in place in the USA, USD12.7 billion less would have been invested in R&D with 117 fewer new medicines and 4,368 fewer research jobs (146). Therefore, pharmaceutical policies involve a trade-off between price controls today and the possibility of fewer innovative medicines tomorrow (143).

Others propose that the pricing of pharmaceuticals in a country does not discourage the industry from investing there, because it takes a global perspective and therefore can conduct development research in any country that meets its regulatory requirements from where it expects to obtain its premium sales (123, 144, 147). This is supported by a study on pharmaceutical R&D in British Columbia (148) that found that the initiation of reference pricing policies did not result in reduced R&D investment. The researchers concluded that the reason for this was that the costs and benefits from the pharmaceutical company's investment in local R&D was a business decision in its own right and independent of a local pricing policy. The study's authors postulate that the government policies that are most likely to affect local R&D investment are those that affect the availability and cost of specialised, and especially academic-based researchers and facilities.

2.3.4 Legal Policies

Legal policies include policies that support the regulation of new medicines and clinical research as well as providing patent protection. Clinical trial applications, assessment of new medicine applications, and changes to existing medicines are the responsibility of a country's Ministry of Health, equivalent government department or agreed regional organisation (e.g., the European Medicines Agency). These organisations adhere to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) that provide the requirements for the regulation of medicines, including Good Clinical Practice (GCP) for clinical research (149).

The impact of the 1995 World Trade Organisation Treaty (WTO), where signatories are required to recognise international patents, will change the industries and policies of these countries because previously they were free to have their own patent laws (133, 144). The WTO Treaty, with its Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), provides 20 years patent protection calculated from the date of patent filing. There is ongoing controversy over whether TRIPS will benefit or hinder developing countries. On one hand, TRIPS may result in pharmaceuticals in developing countries becoming more expensive or not available at all because they will be prevented from making generic copies until the patent has expired. On the other hand, large pharmaceutical companies may invest in manufacturing in developing countries because of the secure patent protection. This investment would bring both economic and technology transfer benefits and may stimulate local R&D into new medicines, especially for diseases neglected by the traditional pharmaceutical industry (150). The Doha Declaration confirmed the rights of countries that are signatories to TRIPS to have some flexibility in their adherence in order to provide essential and affordable medicines to their people (151).

2.3.5 Foreign and Private Investment Policies

These policies may encourage non-government funding for specific drug development projects, for example, building manufacturing facilities. More general measures such as R&D tax incentives can stimulate R&D, particularly in diseases affecting a limited population. However, tax credits that obtain value only when the company earns taxable profits may be of limited value for companies operating in small markets (152).

2.3.6 Expertise, Knowledge Management and Innovation Policies

Other factors that could affect the innovation and success of a country's drug development industry include the knowledge and interactional behaviours of its human resource (153). Efficient knowledge acquisition and innovation is enhanced with the clustering of firms working in related research fields.

The collaborations and alliances formed result in the partners sharing information more readily and all benefit from the collective learning (154). Continuation of competent knowledge transfer can occur when some of the researchers relocate to another region or country. Policies to support knowledge management include maintaining contact with talented expatriates and even using their new networks to expand the knowledge and expertise base (155). These policies to improve knowledge transfer and increase the supply of skilled labour for problem-orientated research are increasingly being supported by public funding (130).

2.3.7 New Zealand

This section on policies that have affected NZ's drug development industry is divided into several sub-sections.

2.3.7.1 New Zealand government agencies affecting its drug development industry and their administration

Until February 2011 NZ had three ministries investing in its local drug discovery and development industry: the Ministry of Research, Science and Technology (MoRST), which became part of the new Ministry of Science and Innovation (MSI) formed in November 2010; the Ministry of Economic Development (MED); and the Ministry of Education (MoE). MSI/MoRST has the main responsibility for research policy and investments, while MED and MoE play secondary roles in research direction and funding but may also contribute to NZ's policy from a business or education perspective. In addition, the Ministry of Health (MoH) provides policy and strategies for medicine use and access through documents such as Towards a New Zealand Medicines Strategy (156) and Medicines New Zealand (157). The MoH policies encompass the quality, funding and provision of medicines (including drug reimbursement by NZ's Pharmaceuticals Management Agency, PHARMAC) but do not directly support NZ's drug development industry.

MSI is a merger of MoRST and the Foundation for Research, Science and Technology (FRST) and it has retained management of government's investments both directly and through its agencies such as the Health Research Council of New Zealand (HRC) and the Royal Society of New Zealand (RSNZ) (158). The MoE is responsible for the administration and funding of the Centres for Research Excellence Scheme (CoRES) through its Tertiary Education Commission (TEC). The MED administers two investment funds: the New Zealand Australia Biotechnology Partnership Fund (in conjunction with New Zealand Trade and Enterprise—NZTE) and the New Zealand Venture Investment Fund (NZVIF). The HRC's research priorities are investigator-lead research in biomedical science and drug discovery projects, especially those that could improve the health of New Zealanders, especially the priority populations (i.e., Maori, Pacific, people with a disability, children and young people, and older adults) (159).

Figure 2 depicts the NZ government ministries that may influence the country's drug development industry and their funding agencies.

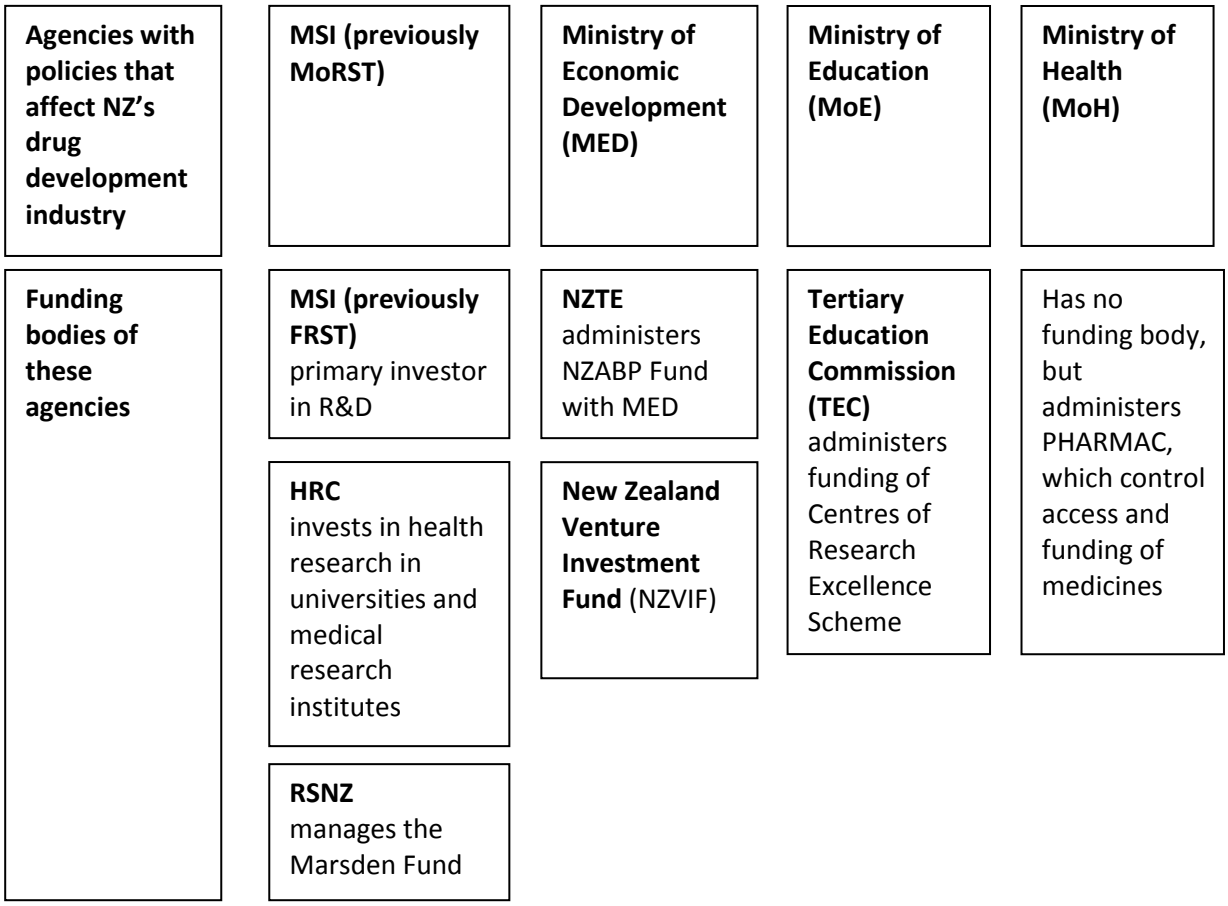

Figure 2 – Landscape of New Zealand Government Ministries and their Funding Agencies

MoRST has regularly released documents covering the Government's policies and strategies for investment in research, science and technology. These documents have consistently stated that the goals of Government investments are to develop a knowledge society, characterised by knowledge-led innovation. MSI was created as part of a government focus on the economic growth potential of science and innovation. It is therefore responsible for advising the Government on NZ's science and innovation systems, and overseeing the Government's science and innovation investments. MSI will also work towards two of the Government's priorities of growing the economy and building a healthier environment and society (160).

Table 4 summarises MoRST policy and strategy documents from 1999 and MSI documents since 2011.

Table 4 – Summary of MoRST's and MSI's Policy Documents

Title of document	Date	Main points
Blueprint for Change (161)	1999	Specifies the government's goals of expanding NZ's knowledge base and technological capability; extending economic and social opportunity; and safeguarding NZ's indigenous biodiversity.
R&D in the Economy (162)	2004	Discusses the importance of R&D in driving economic growth.
Anchor Paper for Picking Up the Pace (163)	2005	Provides key themes for change to the government investment in RS&T such as addressing the under-investment in knowledge and technology; building capabilities in R&D and facilitating across-government coherency in R&D policy .
The Biotechnology Research Landscape in New Zealand; MoRST (164)	2006	A background paper to inform the development of a Biotechnology Research Roadmap. It describes the government's interest and investments in biotechnology.
Science for New Zealand—An overview of the RS & T system; (165)	2006	Included the goal of increasing NZ's public investment from current levels of 0.52% GDP to the OECD average of 0.68% GDP by 2010. A focus on long-term investment in science to create knowledge and utilise it for economic gains.
Biotechnology Research Roadmap (14)	2007	NZ needs to invest strategically in areas where it has a competitive advantage. NZ needs to build relationships with biotechnology research in the Asian region.
New Zealand Research Agenda (166)	2007	Identifies the following investment outcomes: building globally competitive NZ firms; a science and research focus on NZ's strengths, needs and opportunities; and innovative and well-connected research organisations.
Our Strategy 2008–2011; MoRST (15)	2008	Provides four strategic priorities: sharpening the agenda for science; engaging New Zealanders with science and technology; improving business performance through R&D; and creating a world-class science system for NZ.
Statement of Intent 2011–2014 (160)	2011	MSI's vision is that high performance science and innovation systems will improve New Zealanders' wealth and well-being. MSI needs to ensure that NZ's scientists, entrepreneurs and exporters have faster and more responsive access to the support they need.

2.3.7.2 Government investment policies

The NZ government has generally increased its investments in its research funding for human therapeutics through its agencies (e.g., FRST and the HRC) from 2000 to 2007 as shown in Figure 3 (63). The NZ government aims to achieve higher income per capita through sustainable growth and fostering innovation (13) and committed extra funding of NZD205.4 million from 2008 to 2011 for research, science and technology (15, 65). A change in government in 2008 also resulted in policies to

encourage businesses to invest in R&D, boost science and innovation, and improve NZ's economic performance. Further initiatives aim to link science with business by providing government contributions of 20% of firms' R&D spend; technology transfer vouchers for firms to access university and CRI capabilities; assistance to capture the commercial value of research conducted in public research organisations; and funding and prizes for NZ's most talented scientists (167). Therefore, it is expected that the total government investment in human therapeutics research would have continued to show some growth since 2006/2007, however this information is not able to be collated because of the many investment agencies and changes that have occurred since 2008.

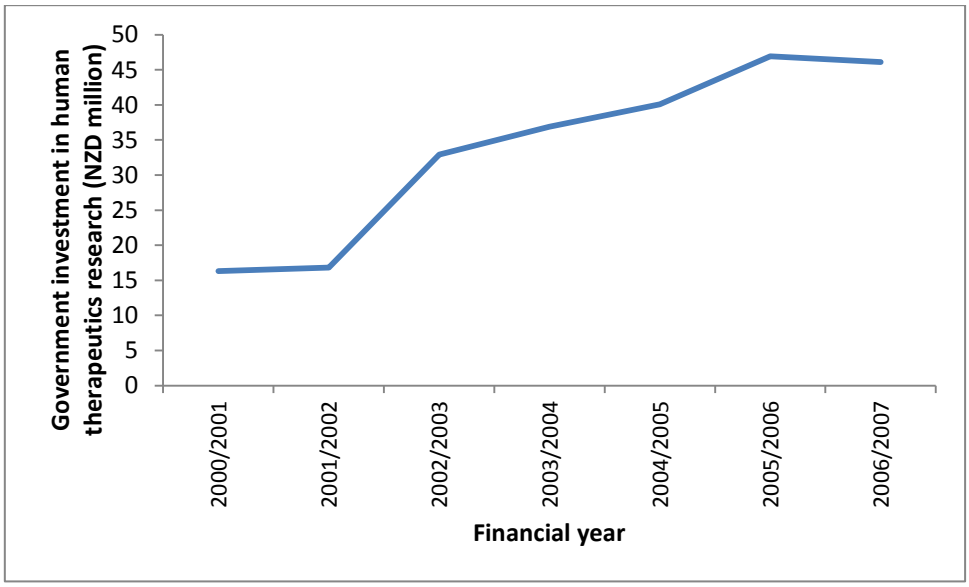

Figure 3 – New Zealand Government Investment in Human Therapeutics Research

Despite these increases in government investment, an issue NZ faces is that its levels of both government and business investment in R&D are low compared with OECD averages. In the 2005/2006 financial year, government-financed gross expenditure on R&D as a percentage of GDP was 0.50% compared with the total OECD average of 0.67% (65) while business enterprise R&D investment at 0.49% in 2002 was approximately a third of the OECD average of 1.6% (66). Country investment in all R&D (i.e., the total of government and private business investment) is also expressed as a percentage of GDP with a world average of 2.0%. The leading countries in 2006 were Israel (4.5%), Sweden 3.9%, Japan (3.2%) and the USA (2.6%) (168). By comparison, in 2003 NZ invested 1.14% of GDP in R&D (13).

In addition, a study by the Australian Expert Group in Industry Studies (169) found that the NZ government investment in health research was significantly lower than most benchmark countries (i.e., Australia, Canada, Ireland, the USA, the UK, the Netherlands and Sweden), most of which are increasing their investment by up to 20% per annum. New Zealand's investment in health research

was just below the median of OECD countries at 0.04% of GDP (169). Health R&D funding can also be compared on a per capita expenditure. Using this measure, the USA is the outright leader spending over USD80 per annum, followed by Sweden, Canada and Australia, with NZ spending about USD7 per annum. NZ would have to increase its spending by 50–100% to match the spend by Canada and Australia (169).

All these figures indicate that NZ has not been making the government and business levels of investment in health and medical research that other countries have made.

2.3.7.3 Pharmaceutical price control policies

It has been suggested that the NZ government is more interested in the efficient use of its drug budget than supporting innovation by the country's drug development industry (170). PHARMAC has a primary objective "to secure for eligible people in need of pharmaceuticals the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided" (171). PHARMAC has a variable but capped annual budget and therefore its decision for subsidising a medicine is more dependent on its relative ranking of medicines that could be funded than its cost-effectiveness. PHARMAC's strategies for managing its budget include negotiation of price and access with pharmaceutical companies, reference pricing and competitive tenders. These have resulted in an average annual increase in NZ's drug budget of 2% between 1994 and 2008, and expenditure that is much lower per capita than that of other OECD countries (170) including Australia, Canada and the USA (172). However, research has shown that PHARMAC subsidises fewer new drugs than Finland, Germany, the Netherlands (173) and Australia (170), and that NZ had a low rate of new drug launches in the 1990s, which was related to lower expected prices of pharmaceuticals (174). These data and other anecdotal evidence have been used by critics of some of PHARMAC's policies and funding decisions (170, 175).

A study by Sood (143) found that in 1992 only NZ out of a group of 19 OECD countries used a global budget as a policy for controlling pharmaceutical costs, though some countries have since introduced them. The policies of PHARMAC have been effective in slowing the growth in spending on pharmaceuticals compared with Australia, Canada and the USA by capping the national medicines budget. However, there are far fewer medicines in the five major drug classes that are subsidised in NZ (91 drug products) compared with Australia (over 650) (172).

2.3.7.4 Legal policies

New Zealand does not appear to have any specific patent policies related to drug development but does for the regulation of new medicines and clinical research (157) and the Medicines Act 1981 (176).

2.3.7.5 Foreign/private investment policies

New Zealand has relatively low business R&D investment of 42.5% compared with the OECD average of 61.9%; almost 45% of NZ's R&D funds are provided by the government compared with an OECD average of 30% (13). This discrepancy may in part be due to NZ's history in the primary sector production where R&D costs are relatively cheap, and the relative absence of large R&D enterprises in NZ. A R&D tax credit scheme was introduced in 2008 to encourage firms to invest more in R&D (177), however a change in government lead to the scheme being abolished after only one year.

2.3.7.6 Expertise and knowledge management policies

Knowledge creation has been a recurrent theme in MoRST policy for many years (refer to Table 4). Recent developments by MSI that may encourage careers and recognise success in scientific and medical research include the appointment of the Prime Minister's Science Advisor, changes to the government funding of research projects and the Crown Research Institutes (CRIs), and funding and prizes for outstanding scientists (158). The NZ industry is supported by the activities of NZTE and NZBio with promotions at relevant international conferences and networking opportunities.

2.3.7.7 OECD Reviews of New Zealand innovation policy

The OECD Reviews of Innovation Policy for New Zealand (13) found that the small domestic market limits the range of economic activities that can be conducted on a large scale, but that the conditions conducive to innovation and entrepreneurship are in place. NZ's main weaknesses for health research and innovation were a lack of investment in business R&D, a fragmented system of government support, insufficient policy co-ordination to encourage foreign investment, geographical distance and inadequate incentives to the public sector research organisations. The report suggested that NZ should ensure that it has a clear policy for innovation and should rationalise the number of funding instruments while modestly increasing the total level of funding. Investment strategies so far have tended towards projects rather than building long-term capabilities, financing research infrastructure and transferring research results to business. The report also identified that NZ is not well integrated into the global economy, even when compared with other small countries and so attracts only low levels of foreign investment. In addition, NZ's tax system does not encourage firms to grow locally and retain headquarters in NZ when overseas expansion occurs. Therefore foreign investment often results in the business shifting overseas resulting in a loss of high-skilled jobs, exports and tax revenues for NZ (13).

2.3.8 Australia

Over the last 25 years, Australia has undergone several phases in its policies that affect its drug development industry. In 1983, more than 75% of its pharmaceutical products were manufactured

locally from imported raw materials and policy focussed on ensuring access to pharmaceuticals. Ten years later this manufacturing industry was a fraction of its size, due to the extensive price controls of the Pharmaceutical Benefits Scheme (PBS) that limited firms' profitability (6, 54). In addition, in the early 1990s Australia was the first country to require a cost-effectiveness analysis as part of a funding application (136).

Despite these earlier issues, several policies and strategies have since encouraged Australia's drug development industry (6). These have taken the form of government investments, including R&D tax incentives, and encouraging foreign and private investment.

Table 5 summarises the programmes and strategies that have been implemented to facilitate the growth of Australia's pharmaceutical industry (178-181):

Table 5 – Summary of Australian Government Policies and Strategies

Programme title	Year/s	Details	Comments
Factor f	1988–1999	Compensation for companies that had prices for products limited by the PBS but were investing in local R&D, manufacturing or exporting	Benefits did not outweigh the costs of the programme or enhance the community's welfare
R&D Start	1997–2007	Funding for more than 40 smaller biopharmaceutical and pharmaceutical firms	
National Medicines Policy (NMP)	1999	Included the objective of supporting a 'viable medicines industry'	Other objectives related to affordability, quality, safety and efficacy
Pharmaceutical Industry Investment Programme (PIIP)	1999–2004	Funding to encourage R&D and production in companies that supplied pharmaceuticals at low prices under the PBS	Sufficient benefits from support of R&D but not from manufacturing
Pharmaceuticals Partnerships Programme (P^3)	2004–2009	Incentives for companies conducting pharmaceutical R&D in Australia.	
R&D Tax Concession	2002–2011	For expenditure on core R&D that involved both innovation and high technical risk; only for companies with Australian-owned Intellectual Property (IP)	The IP criterion was deleted in 2007
R&D Tax Credit	2011	Tax off-set to encourage R&D in Australia; refundable for smaller companies and non-refundable for those with an annual turnover above AUD20 million	

Australia's National Medicines Policy (NMP) meant that the industry needed to be considered as part of any health policy, including issues such as pricing and resulted in the Therapeutic Goods Administration (TGA) employing a more industry-responsive culture (136). A recent analysis of whether the NMP has successfully unified health and industry objectives found that until recently Australia achieved a good balance (142). An attributed positive effect of NMP is that in 2006, Australia was ranked fourth in the OECD for government expenditure on health-related R&D as a percentage of GDP, and its rate of growth since 2000 was second only to Switzerland (182). However, there are concerns that more recent health policies such as the 2005 Australia—United States Free Trade Agreement and the 2007 pricing reforms may affect Australia's balance of policy (142).

Currently Australia's drug development pipeline contains over 450 compounds with 189 of these in clinical development, including 58% in phase II/III trials. More companies in Australia are taking their drugs to phase III, which indicates the success and capabilities in the industry and may also reflect the growing interest from overseas partners entering in collaborative R&D agreements (183). The Pharmaceuticals Industry Strategy Group (178, 184) suggested that the Government can help sustain Australia's pharmaceutical industry advantages by encouraging strategic investment, increasing Australia's attractiveness for clinical trial activity and improving pharmaceuticals skills and education.

Similar to NZ, Australia is conducting more early phase clinical research for international pharmaceutical companies (185) and its phase I clinical trial sector employs over 300 people with an annual revenue of over AUD50 million (178). However, the majority of its contract projects are for phase II and III clinical trials, which makes Australia more vulnerable to the increasing competition from countries with lower costs and larger populations (178). On the other hand, a 2005 pharmaceutical benchmarking analysis ranked Australia ahead of Germany, India, Japan, Singapore, the UK and the USA as a location for clinical trials (186) and it is rated as one of the most cost-effective countries (180).

2.3.9 United Kingdom

The priorities for the UK's Policy Research Programme (PRP) are selected and funded by the Department of Health and include health protection, promotion and reduction of inequalities (187). In 2006, the Department of Health released its Best Research for Best Health (188) strategy document to support the government's ambitions to improve the health and wealth of its people. This document specifies the following goals:

1. Establish the NHS as an internationally recognised centre of research excellence
2. Attract, develop and retain the best research professionals to conduct people-based research
3. Commission research focused on improving health and care

4. Strengthen and streamline systems for research management and governance
5. Act as sound custodians of public money for public good

In addition, the UK Government has implemented a 10 year Science and Innovation Investment Framework 2004–2014 (189) to encourage science teaching and students' science qualifications in schools, maximise the impact of public investment in science on innovation, improve management of public investment in large research facilities, attract R&D to the UK and extend the R&D tax credit.

The pharmaceutical industry invests GBP5,000 million per year in the UK compared with government funding of GBP1,700 million per year on medical research (187). This industry funding occurs despite the UK's pharmaceutical price regulation scheme (PPRS) although recent changes will allow the price of pharmaceuticals to be raised on the basis of new evidence such as increased benefit or new indications (190). It has been suggested that the recent changes to the PPRS, may be a disincentive to pharmaceutical companies continuing to place R&D projects in the UK because the industry will share its pipelines with the National Institute for Health and Clinical Excellence (NICE), which acts on behalf of the NHS and indicates its ability to pay for new drugs (190, 191).

A National Institute for Health Research (NIHR) comprising of the NHS Trusts and UK universities has been established to provide a UK-wide clinical research network to work in partnership with and for the pharmaceutical industry. The NIHR has a faculty of invited researchers from diverse professional backgrounds and experience to lead research projects and develop the skills of the next generation of researchers (187). The NIHR is dedicated to providing the environment to meet industry needs including rapid review of applications for clinical trials, a single point of contact for evaluating the feasibility and patient recruitment for multi-site industry studies and model agreement documents for use throughout the NHS, which is the world's biggest health service (192).

The Association of the British Pharmaceutical Industry (ABPI) and the Department of Health publication Competitiveness and Performance Indicators 2005 (193) reported that the UK drug development industry remained one of the most innovative after the USA, venture capital investment was increasing and that the industry's contribution to the UK economy continued to be large, including a positive trade balance of GBP3.7 billion in 2004, and a contribution to national income approaching GBP7 billion in 2002 (the most recent data available on gross value added).

2.3.10 Canada

Similarly with many other countries, the Canadian government is establishing policies and investing in strategies to foster science and technology-based innovations in the health sector. Health Canada has identified four policy areas for innovation: reform of the health system, regulatory reform of therapeutic evaluations, community development, and science and research. Canada has increased

its funding of science and biotechnology R&D and innovation, provided generous R&D tax incentives, and has created collaborative institutions to assist with technology transfer of innovations (11). British Columbia is emerging as a centre of Canada's academic biomedical research and producing biotechnology spin-out companies (194).

Canada has a complex system for funding health and medical research that involves the Federal Canadian Institutes of Health Research (CIHR), which administers government funding; the Canada Foundation for Innovation (CFI), which supports research infrastructure at universities, hospitals and other non-profit institutions; and the Canada Research Chairs Programme, which supports research professorships. The Canadian provincial governments and non-profit organisations also support health research funding of approximately 40% of the federal government level (169).

2.3.11 United States

The level of investment and the market potential of the USA have resulted in a flourishing pharmaceutical industry, with 90% of pharmaceutical R&D funded by the private sector. The USA has been the pharmaceutical industry's leading innovator and has invented over half of the new product patents from 1974–2003 (6). The USA is one country where medical and pharmaceutical research funding by the government is independent of the funding of medicines. However, it has been suggested that if price controls were introduced that pharmaceutical R&D investments in the USA could be reduced. It has been suggested (123, 135) that most of the rest of the world, with its various forms of price controls, benefits in health status from the investments of the USA pharmaceutical industry.

Since the 1950s the United States government has strongly and consistently invested in medical research and by 1997, 54% of the total public research budget was devoted to the life sciences (60). The government-sponsored National Institutes of Health (NIH) have very large budgets to spend on basic biomedical and medical research, and agencies of the Department of Health and Human Services fund specific medical research projects (169).

There are targeted federal programmes, the Bayh-Dole Act (1980), the Orphan Drug Act (1983), the Hatch-Waxman Act (1984) and the Federal Technology Transfer Act (1986) that aim to stimulate private sector investment into areas where the commercial rewards are not attractive. The Bayh-Dole Act (1980) allows government agencies such as the NIH and university-employed scientists to license knowledge that was discovered in government laboratories and receive royalties from firms that make commercial use of the information (6). This lead to more collaborations and alliances between USA research universities and pharmaceutical companies because the knowledge generated by universities was no longer 'open-source'(23). The Orphan Drug Act (1983) encourages development

of medicines that will not have a large commercial market (fewer than 200,000 people in the USA) and has resulted in more than 220 orphan drug status being approved and marketed in the USA and at least a further 800 compounds in the research pipeline (125). The Hatch-Waxman Act (1984) has promoted pharmaceutical innovation by extending the term of a drug patent to compensate for the clinical and regulatory development times (195). The Federal Technology Transfer Act (1986) subsidises non-commercially viable collaborative research between a federal laboratory and private development (6). The USA's recent healthcare reform legislation includes the American Recovery and Reinvestment Act of 2009, which has allocated USD1.1 billion for comparative effectiveness research (190).

2.3.12 Western Europe

The Western Europe pharmaceutical industry has experienced slower growth than the industry in general. Its companies tend to have older products in their portfolios, less pronounced specialisation in their R&D, and many EU governments have recently embraced policies to retain the R&D of their local compounds and attract larger external contract projects. Some countries, such as Germany and Switzerland, have an established pharmaceutical industry to protect while others have focussed on generic manufacture to assist with cost containment (196). Successive governments in Spain have supported R&D in the pharmaceutical industry, in order to build the capacity to innovate rather than to just copy (197). Initiatives have included a network of science parks to foster innovation, an agency to assist with seed finance and a repatriation scheme to encourage postdoctoral scientists to return to Spain (198). The Italian government has also introduced reforms to promote innovation and incentives for pharmaceutical companies investing in R&D and retaining scientists in Italy. Publicly funded research is financed by a tax on pharmaceutical companies' promotional costs, and companies that conduct R&D in Italy or export their products benefit from premium reimbursement prices (196).

Overall the main policy objective in the EU currently appears to be control of public expenditure on pharmaceuticals, with the industry attracting criticism for the rising costs while it produces fewer new products that represent a real therapeutic advance. Governments are trying to balance limiting expenditure on mature products while rewarding investment in highly innovative medicines (199).

2.3.13 India

Despite being a developing country, India has developed a substantial pharmaceutical industry based on producing high quality medicines at low cost, and has taken advantage of its unique patent situation to manufacture for both its domestic and export markets (6). India's Patents Act (1970) did not recognise product patent protection in drugs and only a new method or process of manufacture could be patented. In addition, the patent life for drug patents was reduced to a maximum of 7 years. This Act stimulated growth because local companies could immediately manufacture products when

the limited patent life expired or could develop a new method not mentioned in the patent of the innovator company. The subsequent development of large scale manufacturing transformed the Indian industry as local companies developed tremendous expertise in developing new and efficient processes to maximise profitability (133, 150).

Pharmaceutical sales in India changed from being dominated by the multinational companies in 1970 to Indian companies having 77% market share in 2004. Exports, including those of medicines that still had patent protection outside India, increased steadily from the mid-1970s. However, the most rapid growth has occurred since 2000 as India signed up to TRIPS, amended its Patents Act and started to export off-patent drugs to developed countries that have higher price realisations. For some Indian companies these exports have become so important that they have invested in marketing and manufacturing through their subsidiary companies abroad, and have become multinational companies themselves (133, 150, 200).

At the same time, the global pharmaceutical industry has taken advantage of India's process development expertise and cost-effective manufacturing while Indian companies have gained greater international exposure and improved access to drug development expertise (150, 200, 201). India also has expertise in developing innovative drug delivery systems that can extend a medicine's lifespan (e.g., by the addition of a controlled release formulation). Development of these products have a lower risk, are less expensive than developing new medicines and have a higher chance of success since they are extensions of well-characterised compounds (201).

New chemical entities have been discovered in India but the usual model is to licence out compounds in the early stages of clinical development. Therefore, Indian companies tend to target disease that interest the large pharmaceutical companies rather than the neglected diseases that predominate in developing countries (200). However, India has successfully developed a hepatitis B vaccine for its own use and is developing other vaccines (e.g., for malaria, leprosy and cholera as well as combination vaccines) to both meet its own health needs and to export to other countries (46).

India has also realised the potential of providing clinical research outsourcing services, building on its established record in quality and speed of conducting clinical trials. As a result, many multinational pharmaceutical companies and contract research organisations have become established in India or formed collaborations with the top Indian firms (55, 202). India has also developed the capability to provide associated activities such as data management, statistics, medical writing and pharmacovigilance (203).

With the pharmaceutical industry seeking innovation from external sources, the Indian Government has taken the initiative with policies to establish research institutes, increase investment, build

infrastructure and promote the collaboration between private companies and publicly funded research laboratories (202). Its 2007 National Biotechnology Development Strategy provided initiatives such as the co-ordination between academia and industry, creation of research institutes to promote interdisciplinary research and improved patent protection (204).

2.3.14 China

Due to its population size and developing economy, China was the world's fourth largest pharmaceutical market in 2010 and is predicted to be the second largest by 2020 (205), so it needs to develop a substantial industry for its own benefit as well as for export. Approximately 97% of current pharmaceutical manufacturing is of generic products and China is predicted to become the second largest producer of generic pharmaceuticals by 2020. All of the largest multinational pharmaceutical companies have wholly owned subsidiaries or joint ventures in China (206).

China's 11th Five Year Plan (2006–2010) continues to make improving science, technology and innovation a priority, especially for diseases of national importance such as vaccines for hepatitis, influenza and HIV (204). The government is investing in pharmaceutical R&D as one of its national priority areas that is intended to develop an industry based on technology innovation and commercialisation rather than just the cheap labour of generic manufacture (207, 208). Government funding of the industry is essential for both drug discovery and commercialisation because private investment is very limited (209).

A special strategy, Major New Drug Creation, aims to independently develop 30 new drugs by 2020, to add to the two compounds already marketed globally (209). There is a particular emphasis on investigating traditional Chinese medicine as a unique source of new medicines (168), although they may be of limited interest to other markets (210). China has developed expertise in chemistry and preclinical services for the pharmaceutical industry with successful organisations employing workers in three shifts for 24-hour-a-day service to their customers (211).

The Chinese government has also implemented a Talent Strategy to encourage citizens who have gained qualifications and experience overseas to return to China. They can access public funding to set up companies as the first stage of the development of significant clusters and biomedical science parks (168). It has been suggested that China does not yet have the technical track record, export focus, regulatory and quality standards, and the more user-friendly business climate that India has developed (1, 212).

2.3.15 Other Countries

There are too many countries with policies that may affect their drug development industry to review in this research. This section covers a range of developed and emerging countries and summarises their policy situation.

Singapore has no natural resources and so relies on innovation for its wealth. In 2000, it launched its Biomedical Sciences Initiative (BMS), which is co-ordinated by the Agency for Science, Technology and Research (A*STAR) (213). The initiative is to expand Singapore into a hub for pharmaceutical R&D and manufacturing, facilitate biomedical research and to strengthen capabilities in clinical research. Policies include those to promote interactions and collaborations with world-class research entities and to create a biomedical hub around A*STAR's research institutes and consortia (214). Singapore's strengths for encouraging drug discovery and development include the world class capabilities of its workforce, well supported infrastructure, strong government investment, favourable tax incentives for local and foreign investors and strong patent laws (215). Singapore has attracted more than 100 firms there to conduct drug discovery, R&D and manufacturing. These have brought in large investments to Singapore and resulting benefits to the economy (213).

South Africa's industry has been hampered by limited government funding for commercialisation of academic projects and difficulty in attracting private funding. South Africa is forming partnerships overseas to upskill and retain its researchers, and the government is under pressure to fund research into areas of its population's unmet medical needs (e.g., HIV/AIDS, hepatitis B and C, dengue fever and tuberculosis) (216, 217). South Africa also has a small pharmaceutical manufacturing industry, however finds it increasingly difficult to compete commercially against the generic production of India; its facilities tend to be older and less well maintained; its regulatory activities are less rigorous and there can be problems finding a skilled and motivated workforce (140). As with many other countries, South Africa has recently conducted a survey of its clinical research industry with a view to taking steps to ensure it maintains its competitiveness for international clinical trials. Policy recommendations to strength South Africa's competitiveness include reducing administrative barriers, building skilled capacity and legislation that supports the clinical research environment (218).

Ireland has a major pharmaceutical manufacturing industry that accounted for more than 11% of GDP in 2004 (219). It arose due to a corporate tax rate of 12.5% that lead to most of the major pharmaceutical companies building their own facilities in Ireland (220). However, Ireland has very few domestic production companies and its economic transformation is under threat from countries that may be even more price-competitive. Ireland's government is expanding its policies to include more investment in medical research, especially for priority areas such as translational health research. A

R&D tax credit of 20% is available (169, 221) to encourage overseas companies to conduct their research in Ireland (220).

Cuba has had a coherent and long-term investment in its biomedical innovative capability to produce its own medicines that could not easily otherwise be sourced overseas due to trade sanctions imposed by the USA and then the collapse of the USSR (55, 217). Cuba has produced the only effective vaccine for meningitis B, which was required to control an outbreak that mainly affected its children and young adults (222). Since that success Cuba has continued to innovate in the biotechnology area and has cholera and therapeutic cancer vaccines in clinical development. Cuba's policies also foster collaboration between its medical system and health researchers in order to identify potential pharmaceutical research projects that would benefit its people (46).

Brazil is similar to India in that in 1971 it passed legislation, Law No. 5772 on Industrial Policy, which allowed local firms to produce copies of patented medicines by reverse engineering. It was intended that this would build pharmaceutical R&D capability in Brazil and provide affordable drugs for local and export markets. However, pressure from the USA and the desire to be a signatory to TRIPS eventually resulted in Brazil changing its legislation. Subsequent health policy has focussed on purchasing low-cost generic medicines and developing its own generic production for supply to Latin America (223). Brazil has policies to promote linkages with other countries and to explore their local biodiversity for potential pharmaceuticals (217).

Table 6 – Policies Affecting the Drug Development Industry of Other Countries

Country	Situation	Policies
Japan	The local industry dominates and even large multinational companies have a relatively low market share. Little export to other markets. Profits on local sales very lucrative, however Japan's expertise in R&D has lagged behind the USA and Europe (224).	Encourage the development of innovative drugs and industry growth. The 5-Year Strategy for the Creation of Innovative Pharmaceuticals and Medical Devices (2007) included the expansion of early-stage clinical trials to promote its clinical studies industry (225).
Malaysia	Does not have the technological capability and investment to be active in innovative pharmaceutical R&D (226). Produces off-patent medicines for local use and contract manufacture for overseas companies (151).	Third Industrial Master Plan 2006–2020 has goals of producing recently off-patent medicines (151). Implementing policies to encourage foreign investment, but is limited by Malaysia's relatively weak patent protection (227).
Taiwan	Is attempting to build an industry but has ongoing issues that include attracting the return of researchers who have moved overseas and making a career in science financially attractive (228).	Statute for Biotechnology and New Medicine Industry Development (2007) provides an internationally accepted legal framework, R&D tax incentives, immigration policies to encourage foreign scientists, investment in science and industry parks (229).
South Korea	Mix of small and large firms that mainly concentrate on microarrays and bioinformatics (217).	Focus on technology transfer and support of a relatively advanced venture capital sector (217).
Israel	Until recently concentrated on generic production and Teva Pharmaceuticals has become a major manufacturing company (230).	Support of academic research that has provided a source of potential pharmaceuticals under development by various companies (230).
Egypt	Lower levels of access to essential medicines compared with Cuba and South Korea (217).	Wants to meet the health needs of its population and provide affordable medicines (217).
Sweden	History of publicly funded biomedical research (115) but also a high level of private research (169). Most prominent success was Pharmacia before being acquired by Pfizer (231).	More recent policies have supported science parks, and provided commercialisation and investment assistance for start-up companies (231).
Finland	Is attempting to use biotechnology as a fourth pillar of its knowledge-based economy, but despite investments the industry has remained marginal (232).	Considering policies to provide more business support and to focus on biotechnology areas that have links with existing industries and niche areas (232).

2.3.16 Summary of Policy Models and the Place of New Zealand

The framework of policy options described in Section 3.3 was used to analyse the different groupings of policy components provided by various countries in order to support their drug development industries. The countries in this comparative analysis provide six very different models of policies that have promoted a drug development industry. In general, the different models have arisen from an historical basis, for example, on the strength of biomedical research, potential profit from innovative medicines, economic returns from contract manufacture or the need to be able to provide affordable

medicines. There are variations in the level of support for some of the policy options between the countries in each of these models, however all countries in the same model have the same focus of policies. In addition, there are many developing countries with policies that may superficially support a drug development industry (rather than no policies at all) but which are not yet sufficiently distinctive to be able to place the country into a specific model.

Model 1–Leading Innovation in the Pharmaceutical Industry

The first model has a range of government investments, encouragement of foreign/private investment and other polices supporting the industry, and no price controls on pharmaceuticals. It describes the unique position of the USA as the pharmaceutical industry's leading innovator.

Model 2–Protection of Traditional Pharmaceutical Industry Base

This model covers countries that have an established pharmaceutical industry with government support, pharmaceutical price controls but with premium prices for innovative products. This model encompasses countries in Western Europe (e.g., Switzerland and Germany) that have mature large pharmaceutical companies, less pronounced R&D specialisation, have failed to keep producing blockbuster products and are increasingly threatened by generic competition.

Model 3–Building on Strong Scientific and Medical Research

This model describes countries (e.g., the UK, Australia, Canada and probably Sweden) where government has supported strong science research and funded internationally acclaimed medical research while employing various methods of price controls on pharmaceuticals. However, only the UK has become a significant contributor to the global drug development industry. There are several other countries, such as Singapore, South Africa and Cuba, which appear to fit into this model, however their industry is at an earlier stage in its development.

Model 4–Supporting Imitation Leading to Innovation

The fourth model covers countries that also have government investment in the industry and some mechanism of pharmaceutical price control but with the unique feature that the current industry developed from expertise originally gained from the production of compounds that were still under international patent protection. India and China have shown the viability of this model and other countries such as Brazil and Israel are attempting this approach.

Model 5–Supporting Contract Pharmaceutical Manufacture

This model describes the countries that have chosen policies specifically to encourage multinational companies to set up manufacturing facilities for export markets by providing tax incentives. The model includes both developed countries (e.g., Ireland) and developing countries in the Asia–Pacific region (e.g., Malaysia and South Korea).

Model 6–No Policy to Support a Pharmaceutical Industry

The last model is of countries where the investment required to support pharmaceutical innovation is beyond their means, and their dilemma is whether it is more economically viable to import costly medicines or attempt to manufacture them locally. Countries in this model are many of the developing countries not already discussed (151). Investment in local medicine production may be considered an attractive policy but in reality there are too many barriers and it is more economical to buy medicines from efficient generic manufacturing countries (222). There may be no policy to support medical R&D, very low levels of investment, or only weak links between government research and industry (140).

Which Model does NZ fit?

New Zealand does not have the traditional pharmaceutical development industry of Western Europe, the process development and manufacturing capability of India and China, the policies to encourage contract manufacturing of Ireland, or the extensive and innovative drug development industry of the USA. New Zealand has consistently funded its medical research community, albeit at lower levels than most OECD countries, has price-regulation for pharmaceuticals through PHARMAC, promotes education and provides research facilities. New Zealand is attracting foreign investment in specific drug development projects, is increasing its networking and international collaborations, and promoting its capabilities overseas. Therefore, NZ's overall policy in support of its drug development industry is most similar to that of the medical research-based model of the UK, Australia and Canada. It is the policies of these countries that are most applicable for NZ to consider, especially regarding levels of investment in the industry (e.g., R&D tax credits), when formulating policy to support its drug development industry.

The general characteristics of the six models and some countries in each model are provided in Table 7 (Table adapted from my publication in Health Policy (134); Appendix VI).

Table 7 – Summary of Policy Models to support a Drug Development Industry

Policy options framework	Policy models					
	1	2	3	4	5	6
	Leading innovation	**Protect traditional pharma industry**	**Medical research**	**Imitation to innovation**	**Contract manu-facture**	**No policy**
Countries in this model	USA	Switzerland, Germany	UK, Canada, Australia, NZ	China, India	Ireland	Many low and middle income countries
Government investment						
Medical research	X	X	X	X	X	
Drug development projects	X	X	X	X	X	
Pharmaceutical price control						
Price-setting/reference pricing		X	X	X	X	X
Premium prices for innovation		X				
Legal policies						
Previously had own patent laws				X		
Encourage generic manufacture				X	X	
Foreign/private investment						
Drug development projects	X	X	X	X		
Manufacturing facilities				X	X	
R&D tax credit	X	X	X	X	X	
Expertise and knowledge management						
Education and facilities	X	X	X	X	X	
Networking and collaboration	X	X	X	X	X	
Promote country capabilities	X	X	X	X	X	
No policy/no capability						X

2.4 Benefits from a Drug Development Industry

2.4.1 Introduction

An increasing number of countries are building an industry based on innovative medicines, production of generics or provision of specialised support services using local skills, expertise and resources to optimise the perceived financial returns. It is expected that life science-related activity will generate highly skilled and well-paid employment opportunities, contribute to economic prosperity and be the foundation for future innovation and growth (114). There are multiple opportunities in the drug development process where countries can provide services to the global pharmaceutical industry, including (102, 233):

- Discovery and development of innovative compounds (high risk and high potential return)
- Production of generic medicines, often using innovative and less expensive methods than the original patent product (low risk and low returns, especially in some very competitive market segments)
- Applying new drug delivery systems to existing products to extend their product lifespan (e.g., by the addition of a once-a-day or controlled release formulation). The development of these products is lower risk and less expensive than developing new medicines and have a higher chance of success since they are extensions of well-characterised compounds (medium risk and medium return).
- Provision of drug development support services, especially for technically challenging areas (e.g., chemical synthesis) or large complex projects (e.g., clinical research) (low risk and low–medium return)

New Zealand is a small country without a strong pharmaceutical industry base and with a limited venture capital sector therefore it is unlikely that a NZ company will have access to the capital and the infrastructure to complete the development of an innovative medicine. This cost has increased to USD1.2 billion (38) if the costs of failed candidates and opportunity costs are included and if it is not included, the mean total cost is estimated to be USD226 million (23). However, raising even this level of investment is a challenge for any drug development company in a small country that has a limited industry (232). There are further costs associated with sales of a successfully developed compound (e.g., production, distribution, sales and marketing), which are projected to be approximately 50% of product sales (23).

Therefore, the potential economic benefits to NZ from its drug development industry could accrue from (a) a compound discovered by a NZ entity that is marketed by a third party while retaining some NZ ownership and (b) from providing services to overseas pharmaceutical companies. The next two

sub-sections discuss the literature pertaining to these two situations and are followed by a brief discussion on the potential spillover benefits.

2.4.2 Economic Benefits from Drug Discovery

The industry's profitability depends on identifying and successfully developing new drug candidates while trying to cap the ever increasing costs of drug development. Research on 118 new drugs introduced between 1990 and 1994, showed a mean return on investment of 11.5% (49). Research in the USA in 2001 showed that the pharmaceutical industry had an average profit of 18.5% of revenues (135). However, more recently, industry returns have decreased (5) and to maintain its growth and profitability the industry will need to increase the number of potential drug candidates identified and have a greater focus on innovative R&D (57).

The pharmaceutical industry is now trying to procure inventiveness by forming partnerships with innovative academic researchers (2, 51), especially those that can offer expertise in designing molecules of the desired therapeutic class or specific drug candidates (23). Academia has the advantages of a more creative culture, tradition of cross-collaborations and lower expenses and these allow higher risk research to be undertaken (58).

There is value in drug discovery research as pharmaceutical companies compete to obtain access to innovations from small companies and academia (234). The industry is willing to negotiate substantial upfront and royalty payments to acquire promising drug candidates. In 2005 the announced payout value by large pharmaceutical companies for alliance deals was USD10.8 billion, of which USD4.2 billion was directed to drug discovery organisations (mainly small firms, but some to universities). Note that alliance deal payouts are typically an upfront payment and further payments are dependent on the drug candidate attaining milestones, so that the USD10.8 billion was not all paid in 2005 but will be paid over many years assuming that milestones continue to be met (23). Another analysis (235) found a similar total announced payout value for 2005 but estimated that the total value of all biotechnology out-licensing deals, (including for deals for which there was no announced value) was at least USD70 billion.

The average payments for all phases of licensed projects have increased in recent years. The typical payments and royalty rates provided in Table 8 summarise data from the work of Kessel and Frank (235). They advise that later stage projects can command payments that are many times higher than earlier stage ones because there is less uncertainty and likely revenue can be more accurately forecast.

Table 8 – Typical Payments and Royalties by Compound Stage of Development

Timing of the deal	Upfront payments (USD)	Royalty rates on product sales	Value of royalty payments (USD)	Value of total deal (USD)
Preclinical	6.5 million		39 million	45.5 million
Phase I	10 million	12–15%	55 million	65 million
Phase II	17.5 million		110 million	127.5 million
Phase III	70 million	18–26%	150 million	220 million

There is an emerging class of drug discovery companies that are dependent on successful drug development outcomes and robust intellectual property (IP) to flourish. They risk erosion of their value by the loss of IP through alliances and financial inputs. The value of and returns from new pharmaceuticals is highly skewed with a small proportion of products being highly profitable and most of this profit is captured by a few large and fully integrated companies. This poses challenges for the smaller specialist firms; even those with successful projects struggle to become sustainable, and those that are profitable are usually then acquired by a major company (23). There are economies of both scale and scope in drug discovery indicating that there is benefit from being able to spread out fixed costs over a number of projects as well as the advantages of applying knowledge gained from one project to another one (23).

The value that a drug discovery organisation can offer to the market is its expertise in designing molecules of a particular class for the desired therapeutic activity or specific drug candidates. An organisation that produces successful drug discovery candidates can obtain very high profits. However, it must maintain the value of its assets, which are drug discovery candidates and specific drug discovery expertise, by continuing to produce desirable potential drug compounds. A drug discovery organisation obtains its revenue from the upfront payments and royalties from selling its candidates to pharmaceutical companies. The evidence suggests that a drug discovery firm that succeeds with a blockbuster drug should use its surplus revenue to become a fully integrated firm rather than remain generating dug candidates in alliance with pharmaceutical companies (23). However, financial limitations may require start-up companies and drug discovery organisations to sell or out-license their products prior to completion of development and they therefore do not realise the whole value chain (196). More recently, new financing alternatives include the sale of royalty streams from future sales in exchange for immediate capital, committed equity financing of shares, partnering to obtain capital and expertise in return for royalty payments from future sales and collaborative development financing (235).

The value of a drug candidate depends on its progress in the drug development pipeline, its relative efficacy compared with the others in its class, the size of the potential market segment and the IP protection held (23). The analysis of the economic or market potential of a compound may begin as soon as a possible indication for the compound has been identified and there are many approaches

used in the industry (236). The analysis usually considers the incidence or prevalence of the disease or condition (e.g., by using models of predicted population demographics), potential competing products on the market or in development, the likelihood of the drug being funded or paid for by patients, and the chances of successful development and registration of the medicine. This potential is assessed against the costs and time of the development programme and its patent situation (6).

However, estimating the economic potential for a compound, especially early in development, can be unreliable because of the large number of unknown factors, including (6, 17):

- The predicted indication and any off-licence use that may occur
- Estimating how many patients will have access to it, which may also depend on reimbursement policies in major markets
- Competitor products and their relative efficacy and safety
- Time of product registration in key markets compared with competitor products
- Level of marketing investment for the product
- Potential for extending the product life-cycle with new dose forms or re-formulations
- Any patent protection issues

Predicting the year of peak sales and duration of sales can be difficult, and with the time delay from product launch until peak sales, data are not available on recently marketed medicines. The time to peak sales is influenced by factors including the order of product entry, the quality of the brand and marketing support (237). An analysis of mean worldwide sales for new drugs introduced between 1990 and 1994 found that peak sales occurred around Year 10 from product launch and appreciable sales still occurred at Year 20 (49). Research on new drugs introduced into the UK from 1980 to 2007 (238) estimated a lifetime of 33 years, with peak sales at 17 years. Another analysis of sales from 1981 to 1992 (239) found that mean peak sales were usually achieved within 10 years of product launch and noticeable sales still occurred at 20–30 years after launch. An analysis of the effect of entry order on sales for nine indications showed that peak sales of the market leader usually occurred between Year 8 and Year 12 from product launch (240). However, research (241) on products introduced in the USA between 1998 and 2008 found that peak sales occurred at 5 to 6 years post launch.

2.4.3 Economic Benefits from Provision of Drug Development Services

Outsourcing or sub-contracting has become an important strategy for companies seeking to solve the issue of a lack of resources (59). It is estimated that the pharmaceutical industry spends USD5 billion a year with contract research organisations (CROs) and this is continuing to rise, especially in developing countries (242). As modern drug development becomes increasingly complex, even very large pharmaceutical companies are finding it too expensive to build in-house capabilities for all the

required speciality areas. It is more efficient for them to contract high technology and niche research sectors to service industry companies that specialise in that expertise (34).

The clinical trial segment of drug development is the most expensive and costs have increased significantly as the number of studies in the average New Drug Application (NDA) has increased from 30 in the early 1980s to 70 in the mid-1990s (57). The pharmaceutical industry is attempting to reduce this expense; one mechanism is to have less phase II and III clinical trial centres in the USA and replacing them with less expensive trial sites in India, China, South America and Eastern Europe (5, 242). The cost of labour in developing countries is lower than in developed countries leading to cost savings at both the clinical study sites and with the Clinical Research Organisation (CRO) services. In addition, the large populations of these countries can lead to accelerated patient recruitment (242). While it is accepted that clinical research can be conducted at lower costs in some countries than in others, the cost savings need to be balanced against the acceptability of the data generated to the regulatory agencies and future prescribers around the globe. Furthermore, conducting studies in a more distant location that may not have all the resources needed may make travel and set-up costs prohibitive (43).

The per participant payments to study sites vary widely depending on the phase of the trial and the protocol requirements and are considered by the industry to be proprietary information and therefore not readily available to the public. However, the cost per participant in a clinical trial in the USA was estimated at USD20,000 compared with USD1,500–2,000 in India (5). An industry report (243) in 2011 provided the following per participant trial costs averaged across all therapeutic areas: USD20,000 for phase l, USD36,000 for phase ll and USD47,000 for phase lll. These costs were higher than those reported in 2006 of USD16,000 for phase l, USD19,000 for phase ll and USD26,000 for phase lll (83).

There have been some anecdotal reports of the annual value of clinical trials to NZ, which range from NZD100 million in 2004 (244) down to a current NZD30 million (245). These data imply that revenue from clinical trials sponsored by the pharmaceutical industry has been declining, a view supported by some (245), however it appears that no accurate records are available to date.

2.4.4 Spillover Benefits

Provision of drug discovery and development services to the global pharmaceutical industry can provide both spillover and economic benefits. Spillover benefits are those that do not accrue to the original creator but are obtained by others who use, copy or adapt knowledge without payment to the originator. For example, academic research into the mechanism of a disease may also lead to new treatments for that disease or provide insights for researchers working on other diseases. Other

spillover benefits from research funding may be societal and economic (246). The failure of a clinical trial is usually enough to terminate the development of a new drug and it could be considered that in this situation the complete value of the project to date has then been lost (247). However, some 'failed' compounds successfully and often serendipitously find life in new indications. The most well-known example is sildenafil (Viagra™), which was initially under development for angina but is marketed for erectile dysfunction (50). Researchers have suggested that even failed R&D projects provide learning to the organisation that can be applied to other compounds, increasing the knowledge economy and may create new innovations (21).

A UK study conducted by the Office of Health Economics (248) estimated that the value of the British Pharma Group of UK-based innovator pharmaceutical companies to the economy was at least GBP1 billion per year. This included manufacturing, R&D and head office activities that provided permanent employment for at least 72,000 people. It did not include income from royalties and licence payments, other benefits such as health benefits for patients, or reputational benefits conferred on the UK due to the industry.

Data from the UK and USA suggests that every monetary unit of public investment in biomedical and health research results in 2.2–5.1 monetary units of company R&D investment (246). A further benefit is from the increased life expectancy, eradication of disease and improved quality of life from the medicines developed. Studies have estimated that the value of these outweigh the investment required in the drug development industry and that every USD1,345 results in the gain of one human life-year, which is valued at USD100,000–160,000 (249).

A report on NZ's biotechnology industry (250) found that for every full-time equivalent job in biotechnology, a further 2.41 jobs are created in the broader economy. It is reasonable to expect that this employment multiplier can be applied to the NZ drug development industry. This result is supported by other NZ research (64) that found, on average over 2000–2009, the human therapeutics sector generated NZD38 million in output, NZD85 million in GDP and 2,000 jobs (including multiplier effects).

2.5 Linking Expertise, Enablers and Barriers, and Economic Benefits

Although the three strands of the literature review were conducted independently as the basis for research into these three research objectives, it was realised that there are significant areas of overlap between them. For example, specific policies have been employed by countries to increase their levels of expertise, promote networking and knowledge transfer, and improve the probability of spillover benefits. Other policies promote innovation and encourage foreign and private investment in the industry leading to increased economic benefits. Finally, the expertise in drug development is

utilised by overseas companies thereby bringing economic benefits to NZ. The inter-linking of these three strands is illustrated in Figure 4.

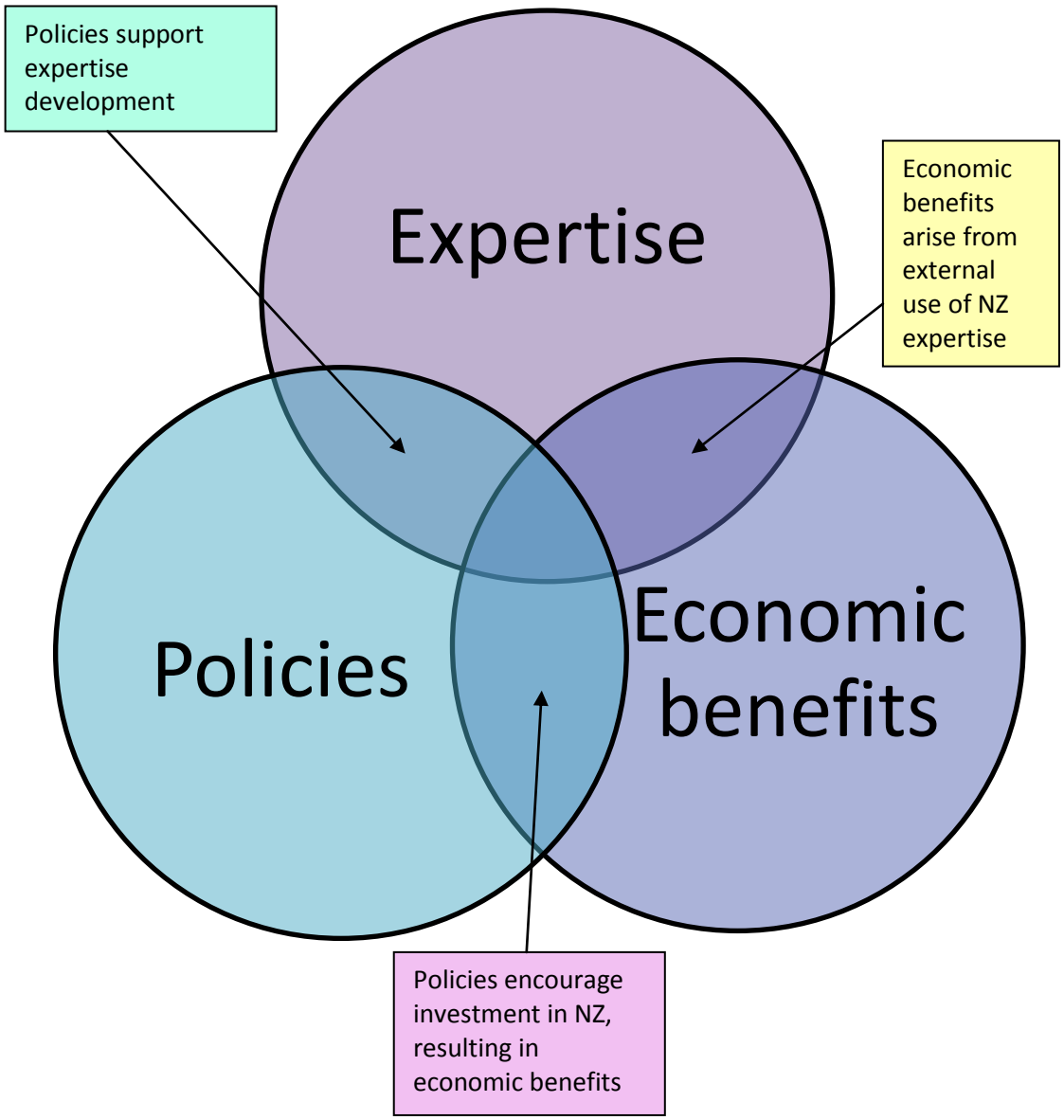

Figure 4 – Inter-linking of Expertise, Policies and Economic Benefits

3 Methods

3.1 Development of Theoretical Frameworks

The initial intention was to develop a single theoretical framework for evaluating NZ's drug development industry. However, it was realised that three separate frameworks would be required, one to assess each of the following: NZ expertise, the enablers and barriers to development of the NZ industry, and the potential economic benefits for NZ from supporting this industry.

This research was to assess NZ's drug development industry in a very broad sense and from three different perspectives—expertise, enablers and barriers, and economic benefits. The implications for methodology was that it needed to involve all aspects of the industry, that is, the research was not an in-depth case-study analysis of a few companies but rather it involved the entire NZ industry.

3.1.1 Expertise

A theoretical framework was developed that would provide an understanding of the different components of the drug development industry being assessed. The related and overlapping streams of literature reviewed and explored included methods of assessing expertise and capability, knowledge management and innovative behaviours. Several publications involving people working in the pharmaceutical and high technology industries were useful for developing specific questions in the research instruments.

3.1.2 Enablers and Barriers

A theoretical framework to assess the enablers and barriers to NZ's drug development industry was developed from reviewing the literature covering health policies, industrial policies and other factors that have affected the growth of drug development and biotechnology industries of a wide range of countries. The framework, discussed in Section 2.3, consisted of the range of policy types that a country could employ when developing its own policies supporting a drug development industry. These include policies for government investments, pharmaceutical price controls, patent protection, foreign and private investment, provision of education and facilities, networking and collaboration, and international promotion of a country's capabilities. Table 9 summarises the policy framework and includes examples.

Table 9 – Summary of Policy Framework

Policy types	Examples
Government investment	Medical research Drug development projects
Pharmaceutical price control	Price-setting/reference pricing Premium prices for innovation
Patent protection	Previously had own patent laws Encourage generic manufacture
Foreign/private investment	Drug development projects Manufacturing facilities R&D tax credit
Expertise, knowledge management and innovation	Education and facilities Networking and collaboration Promote country capabilities Encourage pharmaceutical innovation

The literature review did not reveal any research instruments that specifically addressed evaluating the barriers and enablers of a drug development industry and so these sections of the questionnaires were developed empirically.

3.1.3 Economic Benefits

A theoretical framework to assess the economic returns to NZ from its drug development industry was developed from reviews of the economics and risks of drug development and the clinical research literature. The framework encompassed the economic returns that could be generated for NZ either from successful development of a NZ-discovered compound or from provision of services to the global drug development industry.

The literature review identified methods that had been used to assess the potential economic returns of specific new medicines; however a general approach was taken because of the limited amount of publicly available information on specific medicines in development by NZ companies and because of the lack of access to information that the pharmaceutical industry purchases from market research companies. This more general approach should be valid because the potential value of a compound is dependent on its market potential and the level of risk associated with completing its development. Additionally, there is no standard method employed by the pharmaceutical industry for potential revenue analyses on early stage discovery projects (236).

The quantification of economic benefits from the provision of services to overseas companies was also limited by the amount of information that the participants were willing and able to provide. Therefore, the value to NZ from its drug development industry involved three approaches: the proportion of the support services organisation's revenue from overseas, the value of conducting clinical trials for the pharmaceutical industry (using databases of clinical trial applications to the Ministry of Health), and the potential economic returns from a NZ-discovered compound.

3.2 Data Collection

3.2.1 Introduction

Questionnaires were developed to collect information so that the objectives of assessing the expertise of NZ's drug development industry and the enablers and barriers to the industry in NZ, could be achieved. The questionnaires were administered to the research participants during semi-structured interviews and were conducted as the first data collection step. The questionnaires also collected data that contributed to the objective associated with estimating the potential economic returns to NZ but the interviews revealed that there would be insufficient data and potential anonymity issues to complete the economic objective of my research. However, analysis of the expertise data from the interviews revealed NZ's strengths in drug discovery and clinical research; therefore the economic objective data were supplemented with data from two other separate analyses:

- The value of clinical research to NZ from pharmaceutical industry sponsored clinical research was based on Standing Committee on Therapeutic Trials (SCOTT) clinical trial application databases obtained from the Ministry of Health
- The potential economic returns to NZ from a NZ-discovered compound were based on a hypothetical compound and data from the literature.

Table 10 summarises the steps of the data collection.

Table 10 – Timeline of Data Collection Activities

Objective	January–June 2009	July-Dec 2009	Jan-June 2010	July-Sept 2010	Oct-Dec 2010	Jan-Mar 2011	Apr-June 2011
Theoretical framework development	Literature review and framework development for the expertise, enablers and barriers, and economic objectives						
Expertise		Questionnaire development, ethics approval obtained, pilot testing of questionnaires	Individual interviews for administration of questionnaires	Data analysis (quantitative) showed NZ's strengths in drug discovery and clinical research	Objective completed		
Enablers and barriers		Questionnaire development, ethics approval obtained, pilot testing of questionnaires	Individual interviews for administration of questionnaires	Data analysis (qualitative and quantitative)	Objective completed		
Economic		Questionnaire development, ethics approval obtained, pilot testing of questionnaires	Individual interviews for administration of questionnaires	Data analysis (quantitative), objective partially completed	Expertise results indicated that further economic research should focus on drug discovery and clinical research.		Calculations of value to NZ of a hypothetical compound
						Clinical trial application databases obtained and analysed	

Table 11 describes the source of the research data for the expertise, enablers and barriers, and economic objectives.

Table 11 – Source of the Research Data

Research data source	Expertise objective	Enablers and barriers objective	Economic objective
Drug discovery group participants	X	X	
Drug development company participants	X	X	
Support services organisation participants	X	X	X
Stakeholder participants		X	
Ministry of Health SCOTT clinical trial application databases			X
Assumptions for a theoretical compound obtained from review of the literature			X

3.2.2 Development of the Data Collection Tools

It was realised that five different data collection tools were required to collect data from the research participants. The first assessed the personal expertise and career information of participants from drug discovery groups, drug development companies and support service organisations. A further three questionnaires collected the capabilities for the three different components of NZ's drug development industry (i.e., drug development companies, support services organisations and drug discovery groups), their knowledge management, innovative behaviours and their interactions with other organisations in NZ's drug development industry. They also contained questions on enablers and barriers to NZ's drug development industry. The questionnaire for the support services organisations contained additional questions on their provision of services to NZ and overseas clients. Most of the items in these three questionnaires were the same; however each was tailored for the three different sectors of NZ's drug development industry and included unique questions. The fifth questionnaire was administered to industry stakeholders only and contained just the questions on the enablers and barriers to NZ's industry that were administered to the previous research participants. Copies of all five data collection tools used can be found in Appendices I to V and the data collected from each type are summarised in Table 12.

Table 12 – Summary of the Data Collection Tools

Data collection tool (Appendix)	Expertise objective	Enablers and barriers objective	Economic objective
Personal expertise questionnaire (Appendix I)	X		
Drug discovery group questionnaire (Appendix II)	X	X	
Drug development company questionnaire (Appendix III)	X	X	
Support services organisation questionnaire (Appendix IV)	X	X	X
Stakeholder questionnaire (Appendix V)		X	

All data collected for the expertise and economic objectives were quantitative. This approach was chosen because of the amount of data to be collected, to make it easier to record and code the data and to facilitate data analysis (251). Overall, there was a large amount of information to be collected at each interview and a quantitative approach was the most efficient use of the time available with each participant. Where possible, the quantitative questions were based on previous researchers' work so that comparisons of results could be undertaken. Where appropriate, questions were asked in a quantitative manner by the use of a 5-point Likert scale (e.g., 'strongly agree', 'agree', 'neither agree nor disagree', 'disagree' and 'strongly disagree'). The 5-point Likert scale had been frequently employed by previous researchers in this context and therefore was also used for the newly developed questions. Consideration was given to the use of other graduations in the Likert scale, such as using an even number of options to force an opinion or providing a 7-point scale to try and obtain greater discrimination from the participants. However, the 5-point scale is considered to be the most commonly used format (252) and so was chosen for this research. Some text was emphasised using bold and italicised font to add clarity to the setting out of the questions.

A concurrent mixed-methods approach was used for the data collection for the enablers and barriers objective. However, it was not a true mixed-methods approach because this section of the questionnaires contained six open questions and only one ranking question, which was on the barriers to the industry. This ranking question was therefore 'nested' within the dominant qualitative data questions and was for convergent purposes rather than being complementary (253). This central question of this objective was "What policies and factors have influenced NZ's drug development industry so far?" The mainly qualitative approach was specifically chosen for this objective so that participant's opinions could be explored without biasing or guiding their responses (254) and because it was expected that the responses could be quite complex and varied (255). The six open questions were very broad in scope to allow participants to raise any relevant ideas or issues that could be explored (251, 256). The literature on the current changes in the global pharmaceutical industry and

the policies that different countries have employed in support of their industry were considered when the research questions of this objective were developed. If qualitative research of another country's drug development industry had been available in the literature it may have been used as a basis for the research questions and as a comparison for the results of my research (256).

The ranking question was included to encourage the participants to consider a broad range of possible barriers to the NZ's drug development industry, some of which they may not have directly experienced during their work in the industry. Both qualitative and quantitative data were collected on the barriers to NZ's drug development industry to obtain a broader understanding of the issues facing the industry as a whole (256) and for the purpose of confirmation of results. It was anticipated that the results from the two different types of data would converge therefore confirming and increasing their validity (253). The questions for identifying the enablers and barriers to the industry were expected to be the most difficult in the interview. They were therefore placed at the end of the questionnaires and the qualitative and quantitative data were collected concurrently. Table 13 summarises the type of data collected for each objective.

Table 13 – Summary of the Data Collected

Type of data collected for each objective	Quantitative data	Qualitative data
Expertise objective	X	
Enablers and barriers objective	X	X
Economic objective	X	

The order of the questions in each of the five questionnaires was arranged so that they followed a logical sequence and all the questions on one topic were placed together (255). Even though the questionnaires were completed primarily by the researcher, effort was made to set them out as clearly as possible. This included the use of unambiguous instructions, a simple layout with grid formatting where appropriate, containing each question on one page (i.e., a question was not split over two pages), a clear 12-point Times New Roman font and only small amounts of underlining and bold type (252, 254). Questions were kept as short as possible and care was taken to ensure that each was clearly written and asked only one question (i.e., double-barrelled questions were avoided). The questions were framed to avoid any bias or to influence the response provided (251, 256). The use of both quantitative and qualitative data posed challenges even though this research did not utilise a traditional mixed-method analysis. The two sets of data required more time to set up databases and to become familiar with both forms of research.

3.2.3 Ethical Issues

This research was approved by the University of Auckland Human Participants Ethics Committee (UAHPEC) on 27 July, 2009 (Reference number 2009/267). Potential participants were advised in the Participant Information Sheet (PIS) that their responses would be kept confidential along with the datasets, with access limited to the researcher and supervisors. However, anonymity of the participants and/or their organisation could not be guaranteed because they may be able to be identified by the information they provided, especially if it was unique to their organisation (e.g., due to the type of service they provided). This was made clear to the research participants; however they may not have been considered it to be a risk and may have welcomed the opportunity to have their organisation's expertise identified.

3.2.4 Testing the Data Collection Tools

The five questionnaires were tested with 11 participants representing the four different sectors of the NZ drug development industry to check them for face validity (i.e., that the participants correctly understood what was being asked and were able to provide the information required). The 11 participants represented two drug development companies, two discovery groups, five support services organisations and two stakeholders. A larger scale pilot survey was not appropriate for this research because the number of potential participants in each of the categories was expected to be quite small (252, 257). It was not possible to check the questionnaires for reliability (i.e., that the score provided by a participant is consistent and independent of the time of day or actual day) because it wasn't feasible to interview participants twice.

Piloting the questionnaires also enabled a check of the approximate time required to administer them. It was acknowledged that there could be considerable variation in the time participants needed to answer all the questions. However, it was important that it did not take longer than the time that was advised to the participants, in case they declined to complete all the questions or did not give sufficient thought before answering them. If the pilot testing revealed that the questionnaires needed more than an hour then consideration would have been given to reducing the number of questions, which would not have been desirable (252, 254). The testing confirmed that administration of the questionnaires to participants, except those in the stakeholder category, required up to an hour (as expected and advised in the Participant Information Sheet). The stakeholder questionnaire required approximately 15 to 30 minutes to administer.

The pilot testing did not reveal any major issues but did produce three changes to the planned methodology. First, an amendment was made to a question in the drug development company and support services organisations questionnaires. Originally the drug development companies were asked to rate their satisfaction with each individual NZ support services organisation they used.

However, to ensure that this question could be answered it was made more general by asking participants to rate their satisfaction with the NZ support services organisations in general (i.e., individual organisations were not identified). Similarly, the support services organisations were originally asked to rate their satisfaction with each NZ and overseas drug development company that they had provided services to and this was amended to a rating of their overall satisfaction with NZ drug development companies and with overseas drug development companies.

Second, the pilot testing clarified the details of two questions and the following decisions were made:

- Drug development output for patents was specified to include only the original patents and not the numerous possible additions due to continuations and extensions of the original patents
- The time-point of a participant's career intention into drug development was clarified to be their plans at the time of completing their academic qualifications

Finally, the inclusion criteria for a drug development company was expanded to include companies developing a new indication of an existing medicine (i.e., repositioning of an older drug) rather than just companies developing a new chemical entity or novel compound.

These changes to the questionnaires were approved by the University of Auckland Human Participants Ethics Committee prior to collecting data from the rest of the research participants. The participants used for testing the questionnaires were not re-interviewed because of the amount of time that would be involved and because their responses to the questions that were later amended were clear.

3.2.5 Data Collection Procedures

After consideration of the options, administration of the data collection tools by individual semi-structured interview was chosen in preference over discussion groups and a survey independently completed by the participants. This approach was chosen to ensure a good response rate and would standardise the quality of the responses.

For this research it was expected that structured interviews would have several advantages over focus groups, even though more time would be needed to collect the data. First, it was important that the participants could provide their answers in a confidential environment that was free from any potential influences from other participants. It was felt that participants would be more likely to provide honest, potentially controversial, opinions in an one-on-one interview with the researcher than if they were in a group (253). Second, the slightly different questionnaires for each of the four different categories of participants meant that mixing participants from different groups could cause confusion. Finally, it was expected that it would be easier to arrange individual interviews to fit in

with the busy schedules of participants (258) rather than try and co-ordinate multiple people to be available at the same time and location.

The use of self-administered questionnaires was not considered feasible because of the number of questions to be asked and the mix of quantitative and qualitative questions. In addition, the participants would not be able to ask for clarification of any ambiguous questions and any participant's response that was unclear could not be clarified. Response rates to self-administered questionnaires are often lower than for face-to-face interviews (253) and it was important for this research that a good response rate was achieved because the potential participant pool was anticipated to be quite small.

Face-to-face interviews were conducted where possible and usually occurred at the participant's place of work so that they were comfortable in their surroundings and had access to information if needed to answer questions. Face-to-face interviews were not possible for some participants, especially those not located in Auckland. Some face-to-face interviews were conducted in Christchurch, Wellington and Tauranga, however it was not always feasible to travel to another city for every interview unless there were several in that location at a similar time. Nine interviews were therefore conducted by telephone and two by videoconference. The pilot questionnaires were administered in August and September, 2009 and the rest of the interviews were conducted between October, 2009 and April, 2010. The number of interviews to be conducted, the identification of further potential participants through snow-balling and the limited availability of some of the research participants meant that it was not possible to complete the data collection in a shorter timeframe. However, because of the type of data being collected, it was not anticipated that this would have a significant effect on the results of the research.

Most interviews lasted approximately an hour, although the interviews with stakeholders were generally only 15 to 30 minutes in duration. A brief introduction based on the Participant Information Sheet was provided at the start of each interview and written consent obtained at that point if it had not already been provided. Efforts were made to establish rapport with the research participants by making eye contact, not invading their personal space, dressing appropriately and treating the participants with respect. The first questions collected participant demographic data to help ease the participant into the interview and create some dialogue (255), although some researchers advocate collecting this information at the end of the interview (251).

If a response to any question was unclear the participant was politely asked to clarify their meaning (251). This was particularly important for the qualitative data collection, where often participants' responses were read back to them to ensure all information had been correctly captured (256). The appropriate questionnaire was used to structure the interview and record responses, however the

participants were asked to complete the Likert scale questions so that they could take time to read the question and consider the response options. All responses to questions were written only; the interviews were not recorded. All questions were asked in the same order for all participants, that is, in the same order as they appear in the questionnaires.

3.2.6 Participants

This research aimed to assess NZ's drug development industry and therefore it needed to include as many eligible representatives from the industry as possible (253). The industry comprises companies and organisations that have specialist skills in a wide range of areas such as medicinal chemistry, drug discovery, formulation, manufacturing, analytical services, clinical research, regulatory affairs, data management, statistics, intellectual property management and project management.

A senior representative (e.g., Professor, Chief Executive Officer, General Manager) of every organisation that appeared to meet the inclusion criteria was contacted and asked to participate in this research. If s/he was not able to participate personally but supported the organisation's participation, s/he was asked to consult with another suitable person in the organisation and provide their contact details if they were willing to participate. Some participants in the stakeholder category were identified because of their personal experience in the industry rather than representing a specific organisation. By approaching all potential organisations and potential stakeholders research bias in the participant selection was minimised.

Selection criteria were applied to each of the four industry categories to ensure that participants and their organisations were appropriate to be involved in the research (255). The selection criteria for each of the four categories of participants and organisations are described below.

3.2.6.1 Drug discovery groups

These were expected to be located in academic organisations (i.e., Universities and Crown Research Institutes) and potential drug discovery participants were identified through searches of appropriate websites, contacts at conferences and other information in the public domain. The initial contact was to ascertain whether their research could produce a compound that could be expected to be in clinical trials in the next 5 years. If so, a request to participate in the research was sent. Potential participants and organisations were identified from internet-based searches, industry conferences and snow-balling.

3.2.6.2 Drug development companies

All NZ registered companies that had initiated at least one clinical trial in the previous 5 years involving a novel compound were asked to participate in this research. A novel compound was

defined as a new chemical entity (NCE), or a reformulation or combination of an existing medicine, or a new indication for an existing medicine (i.e., generic medicine manufacture was not included). Drug development companies were identified by searches of clinical trial registration websites, general searches for NZ drug development companies and other information in the public domain (e.g., newspaper articles and advertisements to recruit study participants).

3.2.6.3 Support services organisations

These organisations were much more numerous than the NZ drug development companies because they usually provide their services to overseas pharmaceutical companies as well as to NZ companies. Support services organisations were identified by website searches, in particular the NZBio website, from trade displays at conferences and word of mouth.

3.2.6.4 Stakeholders

This category was used to obtain information from the wide range of organisations and people with experience in drug development. They were included because they may have contrasting or complementary views to the participants in the other categories (255). This category included representatives from government ministries, universities, investors, intellectual property lawyers and NZ affiliates of multinational pharmaceutical companies. Participants in the stakeholder category were only asked questions on the enablers and barriers to NZ's drug development industry and were not involved in the evaluation of NZ's expertise.

3.2.7 Response Rate

It was predicted that this research would involve contacting approximately 60 potential individuals. It was anticipated that the industry interest in the results of the research would facilitate a response rate of at least 50% from each category of participants and that this would be sufficient to allow valid conclusions to be drawn from the data.

Efforts were made to achieve the best response rates (257) by approaching each potential participant individually with a brief but clear request, usually by email but some by telephone, depending on which method they were judged to be more likely to respond to. Initial requests were followed up three times and the possibility of another senior person in the organisation substituting for the original person was offered if necessary.

Offering an incentive (e.g., book or petrol voucher) to participants was considered but discarded because it was anticipated that the participants would be senior representatives of their organisations and it was unlikely that their decision to participate would be influenced by an incentive. Flexibility with the interview time and location, and being well-prepared before conducting

the interview were considered important so that the interview could be conducted as efficiently as possible and participants were more likely to respond openly. It was anticipated that the best incentive to participate would be that the results of the research would be of value to the participants and their organisations and could be used to lobby for more funding and support for NZ's drug development industry.

Only 10 people declined to participate out of the 116 people approached and they were asked to provide a reason for their decision. The reasons were "too busy" (*N* = 2); "felt it would be inappropriate to participate" (*N* = 2); "now based in Europe" (*N* = 1); and the remaining five did not give a reason or would not respond to requests to participate. The 10 people who declined represented stakeholders (*N* = 7) and support services organisations (*N* = 3).

3.2.8 Expertise Data

The data collected to meet this objective included information on each of the participants and on the organisation they worked for. All participants held senior roles and so were able to answer the questions on behalf of their organisation. The data collected on the participants related to their personal expertise while the information on the organisations pertained to their knowledge management and innovative behaviours. Participants' demographic information and organisations' funding and business status were also collected. Note that participants in the Stakeholder category were not involved in the evaluation of expertise.

3.2.8.1 Participant information

The participant information was collected using the Participant questionnaire (refer to Appendix I) and consisted of:

- Current professional role/title
- Demographics–gender, age, qualifications, country of birth
- Percentage of time currently spent on drug development projects
- Drug development competencies–participants were asked to indicate these from a list provided
- Source of these competencies (i.e., from academic qualifications and/or from job experience)
- Number of years experience in drug development, membership of professional organisations and any relevant awards received
- Whether their career in drug development was intentional at time of completing their academic qualifications
- Drug development outputs they have produced or contributed to in the previous 3 years (i.e., patents or intellectual property applications, peer-reviewed publications, conference

presentations, peer-reviewed company documents such as research protocols or reports, and any other relevant outputs)

- Drug development job satisfaction and interest in continuing their career in drug development

3.2.8.2 Organisation information

The organisation information was collected using questionnaires specific to each of the three different industry sectors (refer to Appendices II, III and IV–Drug discovery group questionnaire, Drug development company questionnaire and Support services organisation questionnaire). These three questionnaires had many questions in common plus several organisation-specific items.

The following information was collected for each organisation:

- Range of drug development capabilities in the organisation (selected from a list provided in the questionnaire)
- Qualifications and experience of drug development staff in the organisation
- Perceived knowledge sharing behaviours within the organisation and externally (rated using a 5-point Likert scales)
- Perceived importance of sources for obtaining knowledge (rated using a 5-point Likert scale for each source). These sources are part of a longer list of sources used by Lui et al. (90); this shorter list used in NZ excluded items that were not relevant, such as training of sub-ordinates and interacting with those involved in technology transfer
    - Internal formal training (i.e., internal codified information)
    - Internal meeting (i.e., internal non-codified/tacit information)
    - Asking work colleagues (i.e., internal non-codified/tacit information)
    - Using external networks (i.e., external non-codified/tacit information)
    - Professional publications (i.e., external codified information)
    - Internet (i.e., external codified information)
- Perceived innovative performance of the organisation compared with its peers in the industry (rated using a 5-point Likert scale), for the following items (adapted from Thompson and Heron (113)):
    - Having new ideas
    - Developing contacts with outside experts
    - Making time to follow-through on own ideas and projects
    - Solving problems that have caused difficulty
    - Project planning
    - Innovative output
    - Teamwork

- Communication

The organisation-specific questions asked were:

- For NZ drug development companies:
  - Identification of novel compound/s in development
  - For each compound–source of its discovery (e.g., university, private research), potential indication/s and phase of development
  - Which drug development services were outsourced, whether to a NZ or overseas vendor, the reasons for selection of the vendors used and satisfaction with the services provided
- For NZ drug discovery groups:
  - Identification of compounds in discovery, at least one of which needed to be expected to enter phase I clinical trials in the next 5 years
  - For each compound–stage of discovery, year expected to enter phase I/clinical development, potential indication/s
- For NZ support services organisations:
  - Type of organisation (e.g., private company or public company, government funded organisation, private consultant)
  - Which drug development services were provided to NZ and to overseas companies, why their felt their services were selected over the alternatives and satisfaction with their interaction with the drug development company/s

3.2.9 Enablers and Barriers Data

Information on the enablers and barriers to NZ's drug development industry and how it could be further supported and developed was collected by asking all research participants the following three open questions:

- What factors have encouraged the drug discovery/development industry in NZ?
- What threats are there to NZ's drug discovery and development industry?
- What policies do you think would further support the NZ industry?

All participants, except stakeholders, were asked the following three open questions:

- What factors enabled your organisation to undertake its drug discovery/development projects in NZ?
- What are the main issues affecting your organisation in the next 3–5 years?
- What advice would you give to other NZ drug discovery and development organisations?

Finally, all participants were asked to rank eight suggested possible barriers to drug development in NZ. These barriers were identified through the literature review and from conference presentations. They were to be ranked in order of importance, with '1' assigned to the most important obstacle and '8' the least important barrier. Each participant had the option of specifying an additional barrier that had not been included in the list and then ranking all the barriers between '1' and '9'. If no additional barrier was specified, then that option received a default ranking of 9. The barriers provided were:

- Limited funding
- Limited local expertise and capabilities/experienced people have moved overseas
- Insufficient government policy to support the industry/lack of strategic direction
- Difficulty in determining a lead compound
- Lack of overall co-ordination between NZ's drug development organisations
- Insufficient understanding of the drug development process
- Overseas investors want to move the project away from New Zealand
- Issues with manufacturing or formulation
- Other (participant to specify any other barrier)

3.2.10 Economic Benefits Data

The potential economic benefits that could accrue to NZ are from two sources:

1. From the sales of a NZ-discovered compound that is still at least partially owned by a NZ entity when marketed as a medicine
2. From the provision of services to the global drug development industry

3.2.10.1 New Zealand-discovered medicines

Initially it was intended to calculate the potential revenue from NZ compounds in discovery and development phase and therefore the questionnaires administered to participants from the drug development companies and drug discovery groups requested the following information:

- Drug development companies—for each compound in development participants were asked to provide its potential indication/s, estimated year of launch and peak sales
- Drug discovery groups—for each lead compound participants were asked to provide the year it was expected to enter phase I and its potential indication/s

When questioning the drug development company participants it was found most could provide an indication of peak sales and these were usually a rough estimate. There are a large number of factors that influence the market potential of a compound and create uncertainty around estimations for compounds in early stages of development. Therefore, few pharmaceutical companies undertake

valuations on their development projects and there is no standard method employed (236). The planned approach of calculating the potential economic benefit to NZ from specific compounds in development was replaced with a scenario using a theoretical compound that had expected peak global sales of USD350 million. This approach was considered to be valid because the value to NZ is dependent on the market potential of the compound, the timing of the out-licence agreement and the level of risk associated with completing its development. The previous approach may also have required the application of too much information that was not publicly available and may have compromised participants' anonymity.

The calculation of returns to NZ were based on Kessel's data (235) on typical deal terms by compound stage of development, which was discussed in the literature review (Section 2.4.2). It was assumed that the compound was licensed-out as a lead candidate (i.e., without clinical data) with projected global peak sales of USD350 million. The compound was therefore not expected to be a blockbuster, but one with sufficient sales potential to attract an out-license deal. Sales projections were based on peak sales at Year 10 after product launch, with sales continuing to Year 20, because these timeframes were most commonly reported. Annual sales projections were calculated based on their percentage of Year 10 peak annual sales. The percentages followed a bell-shaped curve distribution around Year 10 with 100% for Year 10 because this was the year of peak sales. The approximately bell-shaped distribution was based on industry research by Cook (259) and Rasmussen (23) and the postulated percentages for each year from product launch are provided in Table 14.

Table 14 – Postulated Percentage of Peak Annual Sales for Year from Product Launch

Year from product launch	Percentage of peak sales	Year from product launch	Percentage of peak sales
1	30	11	90
2	40	12	80
3	50	13	75
4	60	14	70
5	70	15	60
6	80	16	50
7	85	17	40
8	90	18	35
9	95	19	30
10	100	20	25

Annual sales projections were multiplied by the successful phase completion probabilities based on data from DiMasi et al. (29). These successful phase completion (or phase transition) probabilities were discussed in Section 2.1.1 and are summarised in Table 15. Note that it is assumed that out-

licensed preclinical compound has completed sufficient preclinical testing to ensure it can start phase I clinical trials.

Table 15 – Phase Transition Probabilities

Phase transition	Transition percentage probability
Phase I–II transition	71%
Phase II–III transition	45%
Phase III–registration dossier submission transition	64%
Approval of registration dossier	93%

A preclinical out-license deal was assumed, and therefore the overall probability of the preclinical compound being approved for sale is 19% (i.e., 71% x 45% x 64% x 93%).

Royalty payments are estimated as a percentage of sales profit. We have used an average gross profit of 50%, which is the value of sales minus the 'costs of sales' and 'selling and administration costs' (23). This was used rather than the industry's overall profit of around 15%, which includes R&D costs because this was accounted for by including a probability of success factor in our calculations. Royalty payments for a compound with no clinical data was estimated to be 10% of profits, that is, lower than the 12–15% royalties typical for compounds with phase I data (235).

The out-licence of a promising drug discovery candidate could provide income as upfront and royalty payments for NZ's academic medicinal chemistry centres to expand and undertake more commercially directed research alongside their publicly funded research. An average cost of a medicinal chemist or biologist of NZD200,000 (USD168,000) was used to cover salary, rent, equipment and consumables costs (260).

A summary of the assumptions made for the calculation of revenue to NZ from a NZ-discovered compound and the rationale of these assumptions is provided in Table 16.

Table 16 – Assumptions for the Calculation of Potential Revenue to New Zealand from Drug Discovery

Parameter	Assumption	Basis of the assumption
Timing of out-license deal	Preclinical (i.e., without clinical data)	N/A
Local ownership when deal agreed	100%	N/A
Upfront payment	USD6.5 million	Research by Kessel and Frank (235)
Projected global peak sales	USD350 million	N/A
Time of global peak sales	Year 10 after product launch	Data from Danzon and Kim (239), Grabowski (49) and Hoyle (238)
Duration of sales	20 years	Data from Danzon and Kim (239), Grabowski (49) and Hoyle (238)
Sales for Year 1 to Year 20 as a percentage of peak annual sales	Bell-shaped curve, as described in Table 12	Data from Rasmussen (23) and Cook (259)
Probability that the compound is approved for sale	19%	Research by DiMasi and Feldman (29)
Average gross profit on sales	50%	Data from Rasmussen (23)
Royalty payments on sales profit	10%	Research by Kessel and Frank (235)

Where possible sensitivity analyses were conducted to check the validity and the effects of the assumptions made for the original analysis. Later timings of the out-license deal was considered by assuming the compound had positive phase I and phase II data and using the phase transition probabilities described in Table 15. With later out-licensing deals, the probability of the compound successfully completing phase III, product registration and sales increases (29), as summarised in Table 17, leading to higher potential returns to NZ.

Table 17 – Phase Transition Probabilities

Phase transition percentage probabilities[1]	Timing of the out-license deal		
	Preclinical	Post-phase I	Post-phase II
Percentage probability of successfully completing phase I and entering phase II	71.00%	N/A	N/A
Percentage probability of successfully completing phase I and II and entering phase III	31.95%	45.00%	N/A
Percentage probability of successfully completing phases I, II and III, and submitting a registration dossier	20.45%	28.80%	64.00%
Percentage probability of successfully completing phases I, II and III, and approval of the registration dossier	19.02%	26.78%	59.52%

[1] Probabilities are from DiMasi et al. (29)

Other sensitivity analysis used a range of higher peak annual sales, from USD50 million to USD1,000 million, a range of royalty payments (8% to 12%), a range of average gross profit on sales (40% to 60%) and a range of total cumulative sales for the 20 year product sales period. Sensitivity analyses were not conducted on the upfront payment amounts or the probabilities of successful completion of each stage of the drug development process, because these parameters were based on published research from extensive industry analysis.

3.2.10.2 Drug development support services

Two approaches were taken to assess the economic benefits to NZ from the provision of support services to the global pharmaceutical industry. The first approach was to include two questions in the support services organisations questionnaire regarding the level of their organisation's income from overseas. The second approach used clinical trial applications to estimate the value of clinical research to NZ. This was chosen because data from the objective of assessing NZ's expertise in drug development identified NZ's capabilities in clinical research and that often the clinical research was conducted for the pharmaceutical industry and therefore was a source of revenue for NZ. The details of these two approaches are given below.

(1) Participants from support services organisations were asked to provide the percentage of their revenue that was from supply of their services to overseas organisations, the locations of the organisations that they supplied their services to, and their business expectations for the next 3 years (i.e., whether they expected it to increase, remain about the same, or decrease).

For confidentiality reasons participants were not asked to divulge their organisation's annual revenue and since most were private companies or individuals acting as consultants to the industry, this information was not publicly available. However, the information that was able to be collected provided an indication of whether the overall revenue to NZ was likely to change in the next 3 years.

(2) A clinical trial conducted in NZ that involves a new chemical entity; a new or different dose form, delivery system or formulation of an established medicine; or a medicine that does not have consent to be marketed in NZ requires an exemption from the Medicines Act 1981. The exemption from the Act is obtained by applying to the Director-General of Health who will grant approval after receiving a favourable recommendation from SCOTT (Standing Committee on Therapeutic Trials) and the relevant accredited ethics committee. The approval is specific for the clinical trial protocol and investigator sites for which approval is sought (176).

SCOTT application databases were obtained from 1989 to 2011 and the data examined by year using the Committee's 1 July to 30 June reporting system. The information obtained from the SCOTT

application databases was investigated to assess the potential revenue to NZ from clinical research, but also to confirm the accuracy of the stated NZ expertise in this area.

For all applications the databases contained the date when the application was lodged, the trial sponsor name and address and the outcome of the application. The following data were also provided with each application lodged after 1 July, 1998: phase of the clinical trial as specified on the study protocol; expected number of participants in NZ and the number of NZ sites involved; and the expected total number of participants worldwide. Therefore, the total number of clinical trial applications approved each year, the expected number of NZ sites and NZ participants, and the phase of the study were analysed. Note that the few studies specified as being phase II/III were classified as phase II only because the phase II was likely to be the most critical. For trials to be included in this research they must have been recommended or approved by SCOTT. The anticipated NZ contribution to the participant population for each study and the expected average number of participants per study site in NZ was calculated. The sponsor information provided was used to code each trial into one of the following six sponsorship categories:

- NZ drug development company
- NZ affiliate of a multinational pharmaceutical company
- Multinational pharmaceutical company
- NZ CRO
- Overseas CRO
- NZ investigator or institution

The SCOTT information was then used to estimate the revenue to clinical trial sites performing research for the pharmaceutical industry, using an average per participant payment of NZD15,000 (USD12,600). This figure was not publicly available but was confirmed with several NZ organisations that undertake a large amount of the industry-sponsored clinical research. It is lower than estimates from the USA and this may reflect the lower costs of labour and services in NZ. The calculation for each year was based on the number of participants expected at NZ sites and the proportion of trials that were sponsored either directly or indirectly by a pharmaceutical company (i.e., the total number of trials from all sponsor types listed above except NZ investigator or institution). An average per participant payment of NZD15,000 (USD12,600) for the 2010/2011 year was used and reduced by 3% per year going back to the 1998/1999 year, which was the earliest year for which sufficient data were available. Therefore, the revenue to NZ each year could be estimated by multiplying the number of participants expected from industry-sponsored clinical trial applications by the per participant payment for that year. This calculation would not include other possible trial payments such as set-up

fees, ethics application submission, close-out and archiving costs. It also does not include the revenue to NZ from overseas funding of the sponsor costs of monitoring and managing the study sites.

3.3 Data Analysis and Statistics

A database was created in SPSS (Version 14.0) specifically for this research and the quantitative data was entered on an ongoing basis. This allowed for a check, soon after the interview, that the participant had provided answers to all questions. Where possible the database was programmed with field codes as a drop-down list for each variable and this facilitated data entry and the analyses. The data were analysed using SPSS software (Version 14.0) and the results are summarised as number (*N*) and percent (%); or as mean *(M)* ± standard deviation *(SD)* and range as appropriate. A range is given for variables where the standard deviation was very large due to the variability in the data. No formal statistical tests were conducted as the key hypotheses were not comparative. Additionally, ad-hoc comparisons within the dataset could not be undertaken because even though the sample researched contained almost the entire NZ industry the number of participants in each category was too small to allow valid statistical comparisons.

Qualitative data were transcribed from participants' questionnaires into a Microsoft Word template document that had been formatted for importation into NVivo 8 software. The transcription was undertaken as soon as possible after the interview. Transcriptions of participants' responses to the six open questions were individually reviewed for completeness and then imported into NVivo software. The use of NVivo software was chosen over manual coding methods because it should improve the consistency of coding and provide easier navigation around the data (256). These were important features given the large number of responses to be coded and then analysed.

A general inductive approach was used to analyse the qualitative data, which consisted of the participant's responses to the six open questions. The policy framework developed for the categorisation of the policies of different countries was also used as a basis for analysing the data. This approach was chosen because the objective was to identify and describe the most important themes from the responses rather than to generate theory, analyse social practices or to uncover meanings from experiences (261). Therefore, for each question a separate framework of themes and sub-themes was developed depending on the recurring topics emerging from the participants' responses; predetermined codes were not used (256). Once the coding had been completed for a question, the text allocated to each theme and sub-theme was reviewed to ensure it had been coded appropriately, a check was made of whether new themes or sub-themes had emerged, or whether the framework needed to be refined. This reliability checking (256) was conducted several times for coding of each of the six questions. Themes with a large number of text segments allocated to them were particularly scrutinised for sub-themes. Possible links between theme categories were explored

and diagrams drawn to illustrate the relationships. The number of participants whose response to a question was categorised into each theme or sub-theme is provided in the results section as number (*n*) and percent (%) of the total number of participants. The quantitative data on barriers to NZ's drug development industry were compared with the qualitative responses to the industry barriers to assess any convergence of the results (256). Figure 5 illustrates the steps for the analysis of the qualitative data.

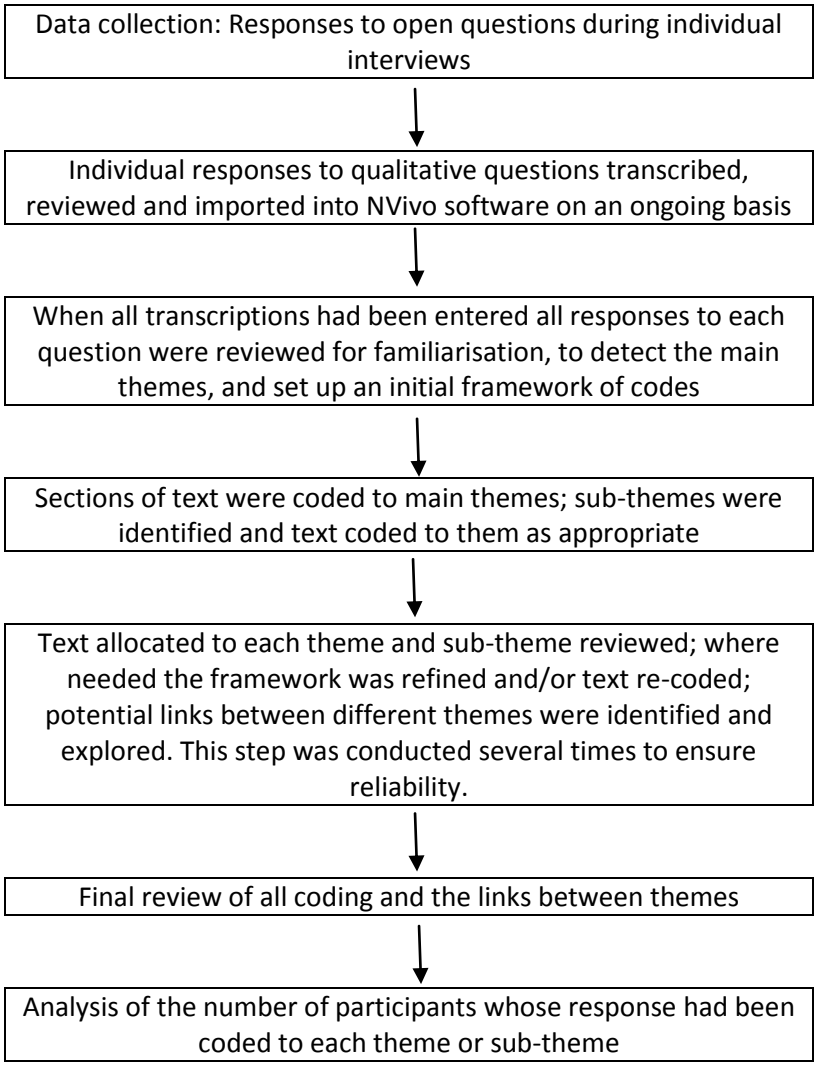

Figure 5 – Steps of the Qualitative Data Analysis

The data, both quantitative and qualitative, were not analysed until data entry was completed and checks had been conducted to ensure all participants' responses had been entered into the databases. As far as possible, attempts were made to collect data for all questions but some participants were not able or willing to answer all their questions. If data were unavailable for a question it was accepted that the number of respondents (N) would be smaller. Where this has occurred, a description of the category that non-responders belonged to is described with the results.

Results

4 Results

4.1 Participant Response Rate

It was anticipated that 60 people would be identified for this research and that approximately 50% would consent to participate. However, more people were identified than expected and the response rate was higher than anticipated. For the evaluation of industry expertise, 60 of the 63 identified people approached consented to participate, giving a response rate of 95.2%. The assessment of industry enablers and barriers included a stakeholder category and 106 of the 116 identified eligible people contacted agreed to participate, giving a response rate of 91.4% (Table 18). A single participant from each identified drug development company, drug discovery group and support services organisation meeting the inclusion criteria was approached, therefore the sample size could not simply be increased if the response rate was lower than expected (257). If the person approached was not available, another senior person form their organisation could be nominated to participate.

Table 18 – Number of Potential and Actual Participants by Category

Participant category	Number identified and approached to participate	Number who consented to participate	Response rate
Drug discovery groups	12	12	100%
Drug development companies	12	12	100%
Support services organisations	39	36	92.3%
Stakeholders	53	46	86.8%
Total	116	106	91.4%

The stakeholder category included those representing NZ government ministries and their agencies, universities (including their commercial entities), NZ affiliates of multinational pharmaceutical companies, those with extensive industry experience who did not fit into the other categories, investors, intellectual property and legal advisors and others. Further details of these participants are supplied in Section 4.3.4.

4.2 Participant Characteristics

This research involved representatives from 12 drug discovery groups, 12 drug development companies, 36 support services organisations and 46 industry stakeholders, giving a total of 106 participants. The gender and role of all participants are given in Table 19. The data confirm that participants were senior personnel from the organisation they represented. There was a predominance of male participants, especially representing drug discovery groups.

Table 19 – Participant Characteristics: Gender and Role

Participant demographics	Organisation represented				
	Drug discovery group *N* (%)	Drug develop-ment company *N* (%)	Support services organisation *N* (%)	Stake-holders *N* (%)	Total *N* (%)
Number of participants	12 (11.3)	12 (11.3)	36 (34.0)	46 (43.4)	106 (100)
Gender					
Male	10 (83.3)	8 (66.7)	25 (69.4)	29 (63.0)	72 (67.9)
Female	2 (16.7)	4 (33.3)	11 (30.6)	17 (37.0)	34 (32.1)
Role in the organisation					
Chief Executive Officer/ General Manager/Director	0 (0)	5 (41.7)	25 (69.4)	22 (47.8)	52 (49.1)
Senior Manager	1 (8.3)	2 (16.6)	9 (25.0)	19 (41.3)	31 (29.2)
Professor/Dean	9 (75.0)	0 (0)	2 (5.6)	4 (8.7)	15 (14.2)
Science Officer/Clinical/ Operations Manager	2 (16.7)	5 (41.7)	0 (0)	1 (2.2)	8 (7.5)

Table 20 provides the characteristics of the participants who contributed to the assessment of NZ's expertise (i.e., participants from the drug discovery groups, drug development companies and the support services organisations). It shows that the majority of all participants (77.7%) were aged 45 years or older, and all participants from the drug discovery groups were over 45 years. The participants were highly qualified and all had a tertiary qualification. The majority of participants (53.3%) had only degrees from NZ, 28.3% of participants had only overseas degrees, and 15% of participants had both NZ and overseas qualifications. The majority of all participants were born in NZ (56.7%), but many were born and educated overseas, especially those representing drug development companies. Twenty-five percent of all participants were born in the UK and the remaining participants were mainly from Australia, Asia and North America.

Table 20 – Participant Demographics: Age, Country of Birth and Qualifications

Participant demographics[1]	Organisation represented			
	Drug discovery group *N* (%)	Drug development company *N* (%)	Support services organisation *N* (%)	Total *N* (%)
Age (years)				
<25	0 (0)	0 (0)	0 (0)	0 (0)
25-34	0 (0)	0 (0)	3 (8.3)	3 (5.0)
35-44	0 (0)	4 (33.3)	7 (19.4)	11 (18.3)
45-54	4 (33.3)	3 (25.0)	15 (41.7)	22 (36.7)
55-64	5 (41.7)	4 (33.3)	10 (27.8)	19 (31.7)
>64	3 (25.0)	1 (8.3)	1 (2.8)	5 (8.3)
Country of birth				
NZ	8 (66.7)	5 (41.7)	21 (58.3)	34 (56.7)
UK	3 (25.0)	4 (33.3)	8 (22.2)	15 (25.0)
Australia	1 (8.3)	1 (8.3)	1 (2.8)	3 (5.0)
Asia	0 (0)	1 (8.3)	2 (5.6)	3 (5.0)
North America	0 (0)	1 (8.3)	1 (2.8)	2 (3.3)
Other	0 (0)	0 (0)	3 (8.3)	3 (5.0)
Highest NZ qualification[2]				
Bachelor degree or equivalent	0 (0)	1 (12.5)	6 (25)	7 (16.3)
Master degree	2 (18.2)	0 (0)	2 (8.3)	4 (9.3)
Medical degree	1 (9.1)	0 (0)	2 (8.3)	3 (7.0)
Post graduate medical	0 (0)	2 (25.0)	7 (29.2)	9 (20.9)
PhD	8 (72.7)	5 (62.5)	7 (29.2)	20 (46.5)
Total participants with NZ qualification	11 (100)	8 (100)	24 (100)	43 (100)
Highest overseas qualification[2]				
Bachelor degree or equivalent	0 (0)	1 (14.3)	6 (35.3)	7 (25.0)
Master degree	1 (25.0)	1 (14.3)	5 (29.4)	7 (25.0)
Medical degree	0 (0)	2 (28.6)	2 (11.8)	4 (14.3)
Post graduate medical	1 (25.0)	1 (14.3)	2 (11.8)	4 (14.3)
PhD	2 (50.0)	2 (28.6)	2 (11.8)	6 (21.4)
Total participants with overseas qualification	4 (100)	7 (100)	17 (100)	28 (100)
Total number of participants	**12 (20)**	**12 (20)**	**36 (60)**	**60 (100)**

[1]Data not collected from Stakeholders, therefore *N*=60

[2]Some participants had a qualification from both NZ and overseas and are therefore included in both sections

4.3 Organisation Characteristics

4.3.1 Drug Discovery Groups

The majority of the drug discovery groups are located in the universities, with funding from a variety of sources, but predominantly government and grant funding. My research found 12 drug discovery groups meeting the research election criteria. These 12 groups had a total of 20 drug discovery programmes underway, all of which originated from the group's own research (Table 21). Of the 20 programmes, seven had identified a lead compound and the remaining 13 were in the lead selection stage. Phase I clinical trials of all 20 programmes were predicted to start in the next 5 years from the

date of the interview: two compounds in 2010, two in 2011, four in 2012, five in 2013, six in 2014 and the remaining one in 2015.

Table 21 – Characteristics of the Drug Discovery Groups

Characteristic (*N* = 12)	**Result *N* (%)**	**Result *M* ± *SD* (range)**
Location of group		
University	10 (83.3)	
Crown Research Institute	1 (8.3)	
Private company	1 (8.3)	
Percent funded by		
NZ government/grants		61.2 ± 32.2% (0-100)
NZ private funding		19.4 ± 25.2% (0-70)
Overseas funding		9.0 ± 13.6% (0-33)
Personal funding		4.2 ± 14.4 (0-50)
Other		5.8 ± 17.3 (0-60)
Drug discovery research area (*N* = 20)[1]		
Oncology	7 (35.0)	
Anti-infective	3 (15.0)	
Cardiovascular and blood products	3 (15.0)	
Diabetes	2 (10.0)	
Neurology	1 (5.0)	
Gastro-intestinal	1 (5.0)	
Anti-inflammatory	1 (5.0)	
Miscellaneous	2 (10.0)	
Anticipated start of phase 1 (*N* = 20)[1]		
2010	2 (10.0)	
2011	2 (10.0)	
2012	4 (20.0)	
2013	5 (25.0)	
2014	6 (30.0)	
2015	1 (5.0)	

[1]Some drug discovery groups were working in more than one therapeutic area or had two distinct programmes in the same area (e.g., oncology).

4.3.2 Drug Development Companies

Most of the compounds under development originated from university or private research in NZ and the drug development companies were funded by a range of sources including overseas investors and private funding from NZ (Table 22). The expected year of product launch was 2011 (one compound); 2012 (two compounds); 2013 (one compound); 2014 (four compounds); 2015 (one compound) and 2016 (one compound). This information was not available for two compounds—one had been discontinued due to lack of efficacy and the timing of the product launch for the second compound was unknown.

Table 22 – Characteristics of the Drug Development Companies

Characteristic (*N* = 12)	**Result *N* (%)**	**Result *M* ± *SD* (range)**
Number of years since company formed		9.5 ± 6.1 years (1 – 21)
Source of compound in development		
University research	6 (50.0)	
Private research	4 (33.3)	
CRI/Government funded	1 (8.3)	
University and private partnership	1 (8.3)	
Percent funded by		
Overseas funding		34.9 ± 40.1% (0 – 100)
NZ private funding		31.2 ± 37.1% (0 – 97)
NZ government/grants		17.6 ± 33.3% (0 – 91)
Personal funding		8.8 ± 28.8% (0 – 100)
Publicly listed company		7.5 ± 26.0 % (9 – 90)
Development phase of most advanced indication		
Phase I	2 (16.7)	
Phase II	8 (66.7)	
Phase III	1 (8.3)	
Discontinued	1 (8.3)	
Therapeutic areas of compound/s in development (*N* = 18)[1] Oncology	4 (22.2)	
Dermatology	3 (16.7)	
Neurology	3 (16.7)	
Cardiovascular	2 (11.1)	
Diabetes	1 (5.6)	
Hepatology	1 (5.6)	
Ophthalmology	1 (5.6)	
Rheumatology	1 (5.6)	
Analgesia	1 (5.6)	
Infectious diseases	1 (5.6)	

[1]Some drug development companies had a compound in more than one therapeutic area, giving a total of 18 programmes in place.

4.3.3 Support Services Organisations

The characteristics of the support services organisations are provided in Table 23. The majority of organisations surveyed were private companies or consultants and so were self-funding. They had been in operation for an average of 11.6 years.

Table 23 – Characteristics of the Support Services Organisations

Characteristic (*N* = 36)	Result *N* (%)	Result *M* ± *SD* (range)
Type of organisation		
Private company	17 (47.2%)	
Independent consultant	8 (22.2%)	
University department	4 (11.1%)	
Public company	2 (5.6%)	
Crown Research Institute	2 (5.6%)	
Charitable Trust	2 (5.6%)	
Hospital department	1 (2.8%)	
Number of years since organisation formed		11.6 ± 10.5 (0.5 – 42.0)
Percent funded by		
Self-funded	84.4 ± 32.2% (0 – 100)	
NZ government grants	9.8 ± 25.6% (0 – 100)	
Publicly listed company	2.8 ± 16.7% (0 – 100)	
Overseas funding	0.42 ± 2.5% (0 – 15)	
Other[1]	2.58 ± 8.7% (0 – 33)	

[1]Other funding includes non-government/private grants and support of the local District Health Board

4.3.4 Stakeholders

The stakeholder category included those representing NZ government ministries and their agencies, universities (including their commercial entities), NZ affiliates of multinational pharmaceutical companies, those with extensive industry experience who did not fit into the other categories, investors, intellectual property and legal advisors and others (Table 24).

Table 24 – Characteristics of the Stakeholder Representatives

Type of stakeholder	*N* (%)
Government ministries and agencies	9 (19.6)
University representatives	8 (17.4)
NZ subsidiaries of multi-national pharmaceutical companies conducting research in NZ	5 (10.9)
Representatives with significant industry expertise	5 (10.9)
Investment representatives	8 (17.4)
Intellectual property and legal representatives	5 (10.9)
Other [1]	6 (13.0)
Total	46 (100)

[1]Each participant represented one of the following: an ethics committee, a District Health Board Research Office, an industry organisation, or was an industry auditor, has extensive regulatory expertise or had undertaken research for the industry.

4.4 Expertise

4.4.1 Participants' Expertise

The participants had a mean of 19.1 years experience in drug development. The main source of participants' expertise in their drug development role was from job experience rather than their qualifications, although participants in drug discovery utilised their qualifications more than the other

participants (Table 25). More than 80% of participants did not intend a career in drug development when they were undertaking their qualifications.

Approximately half of the participants had acquired a specific drug development skill; the most common was training for clinical research (i.e., Good Clinical Practice, Clinical Research Associate or other pharmaceutical industry training). The most common relevant organisations that participants belonged to were NZBio and the NZ Association of Clinical Research (NZACReS) ARCS, followed by the American Association for Cancer Research (AACR) and the NZ Institute of Chemistry (NZIC). Other relevant organisations were the NZ Society of Oncology, the Biometrics Society and the Royal Society of NZ.

Nine participants (15%) had received national or professional society awards recognising the quality and contributions of their drug development activities. These awards included NZBio Biotechnologist of the Year, New Zealand Order of Merit, and other awards from organisations such as the Royal Society of New Zealand.

Table 25 – Participant Expertise in Drug Development

Participant expertise in drug development	Organisation represented			
	Drug discovery group (*N* = 12)	Drug development company (*N* = 12)	Support services organisation (*N* = 36)	Total (*N* = 60)
Time spent on drug development projects (*M* ± *SD*)	63.5 ± 38.6%	66.7 ± 35.6%	55.8 ± 36.9	59.5 ± 36.7
(range)	(2 – 100%)	(10 – 100%)	(5 – 100%)	(2 – 100%)
Source of skills for drug development				
Qualifications (*M* ± *SD*)	30.8 ± 17.8%	13.1 ± 13.7%	19.4 ± 20.0%	20.4 ± 19.1%
(range)	(10 – 50%)	(0 – 40%)	(0 – 80%)	(0 – 80%)
Job experience (*M* ± *SD*)	69.2 ± 17.8%	86.9 ± 13.7%	80.6 ± 20.0%	79.6 ± 19.1%
(range)	(50 – 90%)	(60 – 100%)	(20 – 100%)	(20 – 100%)
Number of years experience in drug development (*M* ± *SD*)	24.7 ± 10.7	16.4 ± 6.8	18.1 ± 9.5	19.1 ± 9.6
Career into drug development				
Intentional *N* (%)	4 (33.3%)	1 (8.3%)	6 (16.7%)	11 (18.3%)
Accidental *N* (%)	8 (66.7%)	11 (91.7%)	30 (83.3%)	49 (81.7%)
Specific drug development skills acquired from[1]				
Qualifications	0	1	3	4
Industry clinical research training	1	2	16	19
Conferences	1	2	1	4
Other (e.g. audits, GLP or GMP)	1	1	5	7
Total number of specific skills	3	6	25	34
Membership of relevant organisations[1]				
NZBio	4	8	6	18
NZACReS / ARCS	0	1	15	16
AACR	2	1	0	3
NZIC	0	1	2	3
AusBiotech	1	2	0	3
Other	2	0	4	6
Total number of memberships	9	13	27	49
Received an award for drug development *N* (%)	5 (41.7%)	0 (0%)	4 (11.1%)	9 (15.0%)

[1]Participants could provide more than one response

Table 26 summarises the drug development outputs that participants had contributed to in the previous 3 years. The most common drug development outputs produced were internal reviewed documents by 80.0% of participants (e.g., reports, study protocols) and conference presentations by 73.3% of participants. Other outputs included reports and presentations outside the organisations (e.g., to regulatory authorities, feasibility reports, company reports) and conducting training courses.

Table 26 – Participants Drug Development Outputs

Drug development outputs		Organisation represented			
		Drug discovery group (*N* = 12)	Drug development company (*N* = 12)	Drug discovery group (*N* = 12)	Drug development company (*N* = 12)
Patents					
Number of participants	*N* (%)[1]	8 (66.7%)	10 (83.3%)	8 (22.2%)	26 (43.3%)
Number of patents	*M* (range)[2]	7.4 (1-23)	4.7 (1-10)	2.5 (1-6)	4.8 (1-23)
Publications					
Number of participants	*N* (%)[1]	11 (91.7%)	8 (66.7%)	17 (47.2%)	36 (60.0%)
Number of publications	*M* (range)[2]	42.0 (6-270)	6.3 (1-15)	12.1 (1-90)	19.9 (1-270)
Conference presentations					
Number of participants	*N* (%)[1]	11 (91.7%)	11 (91.7%)	22 (61.1%)	44 (73.3%)
Number of presentations	*M* (range)[2]	21.2 (4-100)	10.4 (1-65)	16.0 (1-180)	15.9 (1-180)
Internal reviewed documents					
Number of participants	*N* (%)[1]	8 (66.7%)	10 (83.3%)	30 (83.3%)	48 (80.0%)
Number of patents	*M* (range)[2]	21.0 (2-50)	48.6 (2-300)	34.5 (2-100)	35.2 (2-300)
Other					
Number of participants	*N* (%)[1]	3 (25.0%)	4 (33.3%)	10 (27.8%)	17 (47.2%)
Number	*M* (range)[2]	15.0 (2-25)	8.8 (5-15)	7.1 (1-20)	8.9 (1-25)

[1]Number of participants who contributed to the output
[2]Mean number of outputs for the participants who contributed to that output

4.4.2 Participants' Capabilities

Participants were provided with a list of capabilities associated with drug development and asked to indicate which ones they could personally undertake. Merely understanding the process involved was not sufficient for a participant to be able to indicate capability in that field. Once a capability was indicated, participants were asked to specify whether the source of their competency in that area was from their qualifications, job experience or both. The number (*N*) of participants responding to each of these options for the source of their competency is given for each capability.

The results of these questions are summarised in Table 27. As could be expected, the drug discovery groups' expertise is focused on discovery and chemistry/scale-up manufacturing. The drug development companies have extensive expertise in clinical protocol development, regulatory affairs and intellectual property management. The support services organisations have strengths in clinical trial monitoring and management, case report form preparation, database/data management, safety data management, regulatory affairs, clinical protocol development and acting as a study site. All three categories of participants have expertise in the more generic capabilities of project management and report preparation.

Fifteen participants indicated that they had capability in an additional area of drug development. Two drug discovery group participants had extra capabilities; one as an expert witness for intellectual

property litigation cases, and the other had responsibility for the whole preclinical development process. Two drug development company representatives had expertise in fundraising; one also had general management experience. Eleven of the support services organisation participants nominated capabilities in fundraising and strategic/regulatory management (*N* = 4), licensing and business development (*N* = 2), pre-clinical research and documentation (*N* = 2), developing applications for a new chemical entity (*N* = 1), distribution of study drugs (*N* = 1) and patient recruitment for clinical trials (*N* = 1).

Table 27 – Participant Capabilities and Source of Capabilities

Participant capabilities and source of capabilities	Organisation represented			
	Drug discovery (*N* = 12)	Drug development (*N* = 12)	Support services (*N* = 36)	Total (*N* = 60)
Drug discovery *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	11 (91.7) 0 : 2 : 9	5 (41.7) 0 : 1 : 4	4 (11.1) 0 : 1 : 3	20 (33.3) 0 : 4 : 16
Chemistry/scale-up manufacturing *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	5 (41.7) 0: 0 : 5	6 (50.0) 0 : 3 : 3	3 (8.3) 0 : 0 : 3	14 (23.3) 0 : 3 : 11
GMP manufacture of API[1] *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	2 (16.7) 0 : 0 : 2	6 (50.0) 0 : 4 : 2	5 (13.9) 0 : 3 : 2	13 (21.7) 0 : 7 : 6
Formulation *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	2 (16.7) 0 : 1 : 1	5 (41.7) 0 : 3 : 2	3 (8.3) 0 : 1 : 2	10 (16.7) 0 : 5 : 5
GMP[2] manufacture of drug product *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	3 (25.0) 0 : 2 : 1	5 (41.7) 0 : 3 : 2	2 (5.5) 0 : 1 :1	10 (16.7) 0 : 6 : 4
Package / label drug product *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	1 (8.3) 0 : 0 : 1	3 (25.0) 0 : 3 : 0	8 (22.2) 0 : 6 : 2	12 (20.0) 0 : 9 : 3
Analytical/stability data *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	3 (25.0) 1 : 1 : 1	6 (50.0) 0 : 4 : 2	6 (16.7) 0 : 2 : 4	15 (25.0) 1 : 7 : 7
Case Report Form preparation *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	0 (0) 0 : 0 : 0	4 (33.3) 0 : 3 : 1	16 (44.4) 0 : 13 : 3	20 (33.3) 0 : 16 : 4
Database / data management *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	2 (16.7) 1 : 1 : 0	5 (41.7) 0 : 4 : 1	14 (38.9) 2 : 10 : 2	21 (35.0) 3 : 15 : 3
Pre-clinical testing *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	8 (66.7) 0 : 2 : 6	4 (33.3) 0 : 1 : 3	7 (19.4) 0 : 4 : 3	19 (31.7) 0 : 7 : 12
Safety data management *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	1 (8.3) 0 : 0 : 1	4 (33.3) 0 : 4 : 0	14 (38.9) 0 : 11 : 3	19 (31.7) 0 : 15 : 4
Statistics *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	3 (25.0) 0 : 2 : 1	5 (41.7) 0 : 1 : 4	11 (30.6) 0 : 6 : 5	19 (31.7) 0 : 9 : 10
Clinical protocol development *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	3 (25.0) 0 : 2 : 1	9 (75.0) 0 : 7 : 2	21 (58.3) 0 : 16 : 5	33 (55.0) 0 : 25 : 8
Clinical trial management *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	3 (25.0) 0 : 2 : 1	6 (50.0) 0 : 5 : 1	16 (44.4) 0 : 12 : 4	25 (41.7) 0 : 19 : 6
Clinical study site *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	0 (0) 0 : 0 : 0	1 (8.3) 0 : 1 : 0	14 (38.9) 0 : 10 : 4	15 (25.0) 0 : 11 : 4
Report preparation *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	5 (41.7) 0 : 5 : 2	9 (75.0) 0 : 6 : 3	28 (77.8) 0 : 19 : 9	44 (73.3) 0 : 30 : 14
Project management *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	9 (75.0) 0 : 6 : 3	10 (83.3) 0 : 8 : 2	28 (77.8) 0 : 20 : 8	47 (78.3) 0 : 34 : 13
Regulatory affairs *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	2 (16.7) 0 : 1 : 1	9 (75.0) 0 : 7 : 2	19 (52.8) 0 : 15 : 4	30 (50.0) 0 : 23 : 7
Bioanalysis *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	3 (25.0) 0 : 1 : 2	4 (33.3) 1 : 2 : 1	4 (11.1) 0 : 1 : 3	11 (18.3) 1 : 4 : 6
Intellectual property management *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	6 (50.0) 0 : 5 : 1	9 (75.0) 0 : 8 : 1	5 (13.9) 0 : 3 : 2	20 (33.3) 0 : 1 : 4
Other capability *N* (%) Qualification(*N*): Experience(*N*) : Both(*N*)	2 (16.7) 0 : 0 : 2	2 (16.7) 0 : 2 : 0	11 (30.6) 0 : 7 : 4	15 (25.0) 0 : 9 : 6

[1]API = Active Pharmaceutical Ingredient

[2]GMP = Good Manufacturing Practice

4.4.3 Participants' Career Satisfaction

Participants were provided with 5-point Likert scales to rate their satisfaction with their current role in drug development and their interest in continuing their career in drug development. The scales used '1' for participants to indicate that they were 'very unsatisfied' or 'very uninterested' and '5' that they were 'very satisfied' or 'very interested'.

The results in Table 28 indicate a high level of satisfaction from participants in the drug development companies and the support services organisations with mean scores of 4.17. Participants from the drug discovery groups were less satisfied with their current role than the other categories of participants but were more interested in continuing their career in drug development. All three organisation groups showed more interest in continuing their careers in drug development than their satisfaction with their current role.

Table 28 – Participant Career Satisfaction

Participant career satisfaction	**Organisation represented (mean ± *SD*)**		
	Drug discovery group (*N* = 12)	Drug development company (*N* = 12)	Support services organisation (*N* = 36)
Current drug development role	3.75 ± 1.1	4.17 ± 0.72	4.17 ± 0.77
Interest in continuing career in drug development	4.83 ± 0.39	4.50 ± 0.52	4.50 ± 0.89

Figure **6** illustrates the percentage of participants who were 'satisfied' or 'very satisfied' with their current career in drug development and the percentage of participants who were 'interested' or 'very interested' in continuing their career in drug development.

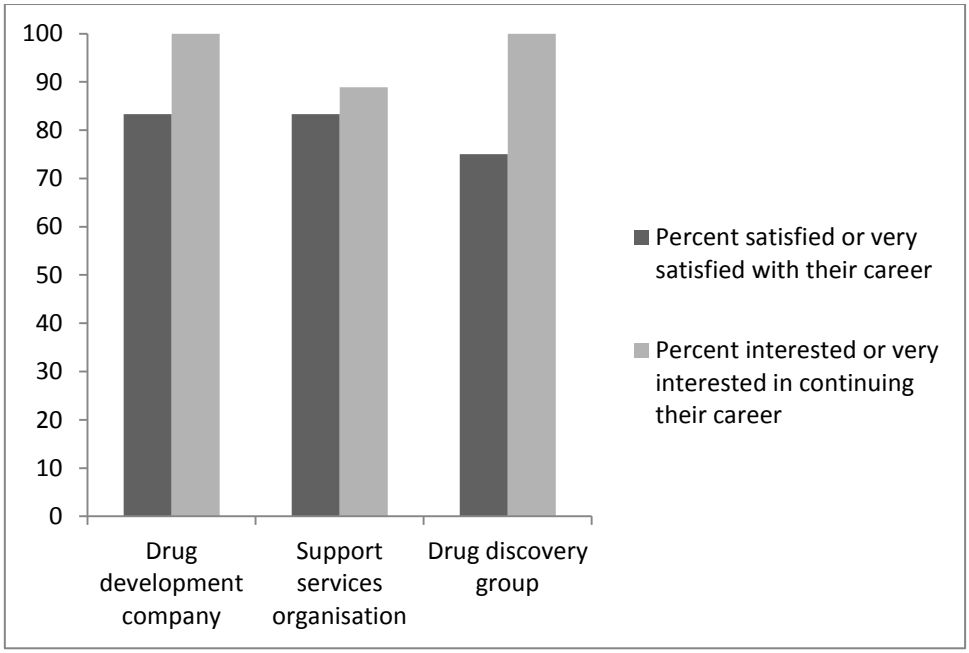

Figure 6 – Participant Career Satisfaction

4.4.4 Organisations' Capabilities

4.4.4.1 Drug discovery groups

Table 29 illustrates the capabilities that the drug discovery groups have access to (i.e., within the group and/or within their network) and which they would have to outsource to some level. Most of the capabilities listed would need to be outsourced because they are required for clinical development including compliance with Good Manufacturing Practice (GMP) production of the active pharmaceutical ingredient (API) and the final drug product to be used in clinical trials.

Table 29 – Summary of the Drug Discovery Group Capabilities

Drug discovery group capabilities (*N* = 12)	Within the group	Within the group's network	Both within the group and its network	Need to outsource
Drug discovery *N* (%)	8 (66.7)	1 (8.3)	3 (25.0)	0 (0)
Chemistry/scale-up manufacturing *N* (%)	4 (33.3)	6 (50.0)	2 (16.7)	0 (0)
GMP manufacture of API *N* (%)	4 (33.3)	0 (0)	1 (8.3)	7 (58.3)
Formulation *N* (%)	1 (8.3)	8 (75.0)	1 (8.3)	2 (16.7)
GMP manufacture of drug product *N* (%)	0 (0)	2 (16.7)	0 (0)	10 (83.3)
Package / label drug product *N* (%)	0 (0)	3 (25.0)	0 (0)	9 (75.0)
Analytical/stability data *N* (%)	2 (16.7)	5 (41.7)	1 (8.3)	4 (33.3)
Case Report Form preparation *N* (%)	0 (0)	3 (25.0)	0 (0)	9 (75.0)
Database / data management *N* (%)	4 (33.3)	4 (33.3)	0 (0)	4 (33.3)
Pre-clinical testing *N* (%)[1]	3 (25.0)	3 (25.0)	3 (25.0)	3 (25.0)
Safety data management *N* (%)	0 (0)	1 (8.3)	0 (0)	11 (91.7)
Statistics *N* (%)	1 (8.3)	4 (33.3)	0 (0)	7 (58.3)
Clinical protocol development *N* (%)	0 (0)	4 (33.3)	1 (8.3)	7 (58.3)
Clinical trial monitoring / management *N* (%)	0 (0)	4 (33.3)	0 (0)	8 (66.7)
Clinical study site *N* (%)	0 (0)	4 (33.3)	0 (0)	8 (66.7)
Report preparation *N* (%)	4 (33.3)	3 (25.0)	1 (8.3)	4 (33.3)
Project management *N* (%)	4 (33.3)	2 (16.7)	2 (16.7)	4 (33.3)
Regulatory affairs *N* (%)	2 (16.7)	0 (0)	1 (8.3)	9 (75.0)
Bioanalysis *N* (%)	1 (8.3)	4 (33.3)	1 (8.3)	6 (50.0)
Intellectual property management *N* (%)	3 (25.0)	3 (25.0)	3 (25.0)	3 (25.0)

[1]Preclinical testing is only to Good Laboratory Practice (GLP) at one facility; the remaining organisations could undertake exploratory preclinical research only

Table 30 provides the number of people in each of the roles in the drug discovery groups, their highest qualification and number of years' experience in drug development. The *N* for each role provides the number of drug discovery groups that have people in the specified role.

Table 30 – Qualifications and Experience in the Drug Discovery Groups

Qualifications and experience – drug discovery groups (*N* = 12)	**Number in the role[1] *M* ± *SD* (range)**	**Qualifications PhD : Masters : Bachelor**	**Years experience *M* ± *SD* (range)**
Research Project Leader (*N* = 12)	1.1 ± 0.3 (6 – 40)	12 : 1 : 0	25.4 ± 11.5 (6 – 40)
Senior Scientist (*N* = 5)	5.4 ± 3.9 (1 – 10)	27 : 0 : 0	12.0 ± 5.7 (5 – 20)
Scientist (*N* = 11)	8.8 ± 6.2 (2 – 20)	97 : 0 : 0	7.2 ± 3.2 (5 – 15)
Technician (*N* = 8)	7.9 ± 5.5 (1 – 15)	10 : 45 : 5	4.6 ± 3.0 (1 – 10)

[1]The results pro rata the amount of time in the role for people who are not full-time

4.4.4.2 Drug development companies

Table 31 illustrates the capabilities that the drug development companies have in-house, the capabilities that are outsourced entirely to a NZ or overseas based vendor, and the capabilities that are provided both in-house and by an external vendor. The main capabilities that are outsourced relate to production of study drug (i.e., GMP manufacture of the API and drug product, formulation, packaging and labelling, and analytical/stability data) and some aspects of clinical research (e.g., database/data management, statistics, clinical study sites, regulatory affairs and bioanalysis). The capabilities that are outsourced to overseas vendors relate to production of study drug while those outsourced to NZ vendors tend to relate to the clinical research programme. Clinical protocol development and report preparation are the capabilities most commonly undertaken entirely in-house by the drug development companies.

Table 31 – Summary of the Drug Development Company Capabilities

Drug development company (*N* = 12)[1]	In-house entirely	Entirely NZ vendor	Entirely overseas vendor	In-house + NZ vendor	In-house + overseas vendor
Drug discovery *N* (%) [*N* = 11]	7 (63.6)	2 (16.7)	0 (0)	1 (8.3)	1 (8.3)
Chemistry/scale-up manufacturing *N* (%)	4 (33.3)	1 (8.3)	5 (41.7)	0 (0)	2 (16.7)
GMP manufacture of API *N* (%)	2 (16.7)	2 (16.7)	8 (66.7)	0 (0)	0 (0)
Formulation *N* (%)	1 (8.3)	2 (16.7)	8 (66.7)	1 (8.3)	0 (0)
GMP manufacture of drug product *N* (%)	2 (16.7)	2 (16.7)	8 (66.7)	0 (0)	0 (0)
Package / label drug product *N* (%)	1 (8.3)	1 (8.3)	9 (75.0)	0 (0)	1 (8.3)
Analytical/stability data *N* (%)	1 (8.3)	2 (16.7)	7 (58.3)	0 (0)	2 (16.7)
Case report form preparation *N* (%)	7 (58.3)	1 (8.3)	1 (8.3)	2 (16.7)	2 (16.7)
Database / data management *N* (%)	2 (16.7)	3 25.0)	2 (16.7)	4 (33.3)	3 (25.0)
Pre-clinical testing *N* (%) [*N* = 11]	4 (33.3)	0 (0)	4 (33.3)	3 (25.0)	1 (8.3)
Safety data management *N* (%)	5 (41.7)	0 (0)	5 (41.7)	1 (8.3)	0 (0)
Statistics *N* (%)	3 (25.0)	4 (33.3)	3 (25.0)	1 (8.3)	2 (16.7)
Clinical protocol development *N* (%)	8 (66.7)	0 (0)	1 (8.3)	3 (25.0)	1 (8.3)
Clinical trial monitoring / management *N* (%)	4 (33.3)	0 (0)	1 (8.3)	4 (33.3)	5 (41.7)
Clinical study site *N* (%)	0 (0)	6 (50.0)	4 (33.3)	2 (16.7)	1 (8.3)
Report preparation *N* (%)	7 (58.3)	0 (0)	1 (8.3)	1 (8.3)	4 (33.3)
Project management *N* (%)	5 (41.7)	0 (0)	1 (8.3)	2 (16.7)	4 (33.3)
Regulatory affairs *N* (%)	4 (33.3)	0 (0)	3 (25.0)	0 (0)	5 (41.7)
Bioanalysis *N* (%) [*N* = 11]	1 (8.3)	2 (16.7)	5 (41.7)	1 (8.3)	2 (16.7)
Intellectual property management *N* (%)	2 (16.7)	4 (33.3)	1 (8.3)	1 (8.3)	4 (33.3)

[1]A company could partly outsource a function to a NZ vendor and an overseas vendor while still contributing to it in-house, therefore some rows will add up to more than 12. Some companies did not require a given capability so *N* = 11 for these capabilities.

Table 32 depicts the number of people in each of the roles in the drug development companies, their highest qualification and number of years' experience in drug development. The *N* for each role provides the number of drug development companies that have people in the specified role in NZ. Note that for some companies, roles are provided by overseas consultants and these people are not included in the table. Other roles are scientists (*N* = 8), animal facilities staff (*N* = 25), quality assurance scientists (*N* = 7), manufacturing specialist (*N* = 2), and safety officer (*N* = 1) in seven drug development companies.

Table 32 – Qualifications and Experience in the Drug Development Companies

Qualifications and experience—drug development companies (*N* = 12)	Number in the role *M* ± *SD* (range)	Qualifications PhD : Masters : Bachelor	Years experience *M* ± *SD* (range)
CEO (*N* = 9)	0.94 ± 0.17 (0.5 – 1)	5 : 1 : 3	16.1 ± 8.5 (5 – 30)
Project Manager (*N* = 9)	1.6 ± 1.4 (0.7 – 5)	10 : 1 : 4	13.4 ± 4.5 (8 – 22)
Study Manager (*N* = 2)	2.0 ± 1.4 (1 – 3)	1 : 0 : 3	4.0 ± 1.4 (3 – 5)
Regulatory Affairs (*N* = 3)	1.7 ± 1.2 (1 – 3)	1 : 1 : 1	6.7 ± 2.9 (5 – 10)
Other (*N* = 7)	6.5 ± 8.4 (1 – 25)	12 : 3 : 3 : 25[1]	4.4 ± 0.9 (3 – 5)

[1]No academic qualification

4.4.4.3 Support services organisations

Table 33 provides the capabilities provided by the support services organisations, to both NZ and overseas drug development companies. The most common services supplied are project management, report preparation, clinical protocol development, clinical trial monitoring/management and regulatory affairs. The support services provided to NZ drug development companies were statistics, CRF preparation, packaging/labelling of study drug, database and management, project management and regulatory affairs. The overseas drug development companies used the support services organisations for project management, report preparation, clinical protocol development, safety data management, clinical study sites, and clinical trial monitoring and management.

Table 33 – Summary of the Support Service Organisations' Capabilities

Support services (*N* = 36) capabilities that were provided	**Recipient of support services**			
	NZ drug develop-ment companies	Overseas drug develop-ment companies	Both NZ and overseas drug develop-ment companies	Total support services organisat-ions with capability
Drug discovery *N* (%)	2 (5.6)	3 (8.3)	1 (2.8)	6 (16.7)
Chemistry/scale-up manufacturing *N* (%)	1 (2.8)	1 (2.8)	2 (5.6)	4 (11.1)
GMP manufacture of API *N* (%)	1 (2.8)	2 (5.6)	2 (5.6)	5 (13.9)
Formulation *N* (%)	2 (5.6)	0 (0)	1 (2.8)	3 (8.3)
GMP manufacture of drug product *N* (%)	1 (2.8)	0 (0)	2 (5.6)	3 (8.3)
Package / label drug product *N* (%)	4 (11.1)	0 (0)	6 (16.7)	10 (27.8)
Analytical/stability data *N* (%)	2 (5.6)	2 (5.6)	4 (11.1)	8 (22.2)
Case report form preparation *N* (%)	5 (13.9)	3 (8.3)	9 (25.0)	17 (47.2)
Database / data management *N* (%)	4 (11.1)	1 (2.8)	10 (27.8)	15 (41.7)
Pre-clinical testing *N* (%)	2 (5.6)	2 (5.6)	4 (11.1)	8 (22.2)
Safety data management *N* (%)	1 (2.8)	5 (13.9)	9 (25.0)	15 (41.7)
Statistics *N* (%)	5 (13.9)	1 (2.8)	7 (19.4)	13 (36.1)
Clinical protocol development *N* (%)	3 (8.3)	5 (13.9)	14 (38.9)	22 (61.1)
Clinical trial monitoring / management *N* (%)	2 (5.6)	4 (11.1)	13 (36.1)	19 (52.8)
Clinical study site *N* (%)	1 (2.8)	4 (11.1)	10 (27.8)	15 (41.7)
Report preparation *N* (%)	3 (8.3)	6 (16.7)	19 (52.8)	28 (77.8)
Project management *N* (%)	4 (11.1)	6 (16.7)	19 (52.8)	29 (80.6)
Regulatory affairs *N* (%)	4 (11.1)	3 (8.3)	12 (33.3)	19 (52.8)
Bioanalysis *N* (%)	1 (2.8)	1 (2.8)	3 (8.3)	5 (13.9)
Intellectual property management *N* (%)	2 (5.6)	1 (2.8)	0 (0)	3 (8.3)
Other capabilities *N* (%)[1]	8 (22.2)	0 (0)	7 (19.4)	15 (41.7)

[1]Other services provided by one support service organisation to NZ drug development companies are: development support, assisting companies raise funding, HPLC training, assistance with preclinical documents, regulatory and intellectual property strategy, tissue bank, general advice and non-GMP manufacture. Other capabilities provided by one support service organisation to both NZ and overseas drug development companies are: ethics and regulatory applications, position on company board, clinical trial participant recruitment, preclinical protocols, research applications of the platform technology, storage and distribution of study drug and strategic planning.

Table 34 provides the number of people in each of the roles in the support services organisations, their highest qualification and number of years' experience in drug development. The *N* for each role provides the number of support services organisations that have people in the specified role in NZ. Clinical research roles include study manager, study co-ordinator and clinical research associate (CRA). Other roles are study nurses (*N* = 25), laboratory staff and analysts (*N* = 3), scientists (*N* = 11), finance officers (*N* = 17), regulatory affairs (*N* = 18) and statistician (*N* = 2) in twelve support services organisations.

Table 34 – Qualifications and Experience in the Support Services Organisations

Qualifications and experience— support service organisations (*N* = 36)	Number in the role *M* ± *SD* (range)	Qualifications PhD : Masters : Bachelor	Years experience *M* ± *SD* (range)
CEO (*N* = 28)	0.95 ± 0.3 (1 – 2)	18 : 2 : 8	19.6 ± 10.2 (6 – 50)
Manager (*N* = 21)	2.8 ± 2.9 (1 – 10)	28 : 11 : 20	12.4 ± 9.0 (1 – 33)
Clinical Research Role (*N* = 22)	6.1 ± 6.2 (1 – 26)	56 : 4 : 84	7.3 ± 4.9 (1 – 25)
Assistant (*N* = 16)	4.2 ± 2.9 (1 – 15)	0 : 4 : 53 : 6[1]	4.6 ± 3.8 (1 - 15)
Other (*N* = 12)	5.9 ± 8.7 (1 – 25)	2 : 0 : 69 : 5[1]	5.2 ± 3.3 (1 – 25)

[1]No academic qualification

4.4.5 Knowledge Management and Innovative Behaviours

Participants were asked to rate their knowledge sharing behaviours both within their organisation and externally. Ratings used 5-point Likert scales ranging from 1 = 'very poor' to 5 = 'very good'. Table 35 shows that all participants rated their organisation's internal knowledge sharing higher than their sharing with other organisations. The poorest knowledge sharing was from the drug discovery groups to the drug development companies, and between the drug development companies. Four participants from support services organisations were not able to rate their internal knowledge sharing behaviours because they were individual consultants and three declined or were not able to rate their knowledge sharing with NZ drug development companies. Four categories could not be rated; the support services organisations did not share knowledge with drug discovery groups and vice versa; the support services organisations did not share knowledge with each other; and because each drug development company shared knowledge with only one drug discovery group this rating was not asked because of confidentiality issues.

Table 35 – Knowledge Sharing Behaviours

Rating of knowledge sharing behaviours *M* ± *SD*	Drug discovery group (*N* = 12)	Drug development company (*N* = 12)	Support services organisation (*N* = 36)
Within their organisation	4.58 ± 0.52	4.33 ± 0.78	4.44 ± 0.72 (*N* = 32[1])
With drug discovery groups	3.25 ± 1.34	N/A	N/A
With drug development companies	2.67 ± 1.72	2. 8 ± 1.5	3.58 ± 1.25 (*N* = 33[2])
With support services organisations used	N/A	4.30 ± 0.78	N/A

[1]Four participants were not able to rate their internal knowledge sharing behaviours because they were individual consultants

[2]Three participants declined or were not able to rate their knowledge sharing with NZ drug development companies

Participants were asked to rate the importance of various sources of knowledge rated on a 5-point Likert scale ranging from 1 = 'not at all important' to 5 = 'very important'. Table 36 illustrates that participants in all three categories rated internal meetings as their most important source of knowledge for their drug development activities. Asking work colleagues and the internet were also highly rated. Internal meetings and asking work colleagues are both mechanisms for obtaining internal non-codified or tacit information, while the internet provides external codified information. The least important source of knowledge was internal formal training, with using external networks and professional publications being of medium importance.

Table 36 – Rating of Sources of Knowledge

Rating of importance of sources of knowledge *M* ± *SD*	Drug discovery group (*N* = 12)	Drug development company (*N* = 12)	Support services organisation (*N* = 35)[1]
Internal formal training (i.e., internal codified information)	2.50 ± 1.31	3.17 ± 1.46	3.71 ± 1.49
Internal meeting (i.e., internal non-codified information)	4.75 ± 0.62	4.08 ± 1.24	4.37± 0.73
Asking work colleagues (i.e., internal non-codified information)	4.25 ± 0.97	4.42 ± 0.67	4.23 ± 0.91
Using external networks (i.e., external non-codified information)	3.93 ± 0.90	4.00 ± 0.95	4.06± 0.94
Professional publications (i.e., external codified information)	4.33 ± 0.89	3.58 ± 1.31	3.63 ± 1.22
Internet (i.e., external codified information)	4.33 ± 1.16	4.33 ± 0.65	3.94 ± 1.11

[1]One participant did not feel able to answer this question

Figure 7 presents the percentage of participants in each category who rated each source of knowledge and 'very important' or 'important'.

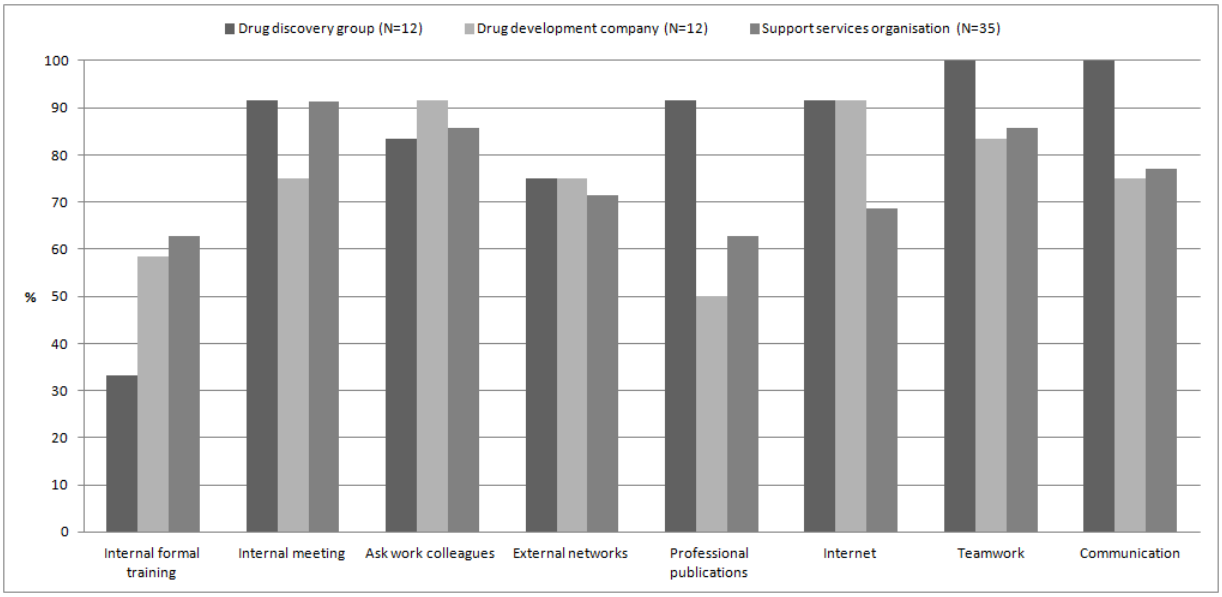

Figure 7 – Percentage of Participants who Rated each Source of Knowledge as 'Very important' or 'Important'

Table 37 presents the ratings of the sources of knowledge as rankings.

Table 37 – Ranking of Sources of Knowledge

Ranking the importance of sources of knowledge	Drug discovery group (*N* = 12)	Drug development company (*N* = 12)	Support services organisation (*N* = 35)[1]
Internal meeting	1	3	1
Ask work colleagues	4	1	2
Internet	2=	2	3
External networks	5	4	3
Professional publications	2=	5	6
Internal formal training	6	6	5

[1]One participant did not feel able to answer this question

Participants were asked to rate their organisation's performance compared with its peers on the following indicators of innovative behaviours using a 5-point Likert scale ranging from 1 = 'very poor' to 5 = 'very good'. Table 38 shows that all categories of participants gave themselves the highest rating for 'having new ideas' and the lowest for 'making time to work on ideas and projects'. Some participants commented that they had too many ideas and therefore insufficient time to work on them all.

Table 38 – Rating of Innovative Behaviours

Rating of innovative behaviours ***M* ± *SD***	**Drug discovery group (*N* = 12)**	**Drug development company (*N* = 12)**	**Support services organisation (*N* = 35)[1]**
Having new ideas	4.75 ± 0.45	4.42 ± 0.67	4.14 ± 0.81
Developing contacts with external experts	4.08 ± 0.67	4.25 ± 0.62	3.80 ± 0.83
Making time to work on ideas and projects	3.50 ± 1.00	3.67 ± 0.65	3.83 ± 0.85
Solving problems that caused others difficulty	4.33 ± 0.65	4.17 ± 0.72	4.40 ± 0.55
Project planning	3.83 ± 0.58	4.17 ± 0.84	4.20 ± 0.72
Innovative output	4.42 ± 0.79	4.33 ± 0.65	3.91 ± 0.89
Teamwork	4.67 ± 0.49	4.17 ± 0.94	4.31 ± 0.72
Communication	4.58 ± 0.51	4.17 ± 1.03	4.09 ± 0.74

[1]One participant did not feel able to answer

Figure 8 presents the percentage of participants in each category who rated each source of knowledge and 'very important' or 'important'.

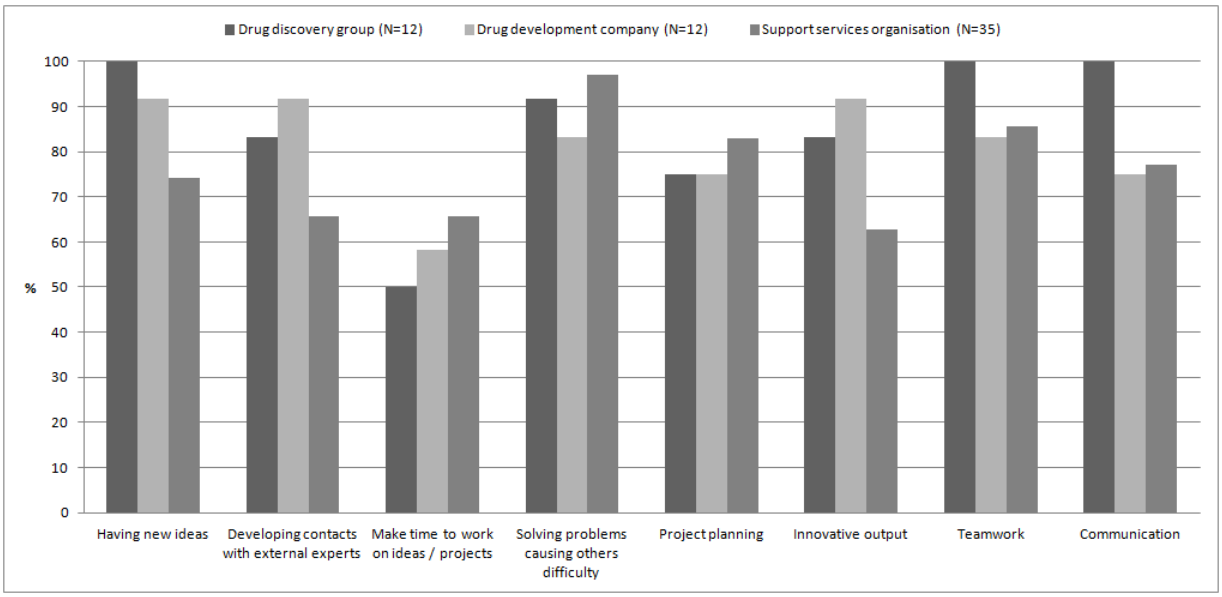

Figure 8 – Percentage of Participants who Rated each Innovative Behaviour as 'Very important' or 'Important'

Table 39 provides the rankings of the innovative behaviours ratings for each of the three participant categories.

Table 39 – Ranking of Innovative Behaviours

Ranking innovative behaviours	Drug discovery group (*N* = 12)	Drug development company (*N* = 12)	Support services organisation (*N* = 35)[1]
Having new ideas	1	1	4
Teamwork	2	4=	2
Solving problems that caused others difficulty	5	4=	1
Communication	3	4=	5
Innovative output	4	2	6
Project planning	7	4=	3
Developing contacts with external experts	6	3	8
Making time to work on ideas and projects	8	8	7

[1]One participant felt unable to answer

The number of patents filed and publications achieved may be considered as indicators of innovative behaviours as well as of expertise. Table 256 provided the data on these indicators as part of the participant's drug development outputs. Sixty percent of participants had contributed to a patent application and 43.3% had been an author on a publication in the three years prior to their research interview.

4.4.6 New Zealand Drug Development Industry Interactions

Nine of the 12 N Z drug development companies contracted to an average of 3.6 (range 1–8) NZ vendors. The main reason for using the vendor selected was because they were based in NZ (66.7%), had the expertise required (22.2%) or were recommended by a third party (11.1%). The second most important reason for their selection was their cost (55.6%) or expertise (44.4%).

Twenty-eight of the NZ support services organisations had provided services to a mean of 3.4 NZ drug development companies (range 1–20) and 29 supply services to a mean of 12.4 overseas drug development companies (range 1–100). The main reason that each support services company felt it had been chosen was because they were based in NZ (64.3%), could provide the expertise required (14.3%), were recommended by a third party (14.3%), had built a relationship with the drug development company (3.6%) or based on cost (3.6%). The second most important reason behind their selection was considered to be due to recommendation by a third party (32.1%), cost (32.1%),

their expertise (17.9%), based in NZ (11.1%) and their relationship with the drug development company (3.6%).

The NZ drug development companies were asked to rate their satisfaction with the NZ vendors they used on a 5-point Likert scale with 1 = 'very unsatisfied' and 5 = 'very satisfied'. Similarly, the support services organisations based in NZ were asked to use the same rating scale to rate their experience of providing their services to NZ drug development companies. The NZ drug development companies and the support services organisations were not asked to identify the organisations that they had worked with; they were just asked to rate their average overall performance. The results in Table 40 shows that on all four indicators of satisfaction the NZ drug development companies rated the NZ support services organisations higher than the support services organisations rated the drug development companies. The NZ drug development companies rated the NZ support services organisations more highly than they rated the overseas support services organisations on timeframe expectations, cost and quality, but not on expertise.

Table 40 – Organisation Interaction Satisfaction

Satisfaction with the interaction ***M* ± *SD***	**Interaction represented**		
	NZ drug development company with overseas support services used (*N* = 10)	NZ drug development company with NZ support services used (*N* = 9)	Support services organisation with NZ drug development companies that services were provided to (*N* = 28)
Expertise	4.70 ± 0.48	4.33 ± 0.71	3.52 ± 0.98
Timeframe expectations	4.00 ± 0.47	4.11 ± 0.78	3.56 ± 0.89
Cost / reimbursement	3.22 ± 1.09	4.11 ± 0.60	3.78 ± 0.80
Quality	4.20 ± 0.63	4.44 ± 0.73	3.40 ± 0.89

Ten of the 12 New Zealand drug development companies contracted to an average of 7.2 (range 1–15) overseas vendors. The main reason given for using the vendor selected was because there was no suitable expertise in NZ (70.0%), a requirement to use a vendor based overseas (20.0%) or because a specific expertise was required (10.0%). The second most important reason for their selection was specific expertise (40.0%), a requirement to use an overseas vendor (20.0%), a specific overseas vendor was recommended (20.0%), no suitable expertise in NZ (10.0%) and cost (10.0%).

The NZ drug development companies were asked to rate their satisfaction with the overseas vendors they used on the same 5-point Likert scale with 1 = 'very unsatisfied' and 5 = 'very satisfied' (Table 40). It was not feasible to contact the overseas support services organisations to obtain their satisfaction with their interaction with the NZ drug development companies because the organisations were not specifically identified. The results show that the NZ drug development

companies were more satisfied with the expertise obtained from their overseas vendors than their NZ based ones, however they were less satisfied with the costs charged by the overseas vendors. The timeframe expectations and quality of service were rated similarly for the NZ and overseas vendors by the NZ drug development companies.

4.5 Enablers and Barriers

4.5.1 Factors Encouraging New Zealand's Drug Development Industry

In response to 'What do you think are the most important factors that have encouraged the drug development industry in NZ?' the 106 participants identified a variety of policies and factors that have encouraged NZ's industry. Review of the transcripts found a range of themes emerging that were grouped into the following four categories: (1) specific supportive government polices and strategies, (2) factors that have occurred as an indirect result of government policies, (3) NZ-specific factors, and (4) external factors. Within each of these four themes, sub-themes of policies and factors were identified. These are summarised in Table 41 and discussed further below.

Table 41 – Summary of Policies and Factors that Encouraged New Zealand's Drug Development Industry

Theme	Sub-theme	Number (%) of participants
Specific government policies	Government investment policies: funding and investments in basic science, medical research and specific drug development projects	25 (23.6)
	Government policies and strategies explicitly supportive of NZ's drug development industry, including biotechnology	13 (12.3)
	Legal policies: Ministry of Health administered regulatory and ethics approval systems	8 (7.5)
	Legal policies: provide NZ's patent protection laws	5 (4.7)
	Pharmaceutical price control policies: the effects of PHARMAC policies	4 (3.8)
Encouraged by government policies	The development of drug development expertise in NZ	40 (37.8)
	NZ reputation for clinical research	27 (25.5)
	NZ reputation for quality research	26 (24.5)
	Universities and their commercialisation activities	22 (20.8)
	NZ is less expensive than other countries	13 (12.3)
	Availability of non-government funding	12 (11.3)
	NZ drug development organisations	8 (7.5)
Non-policy/NZ-specific factors	Kiwi ingenuity and approach to innovation, good at communication and networking	31 (29.2)
	English speaking, western culture	9 (8.5)
	NZBio activities	8 (7.5)
	Geographical isolation—unique botanicals and biologicals, disease-free animals	5 (4.7)
External factors	Changes in the global drug development industry	3 (2.8)

The role of government investment policies for funding different facets of the industry was the most commonly mentioned specific government policy (23.6% of participants). Government funding fell into three main categories—funding of science research in universities and Crown Research Institutes (CRIs) either directly or through funds such as the New Economy Research Fund (NERF) and the Marsden Fund; grants for medical research through the Health Research Council (HRC) and other funding agencies; and funding of specific drug development projects through government agencies such as FRST and NZTE.

Specific government policies and strategies that have been explicitly directed towards supporting and developing NZ's industry were mentioned by 12.3% of participants. These included 'building a knowledge economy' with biotechnology as a priority, the 'Biotech Taskforce and Roadmap', government emphasis on the industry in the last decade, and a consistent government policy and commitment to the industry.

New Zealand's robust legal practices have supported the industry in two areas—through the regulation of clinical trials and new medicines and for patent protection. The Ministry of Health's policies and processes to provide an environment favourable for clinical research were mentioned by 7.3% of respondents. These ensure that NZ's regulatory and ethical review of clinical research submissions and new medicine applications are efficient and meet international requirements. A number of participants (4.7%) advised that NZ's strong intellectual property and patent laws plus the ease of filing patent applications were helpful to the industry.

A less obvious government policy that has supported the industry is the pharmaceutical price control policies of its agency PHARMAC. According to 3.8% of participants the lack of funding of newer medicines for some indications makes NZ a desirable location for clinical research due to its relatively treatment-naïve patients. PHARMAC policies also resulted in some multinational pharmaceutical companies withdrawing their clinical research staff from NZ, however many decided to continue their projects, which has allowed NZ and overseas Clinical Research Organisations (CROs) to become established in NZ.

Overall, more research participants mentioned factors that have resulted from the support of government policies and funding, than mentioned specific polices and strategies, and these factors fell into seven sub-categories (see Table 42). The most commonly stated indirect but encouraging effect of government policies was its funding for science education, basic research and medical schools. This funding has lead to the creation of specialised drug development expertise both within the universities and in commercial organisations (37.8%). This expertise development has been supported by industry champions and people with international experience returning to NZ, leading to the availability of a wider range of drug development capabilities. In particular, it was mentioned

that NZ now has significant expertise in drug discovery, especially at the University of Auckland's ACSRC. This drug discovery expertise has resulted in university spin-out drug development companies that have often obtained overseas funding.

Similarly, government funding for projects including collaborations with researchers overseas has contributed to NZ's reputation for both high quality scientific research (24.5%) and clinical research (25.5%). Funding of NZ's integrated health service and Centres of Research Excellence (CoRES) has also been supportive. New Zealand's reputation for clinical research is assisted by its robust ethics system, legal environment, the accessibility of medical staff and its facilities. Government funding of universities has enabled them to implement initiatives to set up companies (e.g., Uniservices for the University of Auckland) to commercialise researchers' innovations and provide university staff consultancy to external organisations.

New Zealand's comparatively weak dollar has enabled it to be less expensive compared with countries with similar levels of expertise because of lower salaries and other human resource costs. Some organisations in the NZ industry have obtained essential funding both from investors and charities encouraged by tax incentives and a willingness to accept the high risks of drug development. Government policies have directly and indirectly assisted the creation of a cluster of expertise and range of organisations that can provide specialised drug development services both within the universities and in commercial organisations.

New Zealand-specific factors suggested by participants that have encouraged NZ's drug development industry included the Kiwi approach of applying ingenuity to solve problems and an enthusiastic attitude towards innovation (27.4%). This was variously described as the ability to "think outside the box", an attitude to assist each other with problem-solving, excellent at networking and few hierarchical issues. The lure of developing a "mega-drug" and the increasing acceptability of academics commercialising the results of their research has helped create momentum for innovation. Another factor mentioned by 8.5% of participants was that NZ is English-speaking, has a western culture and modern practice of medicine and provision of healthcare that is perceived to provide an advantage over other emerging drug development countries such as India and China. Some participants (2.8%) stated that NZ's relative geographical seclusion provides a unique source of botanicals and biologics to explore for new medicines. New Zealand's isolation has contributed to NZ having disease-free animals, which is important for specific research projects.

Finally, the changes in the global pharmaceutical industry have led to opportunities for NZ as the industry searches for new sources of innovation and provision of support services.

Overall, a phrase that several respondents used to summarise the NZ's drug industry development was that "NZ punches above its weight" in science research, innovation and creative solutions.

4.5.2 Policies and Factors Enabling New Zealand Organisations

Participants were asked to nominate factors that had enabled their organisation to undertake its drug discovery and/or development projects in NZ. This question was not applicable to stakeholders, and many participants indicated that these factors were the same as those that encouraged the NZ drug development industry in general (Table 42). Some participants provided factors that were specific to their organisation; the number and percent of all participants mentioning each of these factors is in Table 43.

Table 42 – Policies and Factors that Enabled All New Zealand's Drug Development Organisations

Theme	Sub-theme	Number (%) of participants
Specific government policies	Government investment policies: funding and grants for basic science, medical research and specific drug development projects	15 (25.0)
	Legal policies: Ministry of Health administered / funded regulatory and ethics approval systems	2 (3.3)
Encouraged by government policies	Universities and their commercialisation activities	13 (21.7)
	NZ reputation for clinical research	11 (18.3)
	NZ less expensive than other countries	6 (10.0)
	The development of expertise in NZ	30 (50.0)
Non-policy/NZ-specific factors	Kiwi ingenuity and approach to innovation, good at communication and networking	3 (5.0)
	English speaking, western culture	2 (3.3)
	NZBio activities	3 (5.0)
	Geographical isolation – unique botanicals and biologicals, disease-free animals	3 (5.0)

Many of the responses in Table 42 related to supporting NZ's clinical research industry and these policies and factors can be further specified as (262):

- The quality, enthusiasm and expertise of the investigators, study sites and CROs
- Good participant recruitment
- Western style healthcare system, including a unique National Health Index (NHI) number (that is allocated at birth) for every individual so that their use of health and disability services can be tracked
- Efficient and internationally acceptable regulatory and ethics assessment and approval systems
- English language and western culture

- High incidence of some diseases (e.g., asthma, hayfever and gout)
- NZ is seasonally opposite to the northern hemisphere, which is helpful for trials in influenza and other diseases that are affected by the seasons. It also means that studies can recruit in NZ when it is peak holiday season in the northern hemisphere.
- Cost-effective with other countries that have similar levels of expertise

Table 43 – Factors that Enabled Individual Drug Development Organisations

Factor	Number (%) of participants
The vision, leadership and expertise of the organisation's founder or director	10 (16.7)
Unique expertise or business opportunity	5 (8.3)
Fortuitous timing of several contributory events, such as the connection of key collaborators or clustering of essential skills in one location	3 (5.0)
Obtained long-term non-government funding or contract	3 (5.0)
Reputation of a key individual or the organisation	3 (5.0)

4.5.3 Factors Threatening New Zealand's Drug Development Industry

In response to an open question, more than half of the participants (52.8%) specified funding issues as a threat to the NZ industry. This issue was suggested by all categories of participants, but most commonly by the drug discovery participants who advised that they "had more ideas for innovations than the funding and time to develop them".

Lack of funding was perceived as a threat in itself but was also linked to four other main inter-linked themes: expertise issues (31.1%), characteristics and size of NZ's industry (36.8%), government policies (41.5%), and a lack of understanding of the industry (21.7%). Each of these threats comprised a subset of factors, many of which were also affected by one or more of the other main threats thereby making a more complex situation than the policies and factors proposed that have encouraged the industry.

External factors mentioned were the current global financial crisis and increasing competition from other countries.

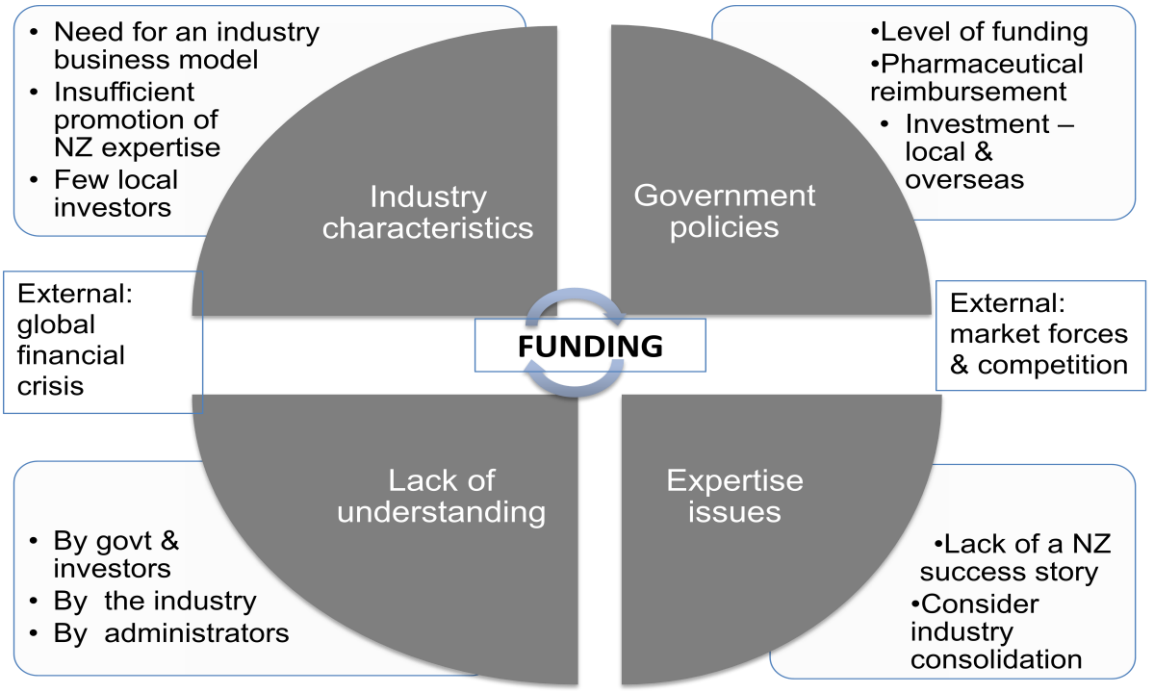

Figure 9 – Threats to New Zealand's Drug Development Industry

Figure 9 depicts the complex interactions of the factors that threaten NZ's drug development industry. For example, government policies around the level and administration of funding through its various agencies may be lower than overseas due to a possible lack of government understanding of the potential returns from this funding investment. A better understanding of the industry by funding and research administrators may lead to more supportive government policies and enable sectors of the industry to remain internationally competitive. This point was made particularly by those involved in clinical research where keeping competitive on 'time-to start' can be critical in securing new projects.

The lack of an economically significant NZ success story to date was suggested to be related to the small pool of expertise in NZ, but also to the small industry size and therefore small number of compounds under development. Another consequence of the small industry is the limited local investment funding available, but that this funding may also be restricted because the local investors may have had little experience assessing the drug development opportunities and so are reluctant to invest in an industry that they did not fully understand. Some respondents suggested that the industry is too fragmented and proposed that better consolidation of the industry would be helpful to overcome expertise issues, improve understanding by the industry and its stakeholders and better promote NZ's expertise overseas.

PHARMAC's pricing and reimbursement policies were mentioned as a threat to the NZ industry by 27.4% of participants. They suggested that the uncertainty of pharmaceutical reimbursement for medicines in development made conducting phase III trials in particular in NZ of lower interest. This was predominantly mentioned in association with therapeutic areas where ongoing supply of the drug after completion of the study and until the medicine is registered and funded is generally expected.

Some respondents (8.5%) suggested that completion of the entire drug development process through to a marketing application was not possible for a country of NZ's size and that NZ should focus on the early development of innovative compounds. The optimal time for NZ companies to consider a partnership, alliance or out-license deal with a larger industry partner should be determined (i.e., before the first clinical trials or at some point in the clinical programme). An industry business model needs to be developed that is appropriate to NZ's circumstances because "the USA biotech model won't work here".

Three people (2.8%) recognised a need to identify someone in their organisation who had the ability and desire to succeed them as they were approaching retirement age. The demographic data of the organisations showed that the age of respondents was over 45 years and in particular the drug discovery organisations were represented by older participants.

4.5.4 Threats to Individual New Zealand Drug Development Organisations

When asked what are the main issues affecting their organisation in the next 3–5 years, most respondents did not identify any issues that were specific to their organisation or they were stakeholders and so this question was not applicable to them. The issues that were of concern were mostly the same ones that were mentioned as threats to the industry in general (Table 44). However, some participants mentioned organisation-specific factors and these are summarised in Table 45. The policies and factors in each table are listed in decreasing order of the number of participants who mentioned them.

Table 44 – Policies and Factors that Threaten All New Zealand's Drug Development Organisations

Policy or factor type	Details	Number (%) of participants
Funding	Lack of both government and investor funding	21 (19.8%)
Competition	Competitor companies overseas (especially India and China); currency fluctuations; competition for NZ sites for clinical trials; need to be cost-competitive;	19 (17.9%)
Government policies	PHARMAC policies; exchange rate fluctuations; regulatory delays; loss of R&D tax credit;	16 (15.1%)
Expertise issues	Loss of skilled people to industry and overseas; need to retain people who have very specific and unique expertise; we don't train enough chemists; need better knowledge sharing; expertise of some NZ consultants is doubtful; difficulty finding adequate skilled staff	13 (12.3%)
Global financial crisis	Economic recession leading to less work available	5 (4.7%)
NZ industry characteristics	NZ population/market is so small; NZ's isolation	5 (4.7%)

Table 45 – Specific Factors that Threaten Individual Drug Development Organisations

Factor type	Details	Number (%) of participants
Specific technical threats	Need positive clinical data; need to have positive audit findings; need to comply with new NZ Clinical Trial Guidelines	5 (4.7%)
Threats due to being a start-up or small organisation	Dependent on finding people with nominated specialised skills; need to constantly buy new equipment to expand services; need potential customers to try something new	4 (3.8%)
Funding	Need a commercialisation deal/ongoing support from a commercial sponsor	3 (2.8%)
Specific competitor threats	Need to be able to compete against specific new market entrants; not taken seriously because we are not a USA or European company	3 (2.8%)
Policy changes	Concerns that government policies may reduce support of drug development	3 (2.8%)

4.5.5 Advice to Colleagues in New Zealand's Drug Development Industry

The participants from the drug discovery groups, drug development companies and support service organisations provided advice to others in the NZ industry. This advice focussed on four key areas: obtaining expertise and advice (23.6%), funding (17.0%), general advice on drug development (16.0%) and the need to have a clear strategic direction and business plan (12.3%).

The most common expertise and consultancy advice was to involve proven experts in relevant fields as early as possible (e.g., in the areas of science, management or on company board) and to heed their advice. Other suggestions were to make the best use of consultants and resources available; use

local advisors where available but also consider overseas expertise; and employ the “best people available” for the project. Regulatory advice was to discuss the project with appropriate medicine regulators in the early stages of development, because their feedback could be very valuable. Other expertise advice was to co-operate locally and network globally so that the organisation kept up-to-date and did not become isolated.

Funding advice included having multiple and longer-term funding streams where possible so that milestones could be met without interruptions to raise more capital, out-license or partner early, and realise that the development costs will be higher than you expect, so allow for contingencies when budgeting.

General advice was to be organised but flexible, open to new ideas, plan ahead, ensure the highest quality work is done, be realistic about the high risks of drug development, and realise that there are no shortcuts to success.

Strategic advice included having a clear vision of the product being developed, what it will cost to produce, focus on your nearest term product, and analyse whether the market both desires and can afford your invention. The importance of having clear go/no-go decision points, a well thought-out business plan, and to abandon a project that does not meet the agreed criteria were suggested. Other advice was to ensure you have a strong intellectual property position and provide the best possible service to the industry.

4.5.6 Policies to Further Support the Industry

The participants provided a wide range of policies and strategies that they suggest could be implemented to further support the industry in NZ and these are summarised in Table 46. These are listed in decreasing order according to the number of respondents who raised each policy type, followed by policies around government attitude and commitment to the industry.

Table 46 – Policies Suggested to Further Support New Zealand's Drug Development Industry

Policy type	Policy aim	Details	Number (%) of participants
Government investment	Increase investment	Targeted funding for drug development projects	18 (17.0%)
		Increase the level of funding generally	17 (16.0%)
	Management of government funding	Provide consistent and long-term funding; a streamlined application process with one funding body; defined funding criteria and transparent process	24 (22.6%)
	Support for science research	Allow publicly funded researchers to benefit personally from their discoveries; investigate some of NZ's natural bioactive compounds; more funding for basic science that could lead to more discovery projects	19 (17.9%)
Foreign and private investment	Encourage both local and overseas private investment	Some form of R&D tax incentive	27 (25.5%)
		Develop a more commercially aware environment to encourage global pharmaceutical companies to invest in NZ; funding policies so that NZ companies remain here and more returns accrue to NZ	23 (21.7%)
Expertise , knowledge management and innovation	Increase the NZ knowledge pool	Provide specific drug development qualifications in NZ; strategies to encourage skilled New Zealanders to return with their expertise and global business contacts; provide attractive career paths in science and research; fund postgraduate training	13 (12.3%)
	Encourage collaborations	Have a database of all NZ's capabilities; provide facilities and support services (e.g., legal and regulatory advice) for them to work together; encourage international alliances and collaborations	11 (10.4%)
Pharmaceutical price control	PHARMAC to work with the industry	PHARMAC to make transparent funding decisions; reduce the antagonism between PHARMAC and the pharmaceutical industry	11 (10.4%)
Legal	Maintain the integrity of NZ patent laws	Ensure NZ patent laws meet the same criteria as competitor countries	4 (3.8%)
	Support for clinical research	Policies to encourage clinical research and to keep NZ competitive (e.g., management of ethics committees and streamline the administration required to set up research)	13 (12.3%)
Other	Government attitude and commitment	Government should state its commitment to support the industry as part of the country's knowledge economy and promote NZ's expertise overseas	13 (12.3%)

Government investment policies were most commonly requested, especially to increase investments, either as targeting funds for specific drug development projects or as a general statement to increase funding, without providing any specific policies. Other government investment policies suggested

related to the management of government funding of drug development and increased support for science research.

Foreign and private investment policies proposed to further develop the industry were encouragement of both local and overseas private investment. Re-instating some form of R&D tax credit was the most frequently mentioned specific mechanism to achieve this, followed by more general policies such as creating a more commercially aware environment to encourage pharmaceutical companies to return to NZ or to increase their NZ research investments and collaborations. Investment policies so that NZ companies continue their R&D locally rather then moving offshore were also suggested.

Policies to encourage expertise and knowledge management included the support of education, provision of a career structure to make research a more attractive option and encourage local and international collaborations. Assistance from government-sponsored central services in areas such as legal issues, regulatory advice and information technology was proposed. Information sharing, especially in areas where NZ's expertise or resources are more limited, could then be improved. Industry consolidation under an umbrella organisation may enable more effective promotion of the country's expertise (e.g., as 'NZ Inc'), however several respondents commented that the current competition between the organisations for scarce funding may prevent this from occurring.

Some participants suggested that NZ's appeal to multinational pharmaceutical companies should be increased. PHARMAC should work with the pharmaceutical industry instead of appearing to confront it and PHARMAC funding decisions should be transparent to the industry.

The legal policies requested were to ensure that NZ patent laws were in line with those of other developed countries and to encourage clinical research. There were some concerns about the proposed changes to NZ's Patents Act 1953; although other respondents suggested that these changes are intended to align NZ with international practices. Previous policies affecting clinical research have been primarily the regulation of clinical trials and new medicines. However, additional policies to support clinical research were to ensure NZ's international competitiveness by streamlining the ethics processes and enable faster review of clinical trial applications. There should be a review of the policies used overseas to see if any would be of value for NZ to implement. It was felt that there should be better co-ordination between the district health boards, including agreement to use standardised documentation. The NZ-specific ethics requirement of Maori consultation could be also managed more efficiently.

The last policy group in Table 46, the government's attitude and commitment to the industry, does not fall into any of the policy types discussed in the policy framework. Participants suggested that the

government should provide its verbal commitment to the industry so that the public understands the value of the industry to all New Zealanders.

4.5.7 Ranking Barriers to New Zealand's Drug Development Industry

Participants were provided with eight possible barriers to drug development in NZ and asked to rank them from '1' (most important barrier) to '8' (least important barrier). They were allowed to identify another barrier that was not in the list of eight provided and then to rank all nine barriers from '1' to '9'. The ranking of the barriers are provided in Table 47—note that the lower the score, the more important the obstacle was deemed to be. The results provided by the four different participant groups were similar, including ranking 'limited funding' as the most important barrier. Five participants (one representing a drug discovery group and four stakeholders) were unable or unwilling to answer this question.

Table 47 – Average Ranking Scores of Possible Barriers to Drug Development in New Zealand

Possible barriers to drug development[1] ***M* ± *SD* (range)**	**Drug discovery group (*N* = 11)**	**Drug develop-ment company (*N* = 12)**	**Support services organisation (*N* = 36)**	**Stake-holders (*N* = 42)**
Limited funding	2.03 ± 1.48 (1 – 5)	2.17 ± 1.75 (1 – 6)	2.59 ± 1.81 (1 – 8)	2.07 ± 1.34 (1 – 6)
Limited local expertise and capabilities/experienced people have moved overseas	3.36 ± 1.89 (1 – 7)	3.25 ± 1.82 (1 – 8)	4.46 ± 2.46 (1 – 9)	3.80 ± 2.32 (1 – 9)
Insufficient government policy to support the industry/lack of strategic direction	3.64 ± 2.06 (1 – 6)	3.67 ± 2.43 (1 – 9)	3.59 ± 2.05 (1 – 8)	3.58 ± 2.25 (1 – 8)
Difficulty in determining a lead compound	6.48 ± 1.90 (4 – 9)	6.17 ± 1.70 (3 – 8)	5.96 ± 1.93 (1 – 9)	5.93 ± 1.89 (2 – 9)
Lack of overall co-ordination between NZ's drug development organisations	5.55 ± 1.97 (2 – 9)	5.42 ± 1.83 (2 – 8)	4.59 ± 2.02 (1 – 8)	4.92 ± 1.74 (2 – 8)
Insufficient understanding of the drug development and regulatory processes	4.64 ± 1.63 (2 – 7)	4.50 ± 1.51 (2 – 6)	4.38 ± 2.09 (1 – 8)	4.58 ± 2.07 (1 – 8)
Overseas investors want to move the project away from NZ	4.48 ± 1.93 (2 – 8)	4.50 ± 2.65 (1 – 8)	4.71 ± 2.26 (1 – 9)	5.37 ± 2.02 (2 – 9)
Issues with manufacturing or formulation	6.85 ± 1.29 (5 – 8)	6.75 ± 1.42 (4 – 8)	6.94 ± 1.30 (5 – 9)	6.76 ± 1.23 (4 – 8.5)
Other	7.18 ± 3.28 (1 – 9)	8.58 ± 1.44 (4 – 9)	7.70 ± 2.71 (1 – 9)	7.94 ± 2.45 (1 – 9)

[1]Where a participant gave the same rank to two or more possible barriers, a mean rank score was given to all the barriers indicated

Twenty participants nominated another barrier in addition to those provided—these were very diverse in scope and each was only specified by one participant with the exception of 'the effect of PHARMAC policies on the attitude of the pharmaceutical industry because it limits the number of

clinical trials they sponsor in NZ', that was provided by four participants. The details of these other barriers nominated and the number of respondents for each one are provided in Table 498.

Table 48 – Other Barriers to Drug Development in New Zealand

Other barriers to drug development in NZ	Drug discovery group (*N* = 11)	Drug develop-ment company (*N* = 12)	Support services organis-ation (*N* = 36)	Industry stake-holder (*N* = 42)
PHARMAC policies limit pharmaceutical industry interested in clinical research in NZ			4	
Need more integration of basic & medical research	1			
Need improved governance of capital investments	1			
Need a national network for specialised tests	1			
Lack of accountability for funding decisions		1		
Reluctance to discontinue compounds not meeting milestones			1	
Length of time required to start clinical trials			1	
Geographical isolation			1	
Need for a private ethics committee			1	
Reluctance of the NZ industry to co-operate with each other due to IP issues				1
Drug development is very difficult, especially in NZ				1
Need for dedicated funding for drug development				1
Time & finance needed for drug development				1
NZ is too small and too far from major markets				1
Co-ordination of clinical trial capability is required				1
Need partner internationally early in the drug development process				1
Need to fund basic science research while also developing commercially viable products				1

Using the mean scores from Table 30, the possible barriers can be ranked for each participant category and these results are shown in Table 49. All four categories of participants were similar in their ratings of the possible barriers to drug development in NZ including the rating of limited funding as the biggest barrier. The support services participants rated limited local expertise and capability lower than the other participants and were also less concerned by investors wanting to move the project away from NZ. Identification of a lead compound and formulation/manufacturing issues were rated as amongst least important barriers. Because few participants nominated a ninth possible barrier, these barriers were rated as least important barriers.

Table 49 – Overall Rankings of Possible Barriers to Drug Development in New Zealand

Ranking of possible barriers to drug development	Drug discovery group (*N* = 11)	Drug development company (*N* = 12)	Support services organisation (*N* = 36)	Industry stake-holders (*N* = 42)
Limited funding	1	1	1	1
Limited local expertise and capabilities/experienced people have moved overseas	2	2	4	3
Insufficient government policy to support the industry/lack of strategic direction	3	3	2	2
Difficulty in determining a lead compound	7	7	7	7
Lack of overall co-ordination between NZ's drug development organisations	6	6	5	5
Insufficient understanding of the drug development and regulatory processes	5	4=	3	4
Overseas investors want to move the project away from NZ	4	4=	6	6
Issues with manufacturing or formulation	8	8	8	8
Other	9	9	9	9

4.6 Economic Benefits for New Zealand

Note that the following exchange rates (as of 18 July, 2011) were used throughout the calculations on the economic returns to NZ: NZD1.00 = USD0.84 and AUS1.00 = USD1.07.

4.6.1 Potential Revenue from Drug Discovery

The returns to NZ per year from a compound with peak annual sales of USD350 million are provided in Table 50. No adjustments (e.g., Net Present Value) have been made because it was assumed that the returns would be invested back into NZ drug discovery almost immediately to fund further research rather than accumulated for future projects. These proceeds to NZ over the average of 30 years from the out-license deal until sales are negligible, would provide total returns of USD48.273 million (i.e., NZD57.468 million). This comprises USD6.5 million upfront payments and USD41.773 million in royalties from product sales. Note that the royalty payments are probability adjusted because the chances of a compound that has not started phase I being approved for marketing is 19.02%.

Assuming that only one third was reinvested in building NZ's drug discovery capability (260), an average of NZD638,531 per year would fund at least three additional scientists to research drug discovery projects for 30 years.

Table 50 – Potential Revenue From the Out-License of a New Zealand-Discovered Medicine with Peak Annual Sales of USD350 Million

Out-license deal after preclinical stage	Percent probability of successful completion	Project sales as percent of peak global sales (%)	Projected sales/ milestone payment per year (USD million)	Project-ed profit (50% of sales)	Projected profit multiplied by percent probability of success	Probability -based payments to NZ (USD million)
Upfront payment	100	N/A	6.500	N/A	6.500	6.500
Successful phase I	71	N/A	0	N/A	0	0
Successful phase II	31.95	N/A	0	N/A	0	0
Successful phase III and registration dossier submitted	20.45	N/A	0	N/A	0	0
Approval of registration dossier	19.02	N/A	0	N/A	0	0
Year 1 sales	19.02	30	105.000	52.500	9.986	0.999
Year 2 sales	19.02	40	140.000	70.000	13.314	1.331
Year 3 sales	19.02	50	175.000	87.500	16.643	1.664
Year 4 sales	19.02	60	210.000	105.000	19.971	1.997
Year 5 sales	19.02	70	245.000	122.500	23.300	2.330
Year 6 sales	19.02	80	280.000	140.000	26.628	2.663
Year 7 sales	19.02	85	297.500	148.750	28.292	2.829
Year 8 sales	19.02	90	315.000	157.500	29.957	2.996
Year 9 sales	19.02	95	332.500	166.250	31.621	3.162
Year 10 sales	19.02	100	350.000	175.000	33.285	3.329
Year 11 sales	19.02	90	315.000	157.500	29.957	2.996
Year 12 sales	19.02	80	280.000	140.000	26.628	2.663
Year 13 sales	19.02	75	262.500	131.250	24.964	2.496
Year 14 sales	19.02	70	245.000	122.500	23.300	2.330
Year 15 sales	19.02	60	210.000	105.000	19.971	1.997
Year 16 sales	19.02	50	175.000	87.500	16.643	1.664
Year 17 sales	19.02	40	140.000	70.000	13.314	1.331
Year 18 sales	19.02	35	122.500	61.250	11.650	1.165
Year 19 sales	19.02	30	105.000	52.500	9.986	0.999
Year 20 sales	19.02	25	87.500	43.750	8.321	0.832
Total (USD million)			**4,399.000**	**2,196.250**	**424.227**	**48.273**

Five sensitivity analyses were conducted to check the validity and the effects of the following assumptions: timing of the out-license deal, peak sales, royalty payment levels, average gross profit on sales and the percent probability of a drug discovery compound being registered for sale.

The effect on the revenue to NZ if a drug discovery compound was out-licensed later (i.e., with phase I or phase II clinical data) in its development was investigated. The calculations for the out-licensing with phase I and with phase II clinical data are very similar to the calculation shown in Table 50. The

only differences are that the upfront payments and the percent probability of successful completions are higher. Table 51 summarises the upfront and royalty payments for a product with peak sales of USD350 million.

Table 51 – Sensitivity Analysis for the Timing of the Out-License Deal

Revenue payments to NZ	Timing of the out-license deal		
	Preclinical	Post-phase I	Post-phase II
Upfront payment (USD million)	6.500	10.000	17.500
Royalty payments (USD million)	41.773	58.347	123.099
Total payments (USD million)	48.273	68.347	140.599

It can be seen that the later out-licensing deals provide higher returns to NZ compared with the returns from out-licensing a preclinical compound (i.e., 142% with phase I data and 291% after phase II). At post-phase III the calculation was not possible because these deals often have a very different structure; the calculation was also irrelevant because currently a NZ compound would not be able to obtain sufficient local funding to achieve this milestone.

A sensitivity analysis was conducted using a range of peak sales of the product (USD50 million to USD1,000 million) while maintaining the compound license-out deal timing while in the preclinical phase. In this scenario the upfront payments remain the same while the royalty payments are affected proportionally by the peak sales, that is, they increase proportionally with increasing peak sales or are reduced proportionally if peak sales are lower than USD350 million. Therefore, if peak sales are USD1,000 million (i.e., a blockbuster product) then the returns to NZ would exceed USD125 million (approximately NZD150 million) and would be tenfold higher than the returns from a compound with peak sales of USD100 million. The results of this sensitivity analysis are shown in Table 52.

Table 52 – Sensitivity Analysis for Peak Sales

Revenue payments to NZ	Peak sales (i.e., at Year 10 from product launch)				
	USD50 million	USD100 million	USD350 million	USD650 million	USD1,000 million
Upfront payment (USD million)	6.500	6.500	6.500	6.500	6.500
Royalty payments (USD million)	5.968	11.935	41.773	77.578	119.351
Total payments (USD million)	12.468	18.435	48.273	84.078	125.851

A further sensitivity analysis was conducted using a range of royalty payments on the original scenario, that is, a compound with peak sales of USD350 million that is out-licensed in the preclinical stage. The original analysis assumed that royalty payments would be 10% of the sales profit, which was lower than the typical royalty payments of 12–15% on compounds out-licensed after phase I. This sensitivity analysis therefore used an upper limit of 12% and a lower level of 8% of sales profit for the royalty payments. The results of this sensitivity analysis (see Table 53) show that the change in the

royalty payment from 10% to 12% or 8% resulted in an increase or decrease in total revenue to NZ of USD2.387 million, which is an increase or decrease of 12.9% on the payments of the original analysis.

Table 53 – Sensitivity Analysis for Royalty Payments

Revenue payments to NZ	Level of royalty payments		
	8% of sales profit	10% of sales profit	12% of sales profit
Upfront payment (USD million)	6.500	6.500	6.500
Royalty payments (USD million)	32.182	41.773	48.273
Total payments (USD million)	38.682	48.273	54.773

Another analysis was conducted using a range of profitability of the compounds sales on the original analysis. The original analysis assumed that the average gross profit on sales would be 50% and therefore this sensitivity analysis considered average gross profits of 40% and 60% as two extremes for this parameter. These produced total royalty payments of USD16.048 million and USD20.822 million, which are the same results as obtained with the sensitivity analysis for royalty payments of 8% and 12%. The results of this sensitivity analysis (see Table 53).

Table 54 – Sensitivity Analysis for Sales Profitability

Revenue payments to NZ	Sales profitability		
	40% of sales value	50% of sales value	60% of sales value
Upfront payment (USD million)	6.500	6.500	6.500
Royalty payments (USD million)	32.182	41.773	48.273
Total payments (USD million)	38.682	48.273	54.773

The further sensitivity analysis was based on varying the total cumulative sales over the 20 year product sales period. In the original scenario, for a product with peak sales of USD350 million at Year 10, the cumulative sales for the period was USD4,392.5 million (i.e., USD4,399 million in Table 50 minus the upfront payment of USD6.5 million). A sensitivity analysis was not conducted on the sales distribution because of the number of possible variations; however an analysis was conducted on a range of cumulative product sales over the 20 year period. This range used was from 25% lower (i.e., USD3,294.4 million) to 25% higher (i.e., USD5,490.6 million) cumulative sales, which would provide total revenue to NZ that is 28% less and 22% higher respectively than the original scenario. The results are presented in Table 55.

Table 55 – Sensitivity Analysis for Cumulative Sales

Revenue payments to NZ	Cumulative sales				
	USD3,294.4 million	USD3,843.4 million	USD4,392.5 million	USD4,941.6 million	USD5,490.6 million
Upfront payment (USD million)	6.500	6.500	6.500	6.500	6.500
Royalty payments (USD million)	31.330	36.551	41.773	46.995	52.216
Total payments (USD million)	37.830	43.051	48.273	53.495	58.716

A final sensitivity analysis considered the effect of lower and higher percent probabilities of the registration dossier being approved. The original analysis was based on a percent probability of 19.02% as generally indicated in the literature, however different researchers obtained a range of values. Therefore this sensitivity analysis considered percent probabilities of success of 10.0% and 30.0% as two extremes for this parameter. These produced total royalty payments of USD28.463 million and USD72.388 million, which are 41% less and 50% more than the original analysis respectively. The results of this sensitivity analysis are presented in Table 56.

Table 56 – Sensitivity Analysis for Percent Probability of Registration Dossier Approval

Revenue payments to NZ	**Percent Probability of Registration Dossier Approval**		
	10.0%	19.02%	30.0%
Upfront payment (USD million)	6.500	6.500	6.500
Royalty payments (USD million)	21.963	41.773	65.888
Total payments (USD million)	28.463	48.273	72.388

A summary of these six sensitivity analyses is presented in Table 57. It can be seen that the two parameters that have the largest effect on the revenue to NZ are the timing of the out-license deal and the peak sales. The level of royalty payments, sales profitability and variability of cumulative sales, all based on peak sales of USD350 million, have smaller effects. The percent probability of the drug discovery compound gaining approval of its registration dossier has a medium-sized effect.

Table 57 – Summary of Sensitivity Analyses

Sensitivity analysis	**Detail and total revenue to NZ (USD million)**					
	Lower end of the range		**Original calculation**		**Upper end of the range**	
	Analysis detail	Revenue to NZ (USD million)	Analysis detail	Revenue to NZ (USD million)	Analysis detail	Revenue to NZ (USD million)
Later out-licence deal	N/A	N/A	Preclinical	48.273	Post-ph I Post-ph II	68.347 140.599
Value of peak sales	USD50 million	12.468	USD350 million	48.273	USD1,000 million	125.851
Level of royalty payments	8% of sales profit	38.682	10% of sales profit	48.273	12% of sales profit	54.773
Sales profitability	40% of sales value	38.682	50% of sales value	48.273	60% of sales value	54.773
Cumulative sales	USD3,294.4 million	37.830	USD4,392.5 million	48.273	USD5,490.6 million	58.716
Percent probability of gaining registration	10.0%	28.463	19.02%	48.273	30.0%	72.388

4.6.2 Revenue from the Provision of Services to Overseas Organisations

4.6.2.1 Revenue from support services organisations

Thirty-two of the 36 support services organisations obtained revenue from provision of their services overseas. These included the provision of specialised clinical trial facilities and sites, monitoring and management of clinical research, data management and statistics, bioanalysis, intellectual property and regulatory services.

The mean revenue generated from overseas comprised an average of 72.2 ± 31.4% of total revenue for these 32 organisations. Only two (5.6%) of the 36 companies expected their revenue from overseas to decrease in the next 3 years. Twelve (33.3%) companies expected this revenue to remain about the same and 22 (61.1%) anticipated that their revenue from overseas would increase in the next 3 years. The location of the organisations that obtained these services from the NZ support services organisations are given in Table 58. The four most common locations were USA, Australia, European Union (excluding the UK) and the UK.

Table 58 – Location of Organisations using a New Zealand Drug Development Support Service

Location of organisations obtaining services from a NZ support service surveyed	Support services organisations that provide services to an organisation in the nominated country *N* (%)
USA	26 (81.3)
Australia	24 (75.0)
European Union (excluding the UK)	16 (50.0)
UK	15 (46.9)
Japan	3 (9.4)
Canada	1 (3.1)
Hong Kong	1 (3.1)
South Africa	1 (3.1)
Korea	1 (3.1)
India	1 (3.1)

4.6.2.2 Revenue from Clinical Trials

The analysis of SCOTT application data identified that overall 98% of trial applications each year were approved, 1.5% were not approved and 0.5% were not initiated by the trial sponsor. The reasons for non-initiation were not recorded in the databases but could include a decision not to proceed after viewing SCOTT questions on the application or the sponsor deciding to withdraw the application.

The total number of trials approved by SCOTT increased about 3.5 times from 33 in 1989/1990 to 118 in 2010/2011, as shown in Figure 10. In general, the number increased from year to year, with a couple of exceptions: from 1998/1999 there was a decrease for three consecutive years until the upward trend resumed; and there was also a decrease in 2008/2009 and 2009/2010, however this trend was reversed in 2010/2011.

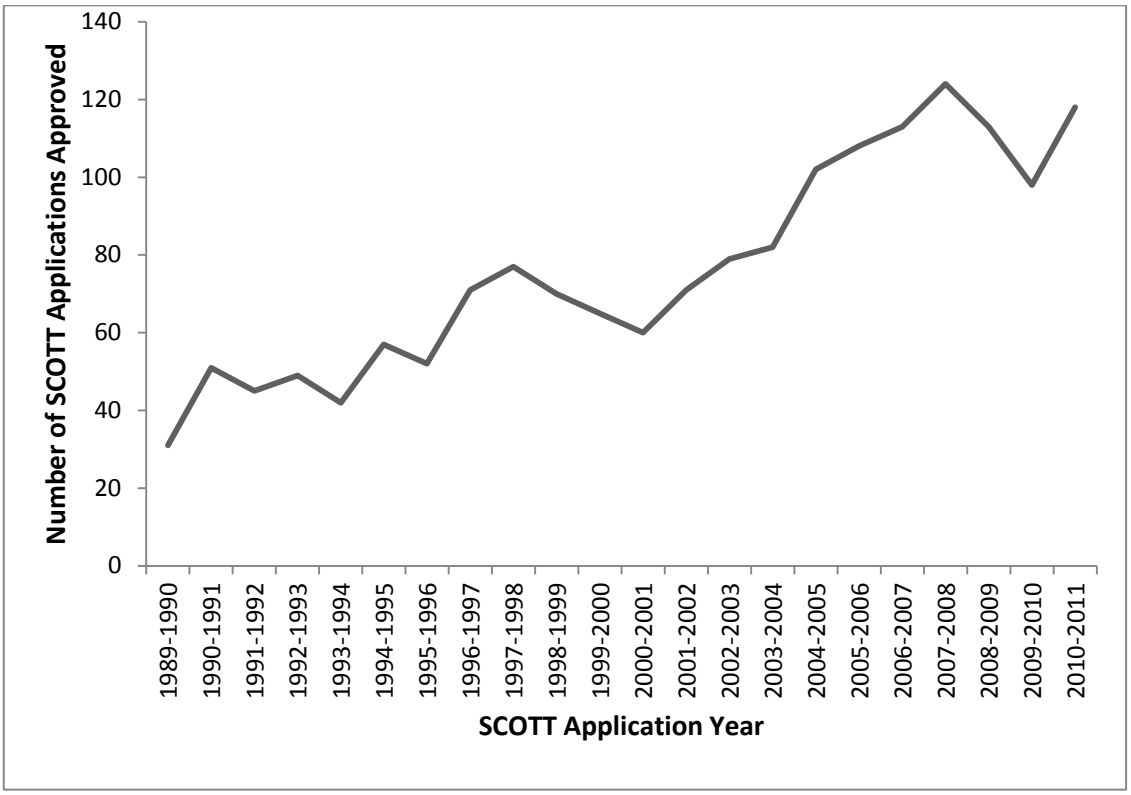

Figure 10 – Number of Approved SCOTT Clinical Trial Applications Per Year

The phase of the clinical trial was available only for applications submitted from 1 July, 1998. Figure 11 shows the number of trials for each year period that were phase I, II, III and IV and Figure 12 gives the proportion of clinical trials that were of each phase. The proportion and number of phase I trials increased substantially over the 13 years, from 4.3% (*N* = 3) in 1998/1999 to 22.9% (*N* = 27) in 2010/2011. The number of phase II trials also increased from 19 to 27 over the same period, but the percent contribution to the total number of trials remained at around 30% until reducing in 2010/2011. The number of phase III trials has varied over the years but overall their proportion has decreased from 67% in 1998/1999 to 50% in 2010/2011. The number of phase IV trials is very low because these are studies generally involve approved medicines and so do not require a SCOTT application.

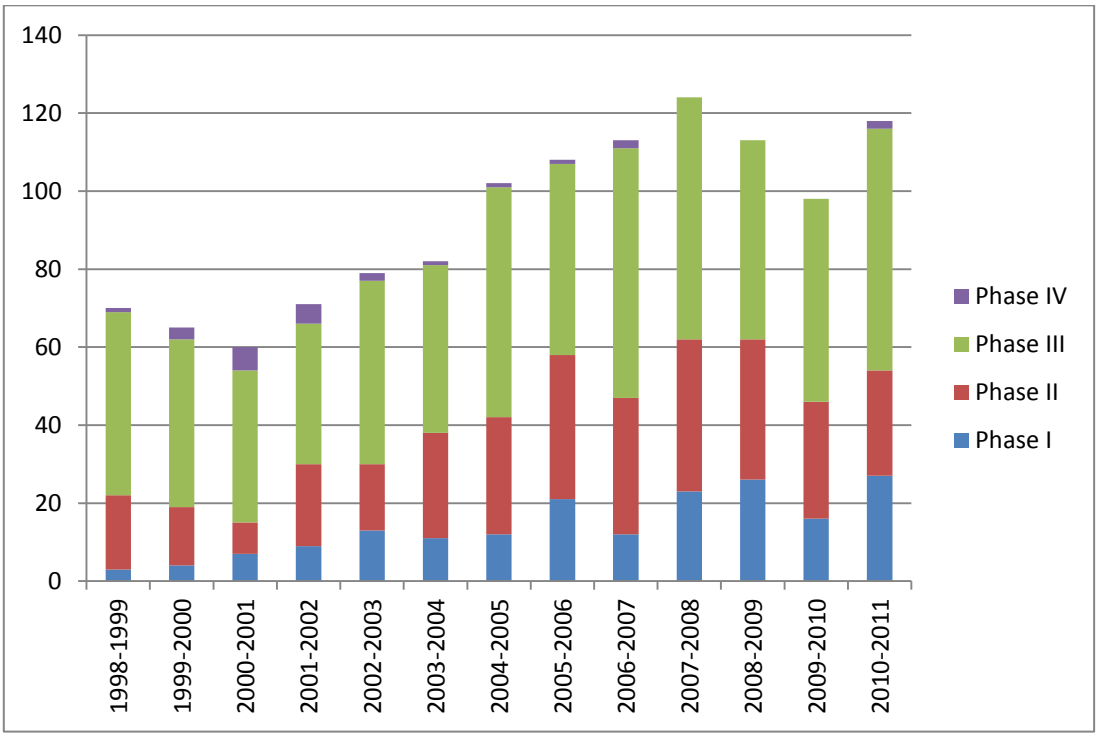

Figure 11 – Number of Clinical Trial Applications by Trial Phase and Year

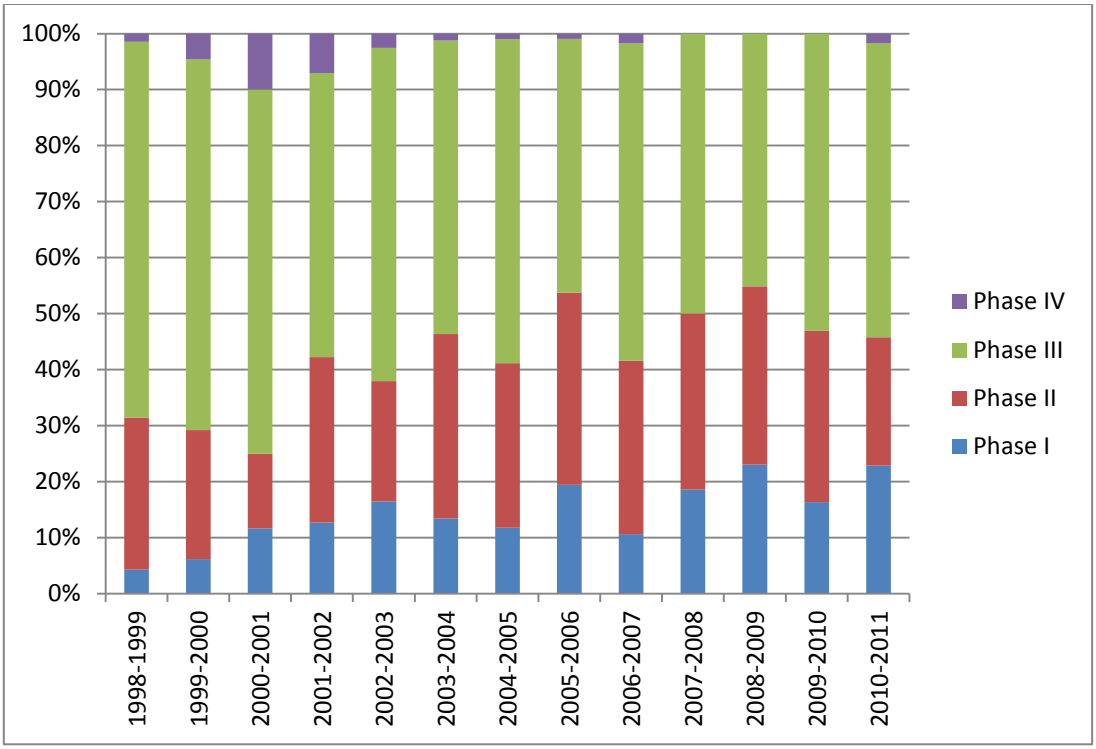

Figure 12 – Percentage of Clinical Trial Applications by Trial Phase and Year

The estimation of the revenue generated from pharmaceutical industry sponsored clinical trials was based on the proportion of applications each year that were sponsored by a pharmaceutical company, either directly or indirectly. Figure 13 depicts the number of clinical trials each year that were sponsored by each of the six sponsor categories and it can be seen that there has been a

changing distribution of the clinical trial sponsors over the period studied. Initially, clinical trials in NZ were almost entirely sponsored by multinational pharmaceutical companies. However, more recently their contribution to the total number of clinical trials has decreased. There has been an increase in both the number and proportion of trial applications lodged by CROs. Initially, the majority of CRO applications were through overseas based organisations, however by 2005 the NZ CROs supplied more than half of the applications and this business has continued to grow. The number and proportion of applications from NZ pharmaceutical/drug development companies has been quite variable but generally increasing over the period.

The number of investigator and institution sponsored trials has remained at similar levels throughout the period investigated and it is only these applications (approximately 10% each year) that are considered not to be ultimately sponsored by the pharmaceutical industry.

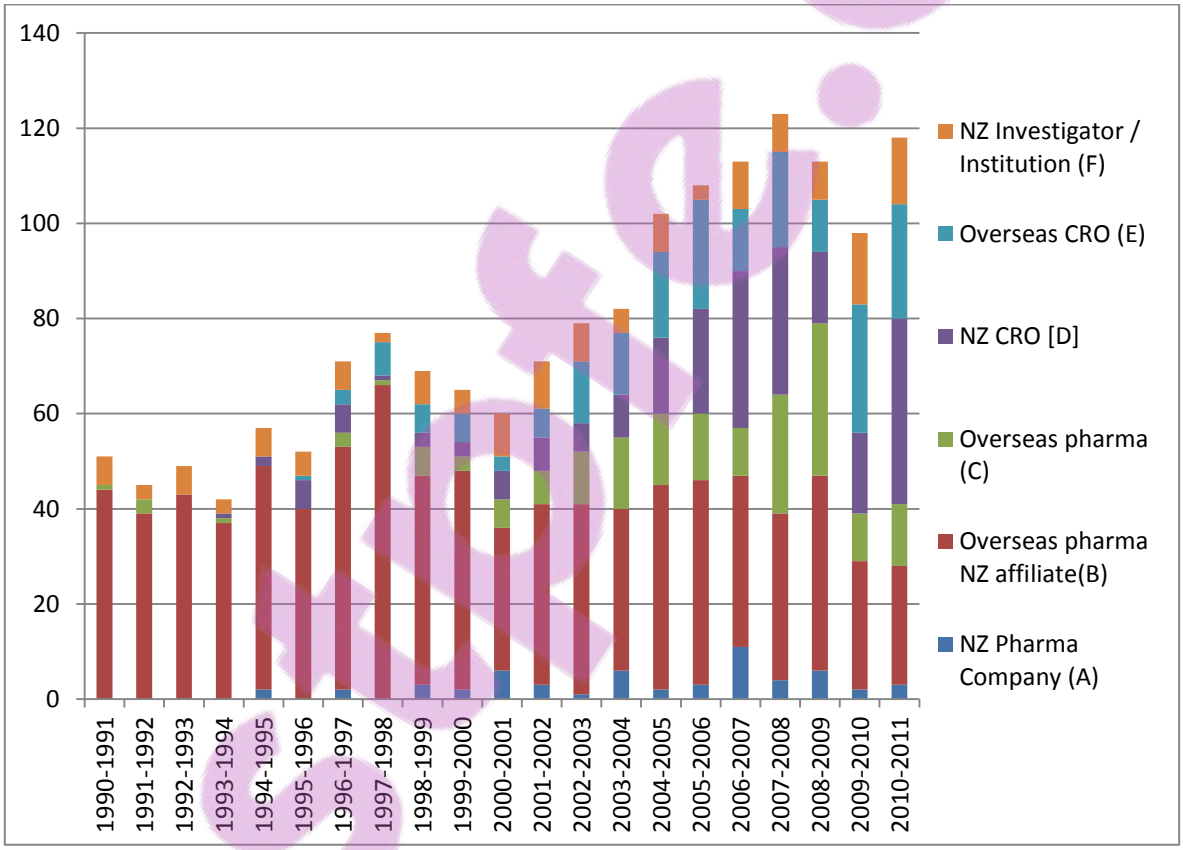

Figure 13 – Number of Clinical Trial Applications by Sponsor Type and Year

The revenue to NZ from clinical trials was therefore calculated based on the percent of clinical trials each year that were sponsored by the pharmaceutical industry, multiplied by the expected number of trial participants and using an average per participant payment to sites of NZD15,000 in 2010/2011. This per participant payment was reduced by 3% each year giving a per participant payment in 1998/1999 of NZD10,407.64.

This method estimated that industry-sponsored clinical research provided NZD121,620 million (i.e., USD102.161 million) in foreign earnings in 2010/2011, and a total of NZD887.143 million since 1998. The annual and cumulative revenue is illustrated in Figure 14 and the calculation is provided in Table 59.

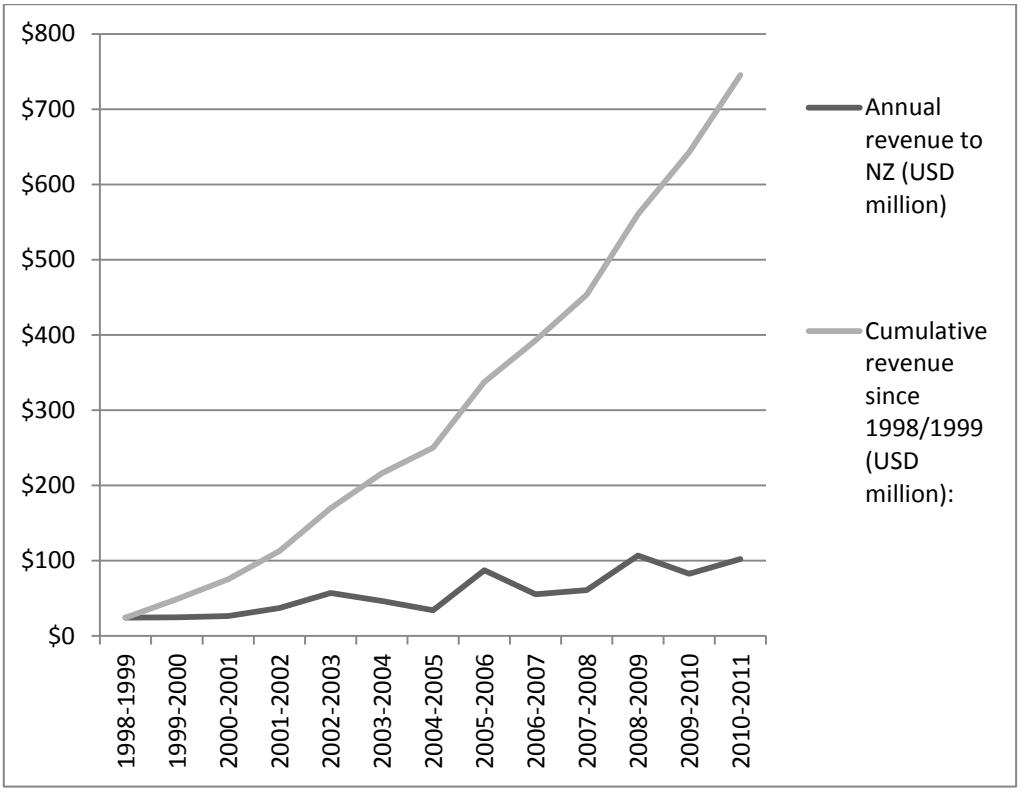

Figure 14 – Annual and Cumulative Revenue from Clinical Research

Table 59 – Revenue to New Zealand from Pharmaceutical Industry-Sponsored Clinical Trials

SCOTT application year	**1998–1999**	**1999–2000**	**2000–2001**	**2001–2002**	**2002–2003**	**2003–2004**	**2004–2005**	**2005–2006**	**2006–2007**	**2007–2008**	**2008–2009**	**2009–2010**	**2010–2011**
Expected participants in NZ	3081	3000	3339	4531	6441	4846	3518	8280	5447	5664	9682	7986	9199
Sponsor type	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*
NZ drug development company	3	2	6	3	1	6	2	3	11	4	6	2	3
Overseas pharma company, NZ affiliate	44	46	30	38	40	34	43	43	36	35	41	27	25
Overseas pharma-ceutical company	6	3	6	7	11	15	15	14	10	25	32	10	13
NZ CRO	3	3	6	7	6	9	16	22	33	31	15	17	39
Overseas CRO	6	6	3	6	13	13	18	23	13	20	11	27	24
NZ investigator/institution	7	5	9	10	8	5	8	3	10	8	8	15	14
Total	69	65	60	71	79	82	102	108	113	123	113	98	118
% Commercial sponsor	89.86	92.31	85.00	85.92	89.87	93.90	92.16	97.22	91.15	93.50	92.92	84.69	88.14
Number participants paid for by an industry sponsor	2769	2769	2838	3893	5789	4550	3242	8050	4965	5296	8997	6763	8108
Average payment per participant (NZD)	10,407	10,729	11,061	11,403	11,756	12,120	12,495	12,881	13,279	13,690	14,114	14,550	15,000
Annual revenue to NZ (NZD million)	28.814	29.713	31.393	44.394	68.050	55.149	40.510	103.690	65.931	72.501	126.972	98.407	121.620
Annual revenue to NZ (USD million)	24.204	24.959	26.371	37.291	57.163	46.326	34.028	87.099	55.382	60.900	106.657	82.662	102.161
Cumulative revenue since 1998/1999 (USD million)	24.204	49.163	75.534	112.825	169.988	216.313	250.342	337.441	392.823	453.724	560.381	643.042	745.203

A sensitivity analysis on the revenue to NZ from industry-sponsored clinical trials used a lower per participant payment of NZD10,000 and an upper level of NZD25,000 (i.e., similar to that published for USA sites). The lower payment produced a return to NZ in 2010/2011 of USD68 million and cumulative revenues of USD497 million. The higher payment generated USD170 million and cumulative revenues of USD1,242 million.

Discussion

5 Discussion

5.1 Reliability and Generalisability

There are several reasons that the results obtained should be a valid and reliable assessments of NZ's drug development industry (256). The sample represented almost the entire NZ drug development industry, and those who declined to participate were small in number and from the larger two categories of participants (i.e., support services organisations and stakeholders). The data were collected during individual interviews in a location of the participant's choice, therefore the participants were in the best situation to be able to provide complete answers without being influenced by the presence of others. The use of NVivo software, coupled with repeated review of coded text ensured that all qualitative data have been accurately coded and analysed. Finally, the use of well-designed questionnaires and SPSS ensured that all quantitative data were captured and analysed. However, the results are NZ-specific and not applicable to other countries, although the methods employed could be used by researchers wishing to assess the drug development industry of other countries.

5.2 New Zealand's Expertise for Drug Development

Assessment of the drug development expertise of the people involved in this industry is usually conducted within pharmaceutical companies either internally or by external contractors and is therefore not publicly available. An assessment of the entire drug development industry of a country does not appear to have been previously conducted and therefore the methodology for this assessment needed to be developed. However, for some parameters the results can be compared with analyses of drug development and biotechnology clusters from other countries. The potential lessons for NZ from these comparisons are also discussed.

5.2.1 Range of Expertise

This research has identified NZ's areas of expertise, especially in drug discovery and the clinical research activities, which include clinical protocol development, clinical trial management, case report form preparation, regulatory affairs and clinical study sites. There is also widespread expertise in the more general capabilities of report preparation, project management and data management. On average the drug discovery groups and support services organisations comprised about 20 people, while the drug development companies were smaller with approximately nine employees. Nine research participants (15%) had received an award for their contribution to drug development, which supports the level of expertise indicated by the industry.

A summary of NZ's drug development capabilities is presented in Table 60. It should be remembered that some areas of expertise do not require widespread availability. For example, formulation and manufacturing expertise tends to be concentrated within fewer organisations because of the large

capital investment required, whereas the clinical research disciplines are available through many of the drug development companies and support services organisations.

Table 60 – Summary of the Expertise within New Zealand's Drug Development Industry Organisations

Drug Development Capabilities	Within the drug discovery groups (*N* = 12)	Within drug develop-ment companies (*N* = 12)	Within support services organis-ations (*N* = 36)	Total NZ organis-ations (*N* = 60)
Drug discovery *N* (%)	8 (66.7)	7 (63.6)	6 (16.7)	21 (35.0)
Chemistry/scale-up manufacturing *N* (%)	4 (33.3)	4 (33.3)	4 (11.1)	12 (20.0)
GMP manufacture of API *N* (%)	4 (33.3)	2 (16.7)	5 (13.9)	11 (18.3)
Formulation *N* (%)	1 (8.3)	1 (8.3)	3 (8.3)	5 (8.3)
GMP manufacture of drug product *N* (%)	0 (0)	2 (16.7)	3 (8.3)	5 (8.3)
Package / label drug product *N* (%)	0 (0)	1 (8.3)	10 (27.8)	11 (18.3)
Analytical/stability data *N* (%)	2 (16.7)	1 (8.3)	8 (22.2)	11 (18.3)
Case Report Form preparation *N* (%)	0 (0)	7 (58.3)	17 (47.2)	24 (40.0)
Database / data management *N* (%)	4 (33.3)	2 (16.7)	15 (41.7)	21 (35.0)
Pre-clinical testing *N* (%)[1]	3 (25.0)	4 (33.3)	8 (22.2)	15 (25.0)
Safety data management *N* (%)	0 (0)	5 (41.7)	15 (41.7)	20 (33.3)
Statistics *N* (%)	1 (8.3)	3 (25.0)	13 (36.1)	17 (28.3)
Clinical protocol development *N* (%)	0 (0)	8 (66.7)	22 (61.1)	30 (50.0)
Clinical trial monitoring / management *N* (%)	0 (0)	4 (33.3)	19 (52.8)	23 (38.3)
Clinical study site *N* (%)	0 (0)	0 (0)	15 (41.7)	15 (25.0)
Report preparation *N* (%)	4 (33.3)	7 (58.3)	28 (77.8)	39 (65.0)
Project management *N* (%)	4 (33.3)	5 (41.7)	29 (80.6)	38 (63.3)
Regulatory affairs *N* (%)	2 (16.7)	4 (33.3)	19 (52.8)	25 (41.7)
Bioanalysis *N* (%)	1 (8.3)	1 (8.3)	5 (13.9)	7 (11.7)
Intellectual property management *N* (%)	3 (25.0)	2 (16.7)	3 (8.3)	8 (13.3)

[1]Preclinical testing is only to Good Laboratory practice (GLP) at one facility; the remaining organisations conduct exploratory preclinical research only

New Zealand's expertise for drug development is supported by the finding that the support services organisations reported that an average of 72.2% of their revenue was from overseas and nearly all the organisations anticipated that their revenue from overseas would increase or remain about the same in the next 3 years.

The Scientific American's "World View 2011—A global biotechnology perspective" (263) reviewed indicators of education for 48 countries. New Zealand had the second highest rate of post-secondary science graduates per capita after Ireland and followed by Australia and the UK. New Zealand had the highest number of PhD life sciences graduates per capita followed by Canada, Australia and the UK. These indicators confirm NZ's expertise in science and medical research, and support the policy proposal that NZ, Australia, Canada and the UK have drug development industries based on their

expertise in these areas. Similar research in Europe found that in 2002, the UK and Ireland had the highest rate of life sciences graduates per capita (264).

5.2.2 Drug Discovery Expertise

The strengths in knowledge creation for drug discovery, as evidenced by 20 distinct programmes in development, reflects the long-term NZ government policy of investing in scientific and medical research (134). New Zealand may not have the resources to develop all of its discovery compounds but it could establish itself as a feeder for the pharmaceutical industry in a similar way to Oxfordshire in the UK. The number of drugs that are being developed by companies with research bases in Oxfordshire has been increasing markedly since 2002 and there is a growing number of companies, many are spin-outs from local universities and some of them have been acquired by overseas companies (126). New Zealand is in a similar situation to the UK with spin-out companies developing its drug discovery compounds, however on a much smaller scale. A direct comparison is not possible because the data from Oxfordshire has a broader scope while this NZ research was limited to drug development projects; however in 2008 Oxfordshire had 142 biotech and healthcare firms while NZ had eight compounds in clinical development. In 2009, the NZ drug development sector employed almost 900 people while 5,000 people were employed in the biotechnology sector in Oxfordshire, which has a population of approximately 640,000 (64, 126). This indicates that the employment by NZ's industry is low even on a per capita basis.

5.2.3 Clinical Research Expertise

New Zealand's expertise in clinical research as reported by the research participants is supported by data from the assessment of its economic returns to NZ that showed that the number of approved clinical trials involving unregistered medicines increased more than threefold from 33 in 1989/1990 to 118 in 2010/2011. Most of these trials were sponsored by international pharmaceutical companies, either directly or, more recently, via clinical research organisations and the increase indicates the global industry's confidence in NZ's clinical research capabilities. The analysis of SCOTT application data identified that area of growth in clinical research is phase I clinical trials which increased from 4.3% of successful applications in 1998/1999 to 22.9% in 2010/2011. The number of clinical trials found here is lower than quoted by Jull et al. (265) for the 1998 to 2003 period. However, their research was based on ethics committee applications and so also included clinical trials involving registered medicines, procedures, processes and medical devices, as well as unregistered medicines. For the same reasons, differences in the percentage of clinical trials for phase III were found. Jull et al. (265) found that approximately 90% of the ethics applications were for phase III clinical trials, whereas over the same time period we found that phase III trials accounted for only about 60% of SCOTT applications.

A study conducted in Norway (266) considered all research projects involving the clinical development of drugs in 2000 and 2004. With 4.5 million people, Norway has a similar population size to NZ and the researchers found that 82.4% of research projects were for phase III and IV—a similar result to Jull et al. A comparison of only phase I–III studies in the two countries shows that while Norway conducted more studies in 2000, by 2004 NZ conducted a similar number as Norway (just over 100 in each country). In fact, Winther et al. (266) found that the number of drug development research projects had been stable for some years and postulated that for their population of 4.5 million their capacity for this type of research had been reached. In contrast with Norway, in NZ the number of phase I–III clinical trials has continued to increase since 2004, especially in the proportion of phase I clinical trials. This reflects the introduction of several dedicated phase I units in NZ and indicates the acceptability of the data generated by the global pharmaceutical industry.

It is difficult to compare NZ's SCOTT application data with that from most countries because of the different systems used and the limited amount of information available from regulatory authorities. It could be possible to estimate the number of clinical trials undertaken in a given country by checking the authorised clinical trial registries, identifying the trials that involve an unregistered medicine and that started in the year being investigated, and also removing duplicate registry entries. In practice, this would be exceedingly time-consuming, especially because clinical trials lodged in the registries include those testing registered and unregistered medicines, medical devices and other interventions and this analysis has not been conducted. However, Thiers et al. (267) conducted an analysis of the number of clinical trial sites by country using the information only on the USA NIH clinical trial registry (www.clinicaltrials.gov). The research collated the proportion of clinical trial sites in each country for multi-centre trials in 2006 and compared it with each country's proportion of sites in 2002. Countries were then ranked based on the increase in their proportion of sites in 2006 compared with 2002. The 30 highest rankings were for predominantly emerging clinical trial countries such as China (1st), Estonia (2nd), Russia (3rd) and India (10th). New Zealand was ranked 37th, which was similar to its traditional clinical research competitors such as Australia (34th), USA (44th), the UK (48th) and Canada (49th). This research therefore indicated that NZ is keeping pace with its traditional competitors but should be aware of the range of emerging countries competing for clinical research projects.

New Zealand is not a key market for the pharmaceutical industry (13), which places it at a disadvantage for conducting later stage clinical trials. However, there are factors that help offset this disadvantage: it is seasonally opposite to the northern hemisphere, it has a relatively high incidence of some diseases (e.g., gout and asthma) and it is able to contribute reasonable numbers of participants at competitive costs. However, NZ also needs to focus on its expertise in the more challenging phase I and II clinical trials where it is likely to remain more competitive.

5.2.4 Knowledge Management

The knowledge required for R&D is generally tacit and complex, which makes it more difficult to share. To compete in a rapidly changing environment, those working in drug development must learn how to effectively share knowledge (268) as an essential basis for innovation (101). The results from knowledge acquisition and sharing questions show that the NZ industry recognises the importance of knowledge management, especially of tacit knowledge that is generally obtained through personal contacts and informal networking. Previous research in high technology Taiwanese firms (90) also found that the internal non-codified (i.e., tacit) sources of knowledge, internal meetings and asking work colleagues, were the most important. The main difference between the NZ and Taiwan results was that the least important source of information in Taiwan was the internet, which seemed surprising for high technology firms. However, all sources had lower ratings in the Taiwanese research compared with NZ and this may be due to cultural differences. Further research using this scale in other countries may be useful to confirm its validity. Table 61 compares the NZ drug development industry and the Taiwanese high technology industry ratings of the knowledge sources and Table 62 compares the rankings.

Table 61 – Comparison of the Ratings of the Importance of Knowledge Sources between New Zealand and Taiwan

Rating of importance of sources of knowledge *M* ± *SD*	NZ drug discovery group (*N* = 12)	NZ drug development company (*N* = 12)	NZ support services organisation (*N* = 35)[1]	Taiwan high technology firms (90) (*N* = 371)
Internal formal training (i.e., internal codified information)	2.50 ± 1.31	3.17 ± 1.46	3.71 ± 1.49	3.26 ± 0.85
Internal meeting (i.e., internal non-codified information)	4.75 ± 0.62	4.08 ± 1.24	4.37± 0.73	3.72 ± 0.78
Asking work colleagues (i.e., internal non-codified information)	4.25 ± 0.97	4.42 ± 0.67	4.23 ± 0.91	3.83 ± 0.69
Using external networks (i.e., external non-codified information)	3.93 ± 0.90	4.00 ± 0.95	4.06± 0.94	3.33 ± 0.90
Professional publications (i.e., external codified information)	4.33 ± 0.89	3.58 ± 1.31	3.63 ± 1.22	3.62 ± 0.78
Internet (i.e., external codified information)	4.33 ± 1.16	4.33 ± 0.65	3.94 ± 1.11	3.18 ± 0.99

[1]One participant did not feel able to answer

Table 62 – Comparison of the Rankings of the Importance of Knowledge Sources between New Zealand and Taiwan

Ranking of importance of sources of knowledge Mean ± *SD*	NZ drug discovery group (*N* = 12)	NZ drug development company (*N* = 12)	NZ support services organisation (*N* = 35)[1]	Taiwan high technology firms (90) (*N* = 371)
Internal meeting	1	3	1	2
Ask work colleagues	4	1	2	1
Internet	2=	2	3	6
External networks	5	4	3	4
Professional publications	2=	5	6	3
Internal formal training	6	6	5	5

[1]One participant did not feel able to answer

Effective knowledge sharing behaviour, especially when an innovation results as a consequence, is associated with increased career satisfaction (110). This research found that the highest rating of knowledge sharing was within NZ's drug development organisations and that these ratings were similar for the three categories of participants. The participants also reported quite high levels of career satisfaction and higher levels of interest in continuing their career in drug development. However, the sample sizes, especially for the drug discovery and drug development groups, are too

small to confirm any strong links. The lowest rating of current career satisfaction was from participants working in drug discovery and this may be due to many NZ compounds failing their phase II and III clinical trials. The poorest knowledge sharing was found to be between NZ drug development companies and between these companies and drug discovery groups. This may be a result of these organisations competing with each other for government funding and private investments.

The finding that the NZ participants reported better knowledge sharing within their organisation than externally is consistent with their stated preference for utilising the more informal sources of knowledge such asking work colleagues, internal meetings and the internet. The preference for internal and informal knowledge sharing may have been driven by NZ's modest-sized drug development industry and relative geographical isolation leading to a 'help-each-other-out' attitude and ease of finding the right contacts to ask for advice. Some research participants suggested that the poorer external knowledge sharing may indicate a level of distrust between the organisations because they are competing with each other for funding or it may reflect the general industry culture of keeping private information confidential. A 1996 report released by the Organization for Economic Co-operation and Development (OECD) estimated that knowledge was the basis of more than half the gross domestic product (GDP) of developed economies (cited by Husted, 2002). Hoarding knowledge may be counter-productive; to obtain maximum efficiency knowledge should be systematically shared rather than randomly distributed (109). It is important that New Zealanders recognise that they may need to make more effort to share knowledge even if it means getting out of their comfort zone.

The trait of New Zealanders to prefer informal and internal knowledge management practices has been previously reported with the suggestion that it may limit their access to specialist knowledge thereby reducing knowledge availability and its potential uses for innovation (67). However, some NZ firms have become successful internationally, despite a lack of local knowledge sources by building an internal knowledge base, high levels of innovation and providing a high level of customisation for key customers. Thus, their knowledge acquisition has an international focus rather than being able to benefit from geographical proximity. It was suggested that these innovative start-up companies could benefit from policies to support their rapid international expansion (154).

The results also show that the average number of collaborations that the NZ drug development companies have with both local and overseas organisations is approximately 10, and the NZ support services organisations supply their services to an average of 13 drug development companies. This indicates that the NZ drug development industry is reasonably well-connected because this collaboration rate is comparable with that of large pharmaceutical companies (23) and the reasons for the collaborations are likely to be similar (i.e., to gain access to necessary expertise and assets).

There was a preference for local vendors to be used by the NZ drug development companies, however overseas organisations were sometimes deliberately selected to extend the company's networks and gain an international presence and connections.

The NZ drug development companies were more satisfied with their interaction with the NZ support services organisations than the NZ support services organisations were with their interactions with the NZ drug development companies. This discrepancy in satisfaction was explained by some NZ support services organisations' participants who indicated that in their experience the NZ drug development companies did not appreciate the high costs of drug development and hoped to obtain a reduced rate because they were a NZ start-up company with limited funds. They also felt that some of the NZ drug development companies did not have sufficient understanding of the drug development process and were looking to "cut corners" to reduce the costs.

5.2.5 Innovative Behaviours

This research into NZ's drug development industry also found that its people exhibit the required strengths in innovative behaviours, which is another important trait for success in the drug development industry. The participants reported expertise in solving problems that have caused others difficulty, especially for problems that may have required an innovative approach or solution. Some participants commented that the low rating they assigned for making time to work on ideas and projects was a reflection of having more ideas than the time to develop them. These results indicate the level of innovative thinking within the NZ drug development sector and this is supported by the number of companies with NZ-discovered compounds in clinical development (as presented in Section 2.1.4). These results support previous research by Smale (67) that reported on the practical approach of New Zealanders to solving problems, often utilising an existing idea and applying it differently or to a new situation using minimal resources. That research also found that New Zealanders tend to undertake their innovation projects in silos, exhibit a strong reluctance to give and receive feedback, have a fear of failure and a view of the world that will limit their deeper understanding of potential markets for their innovations. The researcher concluded that while they have strengths in creativity and problem-solving, New Zealanders have a weakness in commercialising their inventions and understanding their market potential (67). This dichotomy in the NZ entrepreneurial culture that encourages innovation and is open to new ideas but exhibits a low tolerance for failure needs to be overcome for the full benefits of NZ ingenuity to be realised.

Two indicators of innovation for drug development, outputs of the number of publications and patents per year, can be compared with similar data from research of two biotechnology regions, Brisbane in Australia and Gothenburg in Sweden (115). These two clusters do not have the size and scope of the more established and well-recognised USA biotechnology regions such as San Francisco's

Bay Area, San Diego and Cambridge, however they do share some similarities with NZ. All three areas have a relatively small economy with a historical dependence on more traditional industries; all have a research tradition in biomedical sciences, and all have policies of working towards a more knowledge-based economy with biotechnology as a potential base. However, the population of the Brisbane area is approximately 2 million and Gothenburg metropolitan area has nearly 1 million people while NZ has a population of 4 million. Despite the data being self-reported rather than collected independently from search activities and some methodological and timeframe differences, the NZ data collected on the number of publications and patents can be compared with the data from Brisbane and Gothenburg. For the 1997–2001 period, Gothenburg had a total of 750 scientific publications and Brisbane had 861 publications (115), both of which are similar to the average of 718 publications per year that the NZ research found for 2008–2009. The NZ research did not collect the number of patents granted; rather it considered the number of patents "produced or contributed to", which provided a total of 126 from the 60 research participants. This is lower than the 209 patents granted in Gothenburg but higher than the 60 from Brisbane. The per capita results for NZ are generally lower than for Brisbane and Australia, but this may be partly because it includes only the publications and patents that the 60 research participants had been involved in. It is expected that there will be other drug development publications and patents from the NZ industry that these participants have not been involved in. However, given these constraints, as summarised in Table 63, the drug development outputs from NZ indicate that it has a similar level of expertise to Brisbane and Gothenburg.

Table 63 – Comparison of the Drug Development Outputs of New Zealand, Brisbane and Gothenburg

Outputs (per year)	New Zealand	Brisbane (Australia) (115)	Gothenburg (Sweden) (115)
Publications	718	861	750
Patents	126	60	209
Population	4 million	2 million	1 million

The results from Brisbane, Gothenburg and NZ can be compared with another set of data from an analysis of the performance of the biotechnology industries of 18 European countries and the USA (264). The analysis found that in 2002 Switzerland had the highest rate of biotechnology-related publications per capita, with just over 1,000 per million inhabitants, followed by Sweden, Denmark and Finland. It also found that Iceland had the highest rate of biotechnology patents, with more than 150 per million capita, followed by Denmark and Switzerland. While NZ's publication rate is comparatively low compared with the 19 countries analysed, its patent rate in 2008/2009 was similar to the median for Europe in 2002.

Research published in a 2011 Scientific American global biotechnology report (263) provided a rating of 'innovation and entrepreneurship opportunity in biotechnology' for 48 countries and ranked Denmark, Sweden and the USA as the top three countries. The research placed NZ in 14th position, immediately behind Canada and Australia and just above Germany and Austria. The same research ranked NZ 6th (out of the 45 countries for which data were available) for the proportion of all patents that were for biotech applications with very similar rates as Canada and Portugal. It also rated NZ 18th out of 48 countries for its overall capability to generate innovation in biotechnology, placing it between Hong Kong and South Korea. The rankings were based on the results of five key categories: intellectual property protection, industry intensity (e.g., number of companies and patents), enterprise support, education and workforce, and the country's industry foundations (e.g., investment and infrastructure). The five highest ranked countries were the USA, Denmark, Sweden, Canada and Australia.

An OECD review of NZ's innovation system (13) confirmed that the country had good basic conditions for entrepreneurship and innovation, but that the business environment to further encourage firms to innovate and invest in R&D is required. The data from the comparison of NZ with two biotechnology regions coupled with the independent assessments discussed support the research findings that NZ has strengths in innovation.

5.2.6 Expertise and Cluster Development

There is a cluster of drug development organisations, particularly in Auckland, which is NZ's largest city and the location of the majority of its industry and biomedical research facilities. The drug development cluster in Auckland encompasses the University of Auckland, which was ranked 41st in the world in 2010 for 'Life sciences and biomedicine' by the QS World University rankings (269). It has several specialist research centres, offers degrees in medicinal chemistry and biomedical science, recently opened its purpose-built Institute for Innovation in Biotechnology offering facilities for companies and postgraduate students and its own commercialisation agency (270). Auckland is also the location of the majority of the multinational pharmaceutical companies, the industry's support and research organisations, investment community, patient support/lobby groups, business growth and commercialisation organisations, legal and intellectual patent advisors, and consultants with overseas industry experience who have returned to NZ. Most of NZ's spin-out drug development companies with innovative compounds that originated from NZ research in clinical development are based in Auckland.

However, there are pockets of specialised expertise throughout NZ making the industry geographically asymmetric. A country the geographical and population size of NZ does not have the resources for multiple life science clusters and maybe the country's entire drug development industry

should be considered as just one cluster, a 'country cluster'. Figure 15 depicts the location of NZ's drug development organisations; note that the percentage given for each location is for its share of the entire number of NZ industry organisations. Table 64 provides details of the locations of the three facets of NZ's drug development industry; note that the percentages given are for the totals in each column (not the percentage for each row).

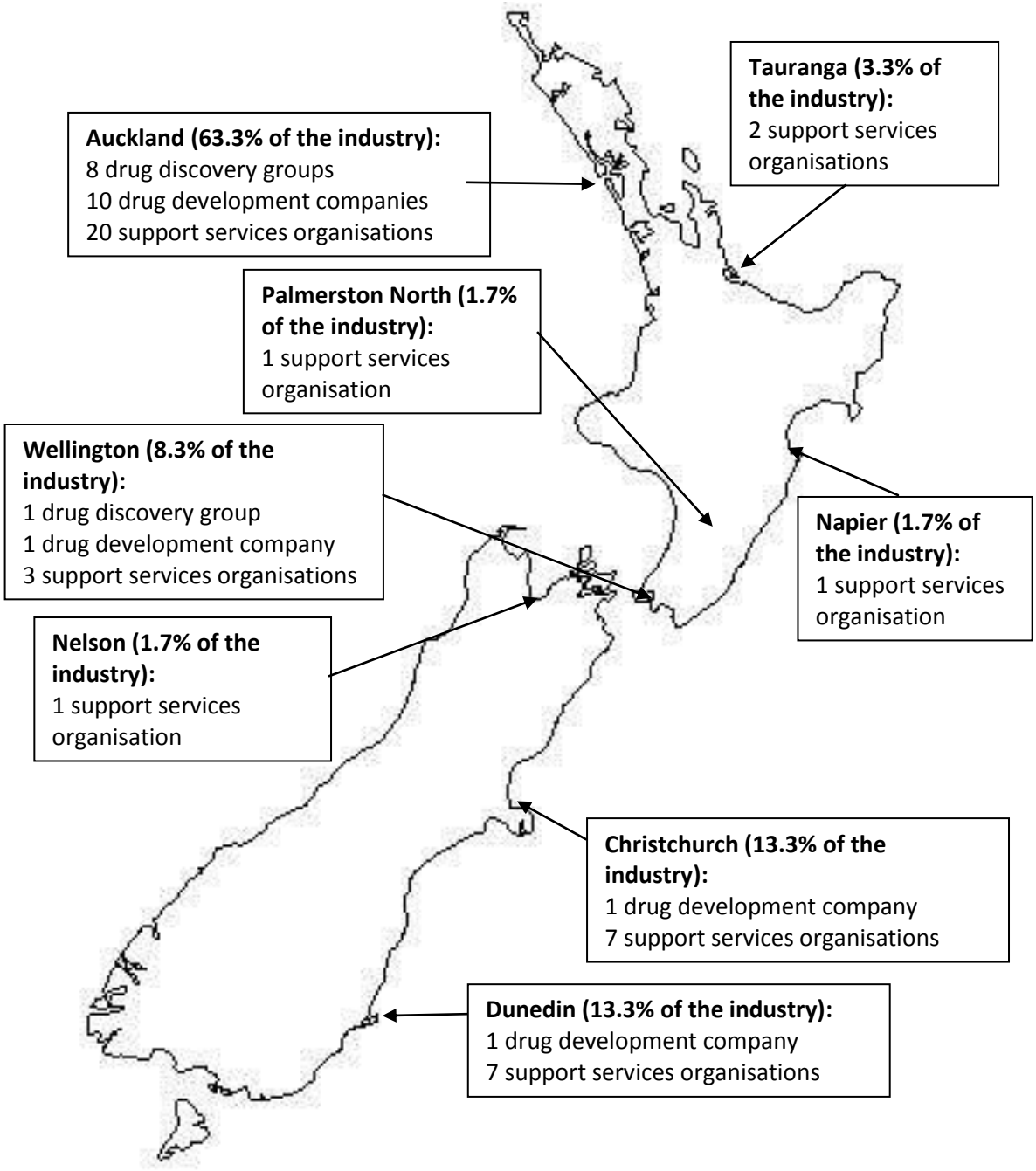

Figure 15 – Locations of New Zealand's Drug Development Industry

Table 64 – Location of New Zealand's Drug Development Industry

Location	Drug discovery *N* (%)	Drug development *N* (%)	Support service *N* (%)	Total *N* (%)
Auckland	8 (66.7)	10 (83.3)	20 (55.6)	38 (63.3)
Wellington	1 (8.3)	1 (8.3)	3 (8.3)	5 (8.3)
Christchurch	0	1 (8.3)	7 (19.4)	8 (13.3)
Dunedin	3 (25.0)	0	1 (1.7)	4 (6.7)
Other	0	0	5 (13.9)[1]	5 (8.3)
Total	12 (100.0)	12 (100.0)	36 (100.0)	60 (100.0)

[1]These five support service organisations are located in Tauranga (*N* = 2), Napier (*N* = 1), Palmerston North (*N* = 1) and Nelson (*N* = 1).

Research in the USA and Canada has shown that the rate and direction of the development of a life science cluster is variable. It is influenced by the strengths on which the cluster was founded but also by chance events within the local economy. Policy and decisions made at a national and regional level, such as the choice of research investments, healthcare expenditure, and technology transfer and economic development offices, exert a strong influence. There is no universal model for cluster development, rather there are many different paths that may lead to a focus on one or more niche areas or a wider range of activities (114, 127). This has implications for the development of NZ as a cluster because although the majority is based in one region, there are components that are located throughout the country therefore national policies rather than regional ones will be more effective. Cluster development in many European countries has been supported by policies to increase the science base and to encourage networking and linkages between all parties in the cluster area (271).

The importance of the drug development industry is recognised at NZ government level as evidenced by the proliferation of targeted and newly resourced organisations and the expansion of existing entities, especially in Auckland. This result agrees with findings from previous research on NZ's biotechnology industry that found that government policies for capability strengthening, research funding and encouraging clusters had been effective (272). It will be important for the NZ government to continue to support the industry cluster as it grows and needs further resources and co-ordination of efforts (127). There is evidence that the triple helix of university, industry and government have all contributed to the industry development so far, however it is important that government continues to support projects that firms would not undertake without a research subsidy (131).

A study of industry organisations and associations in Canada found that they are most effective in influencing the success of the industry cluster they represent when used to align the interests and resources of the diverse industry stakeholders, to articulate their common goals and for the pursuit of further resources (114). New Zealand has industry support organisations such as NZBio, which represents NZ's bioscience based industries, and the NZ Association of Clinical Research (NZACReS),

which fosters and promotes clinical research. There are important reasons why these organisations should continue to provide and encourage formal and informal networking occasions to foster the growing drug development industry in NZ. The aims of networking are twofold: first, to encourage knowledge sharing both locally and internationally as a basis for innovation ideas; and second, so that specific expertise in NZ is recognised by potential collaborators both locally and internationally. The first reason for organising networking occasions is applicable to the industry in general: the extent of engagement in knowledge sharing depends on the level of development of systems and networks for this activity (130). The second reason is NZ-specific: because the NZ preference for knowledge sharing is on an informal basis and with closer colleagues, opportunities for those in the industry to broaden their networks and form trusting relationships with more people may encourage wide knowledge sharing. Recent NZ government initiatives have included support of technology linkages between research organisations and businesses (158). These initiatives will be helpful as research in Europe has confirmed that the crucial public policy challenges are to support knowledge linkages and to facilitate access to funds, skills and infrastructure (130).

Research in Scotland, Sweden and Denmark has found that while biotechnology firms may initially engage local contacts for complementary capabilities and new knowledge, many research partnerships and co-development deals occur with global partners identified through existing or newly created contacts (130). Therefore, the challenge is for the key players in the NZ industry to overcome their natural preference for informal knowledge sharing with long-standing colleagues and to create new contacts, develop relationships and overcome their reticence for self-promotion. Pharmaceutical companies usually initiate their collaborations (130) and therefore global industry needs to be aware of the capabilities that NZ can provide because it may not otherwise consider NZ when seeking a specific expertise. It has been suggested that local networking needs to be supported by local policies and that if there are sufficient people clustered in the same locality knowledge transfer will occur. However, the development of international communication channels requires institutional and infrastructure support (273).

In summary, comparing the results with the literature indicates that the NZ drug development industry has comparable levels of capability with similar regions (Brisbane and Gothenburg), and is supported by the required triple helix of academia, industry and government. The NZ industry exhibits the essential tripod of knowledge creation (i.e., the number of patents and innovative behaviours), commercialisation (i.e., the number of NZ-discovered compounds in development) and knowledge retention (i.e., the length of experience in the industry and their knowledge sharing behaviours). These results indicate that there is a viable industry nucleus that, given appropriate support, could be developed into a life science-based country cluster. New Zealand may be disadvantaged by its relative geographical isolation, but active support of a collaborative cluster and increasing globalisation may

minimise this drawback (128). There is evidence that the number of alliances formed is more important than geographical proximity and that the location of an industry cluster does not affect its competitiveness for an alliance with an industry leader. This is important for NZ because the 20 largest pharmaceutical companies (by revenue) are located in the USA, Western Europe and Japan (234).

5.3 Enablers and Barriers

5.3.1 Enablers of New Zealand's Drug Development Industry

This research has shown that the most influential factors, proposed by the NZ drug development industry that has encouraged its development, have been government policies and their downstream effects. The six policies and factors that were most frequently mentioned by the research participants were:

- Specific government funding of science, medical research and drug development projects
- Growth of NZ expertise in drug development
- NZ's reputation for clinical research
- NZ's reputation for high quality scientific research
- Universities and their commercialisation activities
- Kiwi ingenuity and innovation

Policy analysis conducted during the framework development of this research suggested that NZ's policy to support its drug development falls into the same model as the UK, Australia and Canada however with lower levels of funding (13, 134). The participants in this research indicated that a wide range of government policies, including funding, have encouraged the industry. The supportive government policy types specified by the participants that were also identified in the policy framework are government investment, and legal and pharmaceutical price control policies. The participants did not identify policies to encourage foreign and private investment of NZ's industry as a supportive factor, although limited investment was mentioned as a factor that has hindered industry development. The participants did not specifically mention expertise and knowledge management policies, although these policies influenced the development of NZ's science and research expertise. It is possible that the participants were aware of the specific policies of NZTE and NZBio; however some government policies to support science education and networking have been instigated since the participant interviews were conducted.

Research by Enzing et al. (271) classified the policy instruments that governments could use to stimulate a biotechnology industry according to their goals. Six of the nine policy goals had equivalent categories in the policy framework developed for this NZ research. These were the promotion of basic

research and applied research, support knowledge flow and collaboration, facilitate knowledge transfer from academia to industry, assure the availability of human resources, assist firm creation and encourage business investment in R&D. The two policy goals that were not covered by the policy framework used in the NZ research were those to engage the public about biotechnology research and the use of biotechnology for new applications, although a 2008 MoRST strategy document (15) included engaging New Zealanders with science and technology as one of its four strategic priorities. The classification of policies based on goals did not include the pharmaceutical price control or legal policies provided in the policy framework. Both systems include policies that target the industries as well as policies with more generic applications. Overall, despite the different methods of classifying policy and the differing focus on biotechnology and drug development, the two systems have provided similar results.

Other factors that could affect the innovation and success of a country's drug development industry include its cultural traits, institutional characteristics, and the geography (153). New Zealand's distinctive factors relating to its geographical isolation (e.g., unique botanicals and biologics), and its skilled researchers who have an aptitude for innovation, English as its first language and a western culture, place it in a rare position in the drug development industry. New Zealand's unique situation may give an advantage over other emerging and increasingly competitive drug development countries such as India and China. However, as a much smaller country, NZ needs to focus its industry on niche areas where it has particular expertise or advantages.

When questioned about the policies and factors that have encouraged the development of their own organisation, participants generally mentioned the same issues that had encouraged the industry in general. However, some participants stated factors that were specific to their organisation; the most frequently mentioned factor was the vision, leadership and expertise of a key member of their organisation. This role of the highly entrepreneurial scientist has been acknowledged as a critical element in the early development of the USA biotechnology industry (127). They have been referred to as "star scientists" because of their deep understanding of the science behind their innovation, which is coupled with their industry and business involvement (130).

5.3.2 Barriers to New Zealand's Drug Development Industry

Lack of funding was stated as the biggest threat and barrier to NZ's drug development industry and was also linked to four other main inter-linked themes: expertise issues, the characteristics and size of NZ's industry, government policies and a lack of understanding of the industry. Lack of funding encompassed both insufficient government funding and insufficient private (i.e., local and overseas) funding, both of which are affected by government policies. These responses to the open question on barriers to NZ's industry were supported by the participants' ratings of the list of possible industry

barriers. All categories of participants gave the highest ranking to 'Limited funding', with 'Limited local expertise and capabilities/experienced people have moved overseas' and 'Insufficient understanding of the drug development and regulatory processes' gaining the next two highest overall rankings. These last two barriers relate to the expertise issues, lack of understanding and industry characteristics that were provided in response to the open questions. The low ranking of 'Difficulty in determining a lead compound' is probably because an area of expertise for NZ's industry is drug discovery. Similarly, 'Issues with manufacturing or formulation' is likely to be of low importance because few compounds progress to phase I/II clinical trials while retaining NZ ownership.

An analysis of the inventors of new drugs approved by the USA's Food and Drug Administration (FDA) from 1998 to 2007 found that 8% were discovered by a university and then transferred to a pharmaceutical company (274). A further 16% were discovered by a university before being transferred to a biotechnology company. For most countries the vast majority of their new drugs are discovered by pharmaceutical companies; however the USA, Australia, Canada and Israel are exceptions with more medicines being discovered by their universities or biotechnology companies. It is suggested that, at least in the USA, this situation is due to specific policies of high levels of public funding for academic biomedical research (274).

An issue NZ faces is its levels of both government and business investment in R&D, which are low compared with Organization for Economic Co-operation and Development (OECD) averages. An OECD review (13) also suggested that barriers to NZ's innovation were its lack of investment in business R&D and a fragmented system of government support of R&D and innovation. It suggested that NZ should increase the level of government funding but rationalise the number of funding instruments and this is in accordance with policy requests from the research participants.

The Scientific American's "World View 2011—A global biotechnology perspective" (263) compared government support of R&D/GDP of 48 countries based on OECD data. New Zealand was ranked 30th with a similar level of government investment as Portugal, Italy and Brazil. The document also presented R&D business expenditures/GDP also based on OECD data; NZ was ranked 35th out of the 41 countries for which data were available with similar levels of business investment as Hungary, South Africa and Italy. The highest ranked countries on these indicators were Israel, Sweden, Finland, Japan and South Korea. The rankings for NZ confirm that its levels of investment are lower than the OECD average, particularly for business investment in R&D.

A potentially important issue for all countries is 'brain drain' or diffusion of skilled human capital that occurs as people are lured overseas by perceived better quality of life or career opportunities (155). The loss of skilled people from NZ was stated as a threat to their organisation by 12.3% of participants and was given a high ranking in the ranking of specific barriers question. Participants mentioned that

their organisation contained people whose expertise was unique and highly specialised and that they would be very difficult to replace if they should leave the organisation. On the other hand, international research (263) reported on the brain gain as measured by the relative number of international graduate students studying in 33 countries. New Zealand was ranked 11th, at a similar level as Spain, Italy and Austria, while the USA and UK were the top two ranked countries.

An alternative strategy to implementing policies to reduce brain drain is to accept that this diaspora will occur and focus on using it as a resource to gather knowledge and contacts with overseas experts until they are in a position to return to NZ (155). For NZ, the contribution of a consolidated and well-connected network of expatriates overseas maybe more beneficial and cost-effective than providing incentives to encourage them to return home (275). The importance of the knowledge capital of its returning citizens has been recognised by China as an important catalyst for its emerging drug discovery industry (276). One approach used by countries such as China, is to provide incentives for experienced returnees to build transnational companies that are based locally but have affiliates in the west. In this way the new companies can utilise returned expatriates' skills and global connections but also have international credibility (277).

Some countries have recognised the public-sector bind of innovative academic scientists whose research results can be applied to the development of new medicines and have attempted reforms around commercialisation of academic research (278). The USA's Bayh-Dole Act allowed academic researchers to benefit from their patent filings while not being out-of-pocket because the legal costs were met by their university (6, 279). In addition, much of the leading research in the USA is conducted in private elite universities (278). Reforms of academic R&D in Germany and Japan have been studied—almost all universities in Germany are state-funded while in Japan private universities are common. There is debate on whether the reforms in both countries have been sufficiently far-reaching because the largest biotechnology companies are older firms and not start-ups (278). The participants in the NZ research credited the efforts of the commercialisation arms of some of its universities as a factor supporting drug discovery and development but suggested that there is scope for further improvement.

This NZ research found that the most controversial government policy is funding of medicines through its agency PHARMAC, because it was mentioned as both hindering and assisting NZ's drug development industry. Four respondents mentioned that PHARMAC policies, coupled with a competent western medical system, have assisted clinical research organisations because NZ has some relatively treatment-naïve patient groups suitable for clinical trials of new medicines, especially in oncology and rheumatology. However, 29 participants had the opposing view and advised that PHARMAC policies led to the withdrawal of many multinational pharmaceutical companies from NZ

because there is less motivation for them to invest there. This has resulted in fewer valuable interactions with the international industry and this view has been previously supported in a report on pharmaceutical industry R&D in NZ (280). The updated UK Pharmaceutical Price Regulation Scheme (PPRS) 2009 (281) recognises the importance of a pharmaceutical pricing system that encourages research and rewards innovative new treatments. Therefore, the UK Department of Health and the pharmaceutical industry are working together to establish a database of new technologies in development to assist the NHS with future planning and budgeting. Such collaboration may be useful in NZ and other countries, but could require carefully balancing of economic and medicines policies.

The debate on the influence of PHARMAC on NZ's role as a clinical research destination may continue. Recent research has shown that the number of clinical trials involving unregistered medicines has grown more than threefold in the last 20 years (262), although this positive trend did not occur every year. A decrease in the number of trials occurred for 3 years from 1998/1999 until 2002/2003 may reflect that a number of multinational pharmaceutical companies closed all or some of their NZ-based operations at that time and relocated clinical research functions to Australia or elsewhere overseas. There has been an obvious change in the trial sponsors from entirely pharmaceutical companies in 1989/1990 to predominantly CROs in 2008/2009 (262). This suggests that the apparent withdrawal of the research departments of multinational pharmaceutical companies from NZ has allowed the growth of NZ's own CROs and encouraged overseas CROs to set up an affiliate office in NZ.

5.3.3 Policies to Support Further Industry Growth

New Zealand's industry has developed as a direct and indirect result of government policies coupled with NZ-specific factors and the current changes in the global pharmaceutical industry. However, the research participants suggested a range of policies to support further industry growth; the most commonly stated policies were those around the level and management of government investment. Other policies requested were to encourage private investment, increase the NZ knowledge pool and level of collaborations, education and career development to prevent excessive brain drain, promote dialogue between PHARMAC and the pharmaceutical industry, keep NZ competitive for clinical research and verbal government support. The range of policies employed in NZ so far may have been adequate but possibly lacking in enough importance to enable sufficient success of the sector. However, employment of the range of policies suggested could enable NZ to reach its potential in its areas of specialised expertise and obtain further benefits from this high technology industry. The increased benefits may only be feasible if NZ concentrates on its areas of particular expertise and maintains its reputation for quality and innovation.

An OECD review (13) found that NZ investment strategies have tended towards funding projects rather than building long-term capabilities and enabling the transfer of research results to business. The participants in this research showed some agreement with this finding and requested management policies to ensure long-term and consistent government funding. These requests agree with the Australian Pharmaceuticals Industry Strategy Group, which stated in its Directions Paper that it may be more effective and produce higher economic gains to provide more support to selected projects over a longer period of time than to provide more limited funding to a larger number of organisations for shorter periods of time (178).

International research also found that public funding tends to be short-term, unpredictable and have insufficient flexibility for drug development projects (282). A study in the European Union showed that biotechnology development performance was linked to a co-ordination of funding and the use of a competitive peer-reviewed process (153). This information is encouraging for NZ because policy requests from the industry included one funding agency and a transparent review process.

Since the interviews with the research participants, some of the policies they requested have been implemented. Initiatives to increase the attraction of science as a career include prizes for NZ's most talented scientists and the appointment of a Prime Minister's Science Advisor (167). Knowledge management and collaborations have been assisted by the opening of the University of Auckland's Institute for Innovation in Biotechnology (IIB), a purpose-built incubator facility that also offers access to expertise within the University (270). Other initiatives aim to link science with business by providing government contributions of 20% of firms' R&D spend, technology transfer vouchers for firms to access university and CRI capabilities, and assistance to capture the commercial value of research conducted in public research organisations (167).

Researchers comparing R&D in Japan and South Korea have suggested that concentrating R&D focus allows a country that has more limited resources, such as South Korea, to have a chance of making progress in the selected areas. However, it is very difficult to predict which R&D areas will be successful and in global demand and therefore contribute to the country's future economy (283). Researchers of biotechnology regions in Australia and Sweden proposed that government should support a variety of knowledge-bases and encourage innovations through knowledge sharing, rather than attempting to try to forecast winners (115). Policies should be employed to enhance cluster development and to support the industry rather than a focus on individual firms (128). These findings are of value to a small country such as NZ, especially if it can focus its support on several niche areas and avoid choosing just one area in which to specialise.

Canada has enjoyed a rapid expansion of its biotechnology industry since the 1990s. It is in the same policy category as NZ with an industry based primarily on basic research and early product

development and therefore may be able to provide a model for the development of NZ's industry. The two factors that have encouraged the growth of the Canadian industry have been the attraction and retention of top scientists and continued R&D funding from both government and private sources (284). These two areas are the focus of several of the policies that the NZ industry requested to allow its growth.

In 2010, the NZ government instigated an inquiry into improving NZ's environment to support innovation through clinical trials, because it was concerned that NZ had lost its advantage as a preferred destination for clinical research. The key recommendations detailed in the 2011 Health Committee report (244) were to:

- Simplify and streamline the ethical review process
- Promote collaboration between government departments to co-ordinate and promote clinical trial activity in NZ
- Develop a national health research action plan to foster innovation and commercialisation
- Develop a framework for clinical research throughout the district health boards, and this to be facilitated by a hub

These recommendations either received government support or at least agreement to consider them further. Some of the Committee's recommendations were already being addressed by government agencies and progress should be observed in six to 12 months. Some recommendations that were not supported included bringing NZ's investment in R&D up to international benchmarks, a dedicated fee-charging ethics committee for sponsored clinical research and the establishment of an innovation fund to co-sponsor, with the pharmaceutical industry, clinical trials that addressed NZ-specific health issues. Current fiscal concerns were the primary reason for declining these requests. However, the Committee did support the recommendation that the recent assessment reports of the clinical trials industries of Australia and the UK should be urgently reviewed to ensure that NZ's systems are at least as efficient and effective. Finally, the recommendations by the Committee also included that PHARMAC develop pharmacoeconomic expertise in clinical trials but it was considered that the agency's small size and changes to its processes would not make this option viable (285). Some of the Committee's recommendations, especially those to decrease the time required to obtain ethics and institution approvals, were also suggested by the research participants as part of their overall theme of keeping NZ competitive for clinical trials.

5.3.4 Advice to Others in New Zealand's Industry

Participants' specific recommendations to others in the NZ industry concentrated on obtaining expert capabilities, funding advice and the need to have a clear strategic direction and business plan.

General advice on drug development was also offered. The 60 participants representing NZ's drug development organisations were willing to provide advice as shown by their 110 recommendations to their industry colleagues.

5.3.5 Comparison with Previous Research

The research participants suggested a range of policies and strategies that could further support and develop the NZ industry. These could be categorised as 'push' or 'pull' policies. Push mechanisms are those which directly encourage NZ's drug development industry, whereas pull mechanisms offer the prospect of financial reward once a product has been successfully developed (282). Most of the policies suggested by participants were in the push category, for example, government funding and management, support for science and clinical research. The pull policies include encouraging private investment, prizes for successful research and pharmaceutical price guarantees for medicines approaching product launch. The policies suggested have similarities with those recommended in NZBio's 2009 SIGHT report (63), such as consistent support for basic research, support for entrepreneurs and innovative businesses, linking industry experienced people with start-up companies, production of a skilled workforce and infrastructure, interaction between government and industry and access to funding for proof-of-concept research. However, policies including support of NZ's clinical research industry, creation of a more commercially aware environment and explicit government support of the industry were additional to the SIGHT report recommendations.

The research results have similarities with research into the biotechnology industries of developing countries. This is despite the NZ research concentrating on drug development rather than the broader biotechnology industry, and that NZ is considered a developed rather than a developing country. Comparisons between small molecule and biotechnology-based medicines development is appropriate because it has been shown that the average cost and time investments required for both are similar and that the expected savings developing a biotechnology product have not occurred (23).

A case study approach was used to assess the successful biotechnology sectors of seven developing countries—Brazil, China, Cuba, Egypt, India, South Africa and South Korea (217). A key factor for success was that the industry focussed on addressing local health needs. For example, Cuba developed the first meningitis B vaccine because of a local outbreak of the disease and Egypt has produced affordable recombinant insulin to meet its population's health needs. Long-term funding and coherent policies to support the industry were considered to be significant factors in all seven countries, as it has been for all countries with strengths in biotechnology. Other important features were the leadership of a few key industry individuals, defining the country's niche area to focus its biotechnology research on, close linkages between the universities and industry, promotion of collaborations and clusters, and the creation of private firms where there was sufficient venture

capital (217). These factors were also identified by the NZ research participants; however they also suggested that additional factors, such as robust regulatory and ethics processes, university commercialisation activities and the quality of research, had supported their industry development.

Further research using the same case study methodology was conducted on the barriers to the biotechnology industry in China, India and South Africa (277, 286, 287). Frew et al. (277) identified four barriers hindering the development of this sector in China: private investment to commercialise the novel products arising from government funded research; international credibility and relationships; timely regulations for intellectual property and research; and information and infrastructure to deliver any local innovation to the Chinese marketplace. Of these four barriers identified in China, only the lack of sufficient private investment was considered a hindrance to NZ's drug development industry. Along with most countries, China and NZ have the issue that the cost of developing an innovative medicine may be much higher than the price their domestic market can afford.

Research in India reported seven major barriers to further growth of its biotechnology industry (287). The barriers cited were: poor co-ordination of the multiple regulatory agencies involved; a shortage of highly trained personnel; public-private partnerships have not achieved the desired outcomes; few academics are interested in becoming entrepreneurs; foreign investment is required to supplement domestic funding; national prioritisation is needed to focus research on domestic medical needs; and the high cost of local distribution, especially to rural areas. As with China, the barriers in India are different from those in NZ, which is not surprising since the industries of the two countries have evolved differently. NZ's industry is based on scientific and medical research, whereas the industry in India originally started with the manufacture of medicines for local use and export. However, a common feature for all three countries is the need for private and foreign investment in their drug development industries.

The barriers to the biotechnology industry development in South Africa (286) similarly included a lack of private funding. Other barriers were the sustainability of the country's R&D companies, foreign exchange and intellectual property legislation, and a shortage of people with the appropriate industry skills. There are some similarities between NZ and South Africa—both countries have development companies funded by government and some private investment. However, due to a lack of a sustainable business model both may sell their IP overseas, therefore limiting economic returns and perhaps resulting in the loss of experienced people. Both countries have a limited presence of the multinational pharmaceutical companies and so have reduced spillover benefits that could be gained by closer interactions with these companies.

A study (271) has been conducted into the policies affecting the biotechnology industries of 18 European countries from 1994 until 2006. It found that the most common and long-standing policies were those supporting basic and applied research. For the 18 countries studied, the average annual government funding of biotechnology almost doubled between 1994–1998 and 2002–2005, with Spain and Italy having very large increases. The majority of this funding (averaging 58% in 1994–1998 and 56% in 2002–2005) was for health applications. Besides government investment policies, other recently implemented policies were to support expertise and knowledge management and to encourage non-government investment in the industry. Seven countries that lacked policies to encourage firm creation and business investment in biotechnology in 1998 had implemented them by 2005. By 2005, all countries had a strong emphasis on policies to support new start-ups and to improve technology transfer, including specific programmes to provide seed capital and facilities such as business incubators. It was suggested that these policies could address the issue of Europe being good in science but poor in commercialising its applications. New Zealand appears to be in a similar position, with its reputation for quality science but also its lack of the successful commercialisation of a locally discovered drug.

Further research (288) into the policies of the same 18 European countries linked success in the biotechnology industry with the high importance given to a broad set of supporting policies. A country's biotechnology performance was measured by a combination of science indicators (publication output and citations) and commercial indicators (patent applications, number of firms and amount of venture capital invested). Supporting policies were categorised into biotechnology specific policies (i.e., support of the knowledge base, commercialisation and activities such as public debates) and generic policies around the regulation of intellectual property, product quality and measures to enhance the availability of financial capital. Countries that gave comparable emphasis to specific and generic policies (e.g., Sweden and Denmark) out-performed those that focussed only on specific strategies (e.g., Portugal) or employed mainly generic instruments (e.g., France and Italy). A balance between the most employed policies of supporting basic science and applied research was also found to be important. New Zealand's policies have embraced both specific and generic support, however level of importance afforded them may have been lacking.

The same research (288) also found that a country's biotechnology performance was also influenced by its general economic features: R&D intensity as indicated by Gross Expenditures on Research and Development (GERD) as a percentage of Gross Domestic Product (GDP); ratio of business to government R&D expenditures and a percentage of GDP; and the number of researchers as a percentage of total employees. Countries of small economic size but with a high R&D intensity, knowledge intensive labour force and important local R&D companies can be major contributors to the biotechnology field (e.g., Finland and Sweden). This suggests that smaller countries may benefit

from improved co-ordination and strategies to focus on niche areas and NZ should also be able to benefit from its small size. A comparison of this research into 18 European countries with data from the USA (264) found a slightly stronger emphasis on biotechnology in the USA but that the best-performing European countries (Switzerland, Denmark, Sweden and Finland) were achieving better than the USA in biotechnology. The research also found a positive correlation between scientific performance (i.e., publications and their citation rates) and commercial performance (i.e., patent applications, biotechnology companies and venture capital invested).

Collaborations between developed and developing countries have also been studied (289). There are benefits to both countries from policies to support these partnerships, including improved access to each other's markets. Additionally, the developed countries obtain access to lower cost R&D while the developing countries benefit from exposure to new technology. The United States has the highest number of collaborations with India and China, which is likely to be due to its dominance in the biotechnology sector. Other countries collaborating with developing countries include Germany, the UK, France and Canada. Despite being a developed country, NZ's industry is probably too small for it to be of interest to a collaboration partner in a developing country however alliances between NZ and other developed countries could be of benefit to both parties.

5.4 Economic Benefits

5.4.1 Potential Revenue from Drug Discovery

The revenue from an out-licensed product depend primarily on the peak global sales and the timing of the out-license agreement. The estimate of potential returns to NZ from a theoretical drug discovery compound with peak global sales of USD350 million totalled USD48.273 million. The assumptions made for the calculations were based on the literature, and therefore the predictions may be limited by the data publicly available, however even the worst case scenario provides some revenue to re-invest into drug discovery research. The calculations assumed that the compound was still entirely locally owned when out-licensed and has shown that a compound achieving even modest peak global sales (USD350 million) has the potential to produce reasonable returns. The returns could continue for 20 years and provide a drug discovery organisation with stable returns to upscale its drug discovery capabilities, although the scale of revenue will depend on the success of the compounds.

The revenue returned to NZ is similar to the USD45.5 million typical value of a preclinical deal as suggested by Kessel and Frank's (235) research. However, the potential returns estimate to NZ included a probability of success weighting because there is only a 19% possibility that a preclinical compound will be registered for sale. The results and sensitivity analyses show that the revenue from an out-licensed product depend mainly on the peak global sales and the timing of the out-license agreement. This effect of the timing of the out-license agreement could be expected because it is a

consequence of the size of the upfront payments that increase dramatically with the clinical progress of the compound (235).

There is an emerging class of drug discovery organisations that are dependent on successful drug development outcomes and robust intellectual property to flourish (23). Even drug discovery organisations with successful projects may struggle to become sustainable, and profitable ones are usually acquired by a major company. Frequently, the contract-only drug discovery model is used as a temporary funding mechanism for the fledgling organisation before expanding into an integrated drug development company (23) with the hope of gaining superior financial returns (232). It is recognised that successful drug discovery organisations generally develop into an integrated drug development company or are acquired by a pharmaceutical company, however this research was to ascertain whether the initial returns would be sufficient to support the first stage of this process, that is, the growth of a drug discovery cluster.

Despite an increase in the number of NZ-discovered compounds in clinical development (refer to Table 2, pages 13-16) until 2007, this number appears to have been static over the last 4 years. In total, 22 new chemical entities, identified by NZ researchers, have entered clinical trials. One compound from the University of Auckland, amsacrine, was marketed by Parke-Davis as a second-line therapy for leukaemia but is now only available in a limited number of countries. The University of Auckland's ACSRC has been responsible for the identification of at least eight compounds that have reached clinical development for oncology indications, including compounds in the spin-out companies Proacta Inc and Pathway Therapeutics. A summary of the progress of the 22 compounds is provided in Table 65. The returns from NZ's drug discovery expertise to date has been limited, with the publicly disclosed returns consisting of approximately NZD10 million each to the University of Auckland and IRL from out-license deals (63).

Table 65 – Summary of New Zealand-discovered Compounds

Stage of development	Number of compounds still under development	Number of compounds that have stopped or stalled in development
Phase I	1 (PWT33597)	3 (XR-5000, XR-11576, XR-5944)
Phase II	6 (Nexagon, MIS416, BCX-4208[1], DiabeCell, NNZ2566, PR104)	8 (MitoQ, Chitin, AVAC, PVAC, PEHR0214, Fosodine, Laszarin, CI-1033)
Phase III	0	2 (Glypromate, DMXAA[2])
Unknown	1 (MGX-008)	0
Marketed	1 (Amsacrine)	0
Total	9	13

[1]BCX-4208 was previously found to have insufficient efficacy when used to treat psoriasis but is now being tested for efficacy in gout.
[2]DMXAA failed to show sufficient efficacy in a phase III study sponsored by Novartis but is now being investigated as part of combination therapy, sponsored by The Swiss Group for Clinical Cancer Research.

The majority of NZ's drug development companies have been only developing one compound at a time. It is relatively easy to set up a new company based on university-developed technology, the challenge is to ensure it has sufficient resources to translate the discovery into a drug candidate (128). The creation of multiple start-up companies with limited pipelines and funding may have strained NZ's pool of expertise for drug development, leading to people 'learning on the job'. This suggestion is supported by data from the expertise objective that show only 18.3% of participants intended a career in drug development when undertaking their academic qualifications and that they had obtained an average of nearly 80% of their drug development skills from experience rather than from their qualifications. This learning on the job factor may reflect the NZ attitude of enjoying problem-solving but may also have contributed to a lack of commercial success to date.

Even though only about 19% of preclinical compounds are successfully registered as medicines, with the number of NZ compounds that have been placed in clinical development, it could be expected that there would have been more commercial successes. With the exception of some University of Auckland compounds, most have had their clinical development undertaken by start-up NZ development companies. The high failure rate of NZ compounds, especially in phase II, may be a result of NZ companies using less stringent criteria used to progress compounds. It has been documented that start-up companies are more likely to move their products from phase I to phase II within 2 years than mature firms are and this may reflect a reluctance to discontinue projects where a large investment has already been made. Start-up companies are also more likely to have poor results from their phase II trials and so less likely to progress into phase III (33). However, small and medium-size firms with phase II and III projects, enjoy significantly higher success rates if they have an alliance with a larger company. This suggests that the experience of the larger partner enhances the success rates and therefore both parties benefit (33). These findings also demonstrate the importance of the more rigorous go/no-go criteria imposed on development projects by the larger pharmaceutical

companies (23). The NZ industry may benefit from early alliances with larger pharmaceutical firms and exposure to the rigour that they apply to progressing drug development candidates. This situation is not unique to NZ; it has been recognised by researchers into Finland's biotechnology (232) industry and the industry in general (128).

The data in Table 2 (pages 13-16) also suggest that, even at its peak, the number of drug discovery and development companies in NZ is low, with about one new company being created each year. This is lower than that of other countries with relatively small drug development industries. For example, Finland had a peak of 15 new firms in 2001 before this growth was reduced as a result of the global recession and investors became cautious about investing further in the industry (232). Australia's drug development pipeline contained 189 compounds in clinical development in 2008 (183) and while the number of companies involved is not known, this number of compounds is about 15 times higher than in NZ. Canada has approximately 175 companies specialising in human therapeutics (284) and Oxfordshire in the UK has 142 biotechnology and healthcare companies (126). While the figures from other regions and countries may all use slightly different criteria, it seems clear that NZ's industry is still very small and appears to be static. Policies to increase the success of university-based drug discovery include interdisciplinary institutes to improve collaborations and to connect scientists with clinicians (290).

The research methodology applied to NZ could be used by similar countries to estimate their potential revenues from drug discovery and clinical research. Countries that have limited resources cannot support a fully integrated pharmaceutical industry, which is an expensive and risky enterprise. Instead they should initially focus on their niche areas of expertise (232). The optimum time for an organisation to out-licence a product is with positive phase II results, because at this time, the maximum amount of data has been generated for the development expenditure. However, data on biotechnology license deals in 2008, suggest that approximately half involved preclinical projects and that approximately 20% were for compounds after phase II. Even though the value of license deals after phase III are much higher because the risk of failure is greatly reduced, many biotechnology companies cannot wait that long (284). Although these data are specific for the sub-group of biotechnology companies, the same situation is expected to exist for drug discovery and development organisations.

Venture capitalists prefer to invest in projects that produce a return within 3 years, therefore the 10 or 12 year investment needed to develop a new medicine makes it of lower interest (290). Licensing out a drug development candidate is a viable option for an academia-based discovery group that has limited access to funding (291). Another option to maximise academic expertise is through industry

partnerships to fund specific research projects. An example of this model is the collaborative research funding and alliance between GSK and Imperial College London Scientists (2).

There are several industry factors that should encourage drug discovery groups that are focussed predominantly on small molecule research: (1) the pharmaceutical industry has been downsizing its own drug discovery capability (292); (2) it needs to rapidly increase its discovery output to maintain its profitability (57); and (3) the majority of new medicines continue to be small molecules with macromolecular drugs (such as hormones and antibodies) representing only a small proportion (293). New Zealand's research has led to successes primarily with small molecules and many have potential indications in oncology (63). Oncology is an area of global industry focus indicated by having the highest number of clinical trials registered on the ClinicalTrials.gov database for a 24-month period from October, 2005 (294) and is now the therapeutic area with the highest industry investment (32, 134). Oncology is a challenging indication with long development times and high compound attrition rates. However, the industry's interest has been encouraged by the explosion of knowledge around cancer mechanisms and potential therapeutic targets as well as the relatively favourable reimbursement opportunities (295).

An analysis of whether new drugs have been first-in-class or follow-on products has found that it is not uncommon for many companies to have been researching in the same target area and to be developing similar drugs at the same time. The product that eventually reaches the market first may not be the one with the earliest patent filing or phase I trial (296). Drug discovery groups should not therefore be overly concerned that their compounds need to be the first of a new class, rather that they should have some advantage over competitor products and that the development pathway is undertaken as rapidly as possible. The similarities in research areas is due to some disease areas being increasingly targeted coupled with improved knowledge sharing in the scientific community (296).

Barden and Weaver (297) has described the emergence of 'micropharma' defined as "academia-originated, biotech start-up companies that are efficient, flexible, innovative, product-focussed and small" (p.85). They suggest that to be successful, micropharma organisations must achieve the following goals with their discovery compounds:

1. A product that has efficacy in a recognised animal model of human disease
2. At least partially understand its mechanism of action
3. Attractive preliminary pharmacokinetic data
4. Positive preliminary toxicology data
5. Robust intellectual property protection

Although NZ drug discovery groups are generally based in academia and therefore are not biotechnology companies, they should still attain the above information for their compounds to attract the best terms for an out-license deal.

Research has shown that in the last 40 years the FDA has approved 153 new drugs, vaccines and new indications for existing medicines that were discovered in public sector research institutions (298). This information should be encouraging for NZ's drug discovery scientists, and should influence government decisions on funding levels and other policies affecting its drug development industry. It should be noted that while the links between academia and industry are important for developing biomedical discoveries, the cultural differences between the two types of organisations can be challenging making these relationships difficult to manage (299).

A study in the USA has shown a positive relationship between the NIH's investment of academic basic biomedical research and pharmaceutical industry innovation (as measured by the number of new molecular entity applications). There is a substantial time delay of 17–24 years from the time of public investment, but the beneficial return on investment reflects a long history of public investment in academic biomedical research in the USA (300). New Zealand's level of public funding of research is much lower; however the sustained history of investment has contributed to the number of NZ drug discovery innovations.

5.4.2 Estimated Revenue from Clinical Research

New Zealand has been generating significant foreign earnings from its clinical trials industry. Our research calculated that the income accrued from industry sponsored clinical trials of USD100 million in 2010/2011 is similar to the upper estimate made of the industry in 2004 (244). This income generally increased over the period studied, contrary to the popular perception that the NZ industry was in decline. The value of clinical trials in Australia is estimated to be AUD450 million per year (USD482 million) (301), which is comparable on a per capita basis with NZ. Global outsourcing of clinical trials is expected to rise from both larger pharmaceutical companies seeking to lower fixed costs and from smaller specialty pharmaceutical companies that lack the infrastructure to conduct trials themselves (302). While NZ's size will limit the number of participants and sites it can provide for industry-sponsored clinical trials, it does facilitate rapid review of clinical trial applications through centralised processes. The steady increase in the number of industry-sponsored clinical trials indicates that NZ's capacity for clinical research is not yet saturated. The increase is predominantly due to the rise in the more challenging phase I studies (262), which is encouraging for a smaller country that is unable to enrol very large numbers of participants into research projects.

These are positive indications for NZ's clinical trials industry and an analysis of its environment to conduct clinical research has been undertaken. A Health Committee Report of the government inquiry (244) recommended simplifying and speeding up the ethical review process; promoting collaboration between government departments; the development of a national health research action plan; and a framework for clinical trial research activities. These recommendations are intended to encourage further growth of the NZ clinical research industry in an increasingly competitive environment. Our research results show some volatility in the revenue from the number of clinical trials placed in NZ and so the recommendations of the Health Committee Report should be carefully evaluated with a view to implementation.

Like NZ, Australia has been reviewing its competitiveness for clinical trials and assessing ways to improve its local research environment. Some of the recommendations of its Clinical Trials Actions Group (301) (e.g., rapid ethics review and less administration to allow more rapid start-up of clinical trials), match those suggested by the NZ industry. Similar initiatives have been undertaken in the UK (188). A National Institute for Health Research (NIHR) comprising of the National Health Service (NHS) Trusts and UK universities has been established to provide a UK-wide clinical research network to work with the pharmaceutical industry (187). The NIHR is dedicated to providing the environment to meet industry needs. This includes the rapid review of clinical trial applications, a single point of contact for evaluating the feasibility and patient recruitment for clinical studies, and access to the NHS which is the world's biggest health service (192).

Emerging clinical trial destinations such as Singapore, India, China and Eastern Europe are also implementing clinical trial policies and keenly promoting their expertise (1, 214, 242). An analysis of global trends (303) identified that there is an increasing industry focus on sites in North East Asia, Eastern Europe and Latin America, at the expense of the traditional clinical trial destinations of Western Europe and the USA. Another trend is that the smaller countries with established clinical research industries (e.g., Scandinavian countries, Singapore and Hong Kong) are also losing ground. This, in particular, should alert New Zealand to the increasing competition it will face as a destination to conduct clinical trials. Industry-sponsored clinical trials in Asia have increased from providing 5.9% of sites in 2005 to 9.7% in 2010. The sites are predominantly for large scale phase III trials, with the majority conducted at sites in India, China and Japan although the number of proof-of-concept phase II trials is increasing in South Korea and Taiwan (304).

India allows phase II and III trials to be conducted on a compound as long as the same study is being conducted in another part of the world. India has a pool of well-educated, English-speaking professionals to conduct the research and a vast heterogeneous population available to participate. To take advantage of the opportunity, many multinational pharmaceutical companies and CROs have

set up affiliates in India and formed collaborations with the most advanced Indian firms (55, 202). In 2006, it was estimated that the value of clinical trials conducted in India was about USD100 million and this was predicted to rise to USD1 billion by 2010, representing more than 20% of the world's investment (233). However, there are also some factors that may limit the amount of drug development research that is conducted in India, including the government's concerns about its poor people being enrolled in clinical trials, cultural issues about using animals for research, and the high turnover of skilled workers as they leave to work overseas (1).

The lure of the Chinese market has encouraged most global pharmaceutical companies to conduct R&D there as a mechanism for building connections with regulatory agencies (210). As a result, China is developing its capabilities to provide both clinical study sites and CRO services to be competitive particularly for phase III clinical trials (205, 242). China has well-equipped hospitals, highly educated staff (1) and the cost of clinical trials maybe only a half or less of conducting them in the USA (205, 210). China has a high prevalence of some types of cancers (e.g., lung and stomach) and large numbers of treatment-naïve patients, which adds to its attraction to the pharmaceutical industry (205). However, there may be metabolic differences between Asian and Caucasian patients, which must be considered as well as some concerns over the protection of patients' confidential information (1).

5.5 Linking Expertise, Enablers and Barriers, and Economic Benefits

The literature review, framework development, results and discussion illustrate that the three objectives of expertise, policy and economic benefits are inter-linked. New Zealand expertise in drug development has increased as a result of government policies and funding to support science and medical research as well as specific drug development projects. Clinical research expertise developed through legal policies that provided internationally accepted regulatory and ethics systems.

The development of expertise has lead to economic benefits for NZ, especially from provision of clinical research services to overseas pharmaceutical companies. However, participants representing NZ's drug development companies stated that an average of 35% of their funding was from overseas investors, therefore providing another revenue stream to NZ. This was used to either purchase expertise from other NZ entities or from overseas organisations, usually in circumstances where NZ expertise was not available. The interactions between the NZ organisations and their overseas investors have also provided expertise through knowledge sharing. This has led to an expansion of the limited pool of people experienced in drug development activities. These people can then use their expertise to assist other NZ drug development organisations, leading to further knowledge transfer.

The economic returns to NZ should encourage policies to support further expertise development and investment in the industry. The results of the expertise assessment indicate that a coherent and globally recognised country cluster could be created. However, policy initiatives such as promoting external knowledge sharing and collaborations, education and career development, encouraging R&D investment, as well as support from the industry organisations, will be needed for this to occur. Policies to encourage the pharmaceutical industry to form partnerships with NZ's academia and local firms could also be important to the country's industry development. These partnerships could enhance NZ expertise and increase industry investment in NZ science and drug discovery. Figure 16 illustrates this inter-linking of expertise, policy and economic benefits.

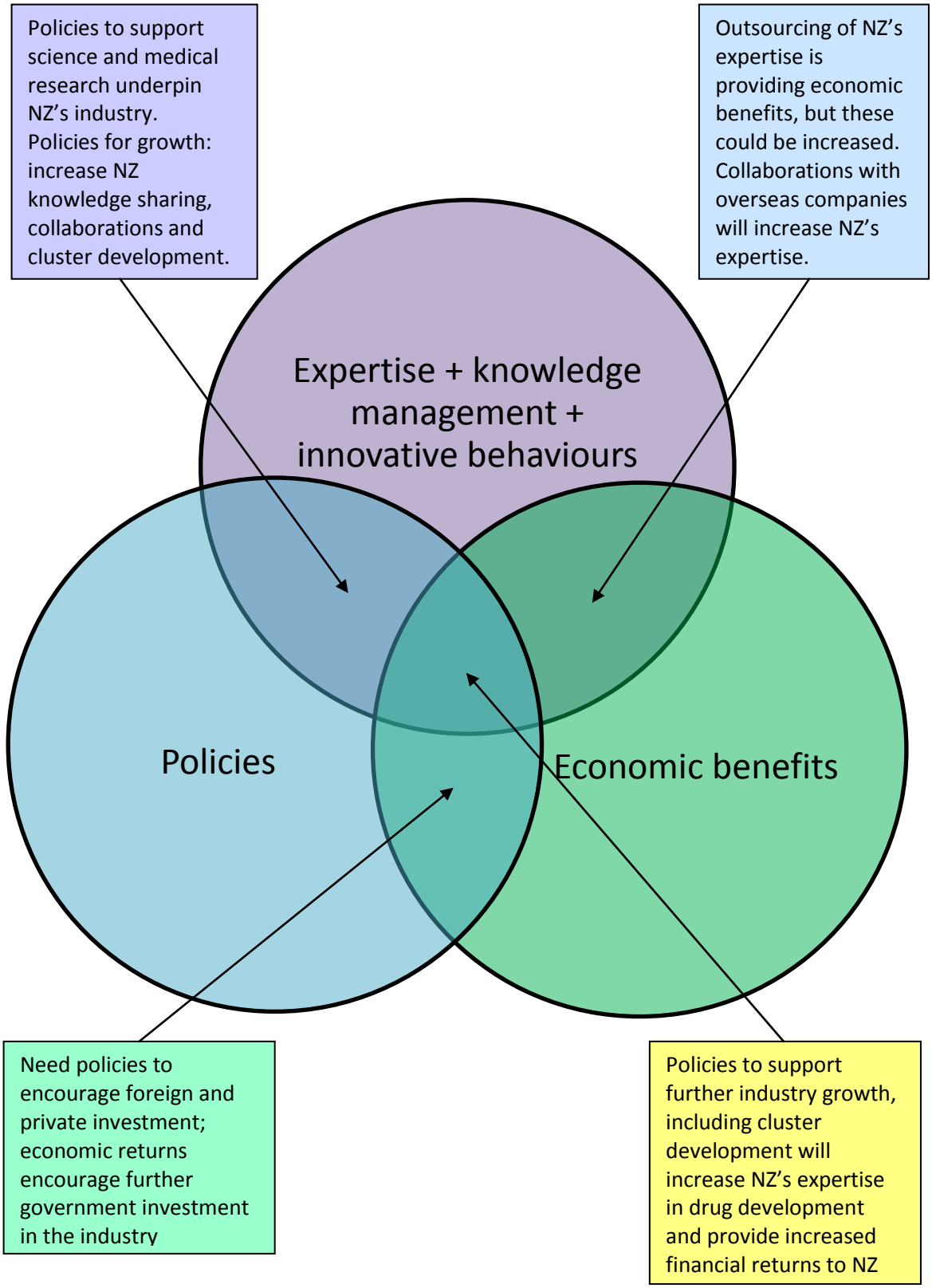

Figure 16 – The Inter-linking of Expertise, Policy and Economic Benefits

5.6 Limitations of the Research

The research has several limitations that should be taken into account when considering the results. The response rate was higher than expected, however the 10 people who declined were in the

support organisation or stakeholder categories and their responses may have affected the results. The participants representing the 'researcher' sub-category of support services organisations were selected due to their high profile for clinical research, which may have been a biased method of selection.

Another limitation is that the data is self-reported. This is an issue faced by most questionnaire-based research because respondents may accidentally or deliberately neglect to provide full information. Responses may also have been influenced by the participants wanting to provide what they thought the researcher wanted to hear, although the questions and information provided were worded to try and minimise this bias.

The third limitation is that the interviews were conducted over a period of 9 months. However, because the interviews were all to be conducted by one interviewer and the availability of some of the research participants was limited, it was not feasible to undertake them in a shorter timeframe.

Conclusions

6 Conclusions

This research has contributed to our understanding of three areas of the drug development literature: assessment of a country's expertise, enablers and barriers to industry development and an estimation of the economic returns. The contributions have been based on NZ's drug development industry but may be relevant to other countries, particularly those with smaller industries. The research has assessed NZ's entire drug development industry rather than a detailed case-study involving only a few organisations.

First, the research has identified the expertise of the senior representatives of NZ's drug development industry as indicated by their length of experience, number of outputs and awards received. There is specific expertise in drug discovery, as indicated by the number of novel compounds that NZ research has identified, and in clinical research, as shown by the increasing number of clinical trials involving unregistered medicines. The organisations display appropriate knowledge management and innovative behaviours, however increased external knowledge sharing, networking and collaborations would assist the development of NZ as an industry cluster. New Zealand's identified expertise could be used to specifically target pharmaceutical companies that require innovative drug discovery compounds and well-regarded destinations for clinical research, especially the more challenging phase I and II trials. There have been a number of innovative, locally discovered compounds entering clinical development in recent years, however only one compound has been marketed. Many NZ compounds have failed their phase II or III clinical trials, which is not unexpected given the high risks of drug development. However it may also indicate that the NZ drug development companies could benefit from the increased expertise that both a NZ industry cluster and alliances with larger pharmaceutical companies would provide.

Second, from the literature review of policies that countries have used to support their drug development industry, a framework of five different policy categories was developed. This framework was used to propose six policy models to categorise each country's strategy and to indicate which model NZ has adopted. Further, this provided insights that may assist NZ to learn from other countries that are successfully building a drug development industry. The framework was also used to categorise the policies and factors that NZ's drug development industry identified as enabling and hindering its development and the policies suggested to further support the industry's growth. Funding policies, both direct and indirect, have been the most important factors influencing NZ's industry development and were also the most commonly requested policies to further grow the industry. Specific government funding has supported the growth of expertise and therefore NZ's reputation for quality medical and clinical research. However, NZ's total R&D investment, both government and business, is low compared with OECD countries and this issue should be addressed,

especially as competitor countries continue to increase their investment. Policies to support the creation of a formal NZ-wide drug development cluster that could share specialised services such a regulatory and legal advice would obviate the need for each NZ drug development company to individually seek or replicate these services. New Zealand's limited pool of expertise could be augmented by policies to support careers in drug development, promote knowledge sharing and increased alliances with the pharmaceutical industry. The number of NZ-discovered compounds in clinical research has not changed appreciably in the last 8 years and government support is required to increase this number to create a larger portfolio of potential medicines.

Finally, the economic analyses have shown that clinical research provides substantial revenue to NZ and that drug discovery could also provide significant returns. The revenue from pharmaceutical industry-sponsored clinical trials has increased over the last 13 years as NZ expanded its expertise and reputation for high quality research. New Zealand's clinical trials industry needs to be supported to ensure it remains competitive, despite challenges from an increasing number of countries also offering to conduct industry-sponsored clinical trials. Policies requested by the research participants to improve NZ's clinical trials environment included more rapid ethical review of applications, streamline the administration required to start a clinical trial and ensure costs remain competitive with overseas. Support in the form of increased funding, career development and facilitation of collaborations, is also required to expand NZ's drug discovery expertise so that the potential returns can be realised. These returns are dependent primarily on the timing of the out-licence deal and product sales, therefore conducting early phase clinical research before out-licensing the product may increase the revenue to NZ. A proportion of the returns from out-license deals could be reinvested to increase the number of NZ-discovered compounds by employing more research medicinal chemists and biologists. Out-licensing of NZ-discovered compounds has the advantage of potentially providing ongoing revenue to NZ rather than the fee-for-service revenue generated by clinical research, however if provided with further support both sectors of NZ's industry could provide increased returns.

The research results are specific to NZ and cannot be transferred or applied directly to another country. However, the method of assessing the viability of a drug development industry from the three overlapping perspectives of expertise, enablers and barriers, and economic returns could be implemented by another country or region with a similar sized industry to NZ. In addition, the method could be adapted to evaluate the larger drug development industry of a more advanced country. Generally, individual companies in the industry are assessed by commercial organisations and compared with their peers; an assessment of an entire country's drug development industry has not previously been undertaken, although there has been research into biotechnology industries and clusters.

It is difficult for a country that does not have a strong tradition in pharmaceuticals to create a high technology drug development industry (232). Despite NZ's expertise it has been able to grow only a limited industry based on its own discovery compounds. However, it is clear that countries of small economic size but with a high R&D intensity, knowledge intensive labour force and successful local R&D companies can be major contributors to the biotechnology field (e.g., Finland and Sweden). This suggests that smaller countries may benefit from improved co-ordination, and strategies to focus on niche areas may allow more effective knowledge sharing as there are relatively few parties involved (288). A NZ drug development cluster should be able to benefit from the effective and close connections that are possible due its small size and build on its specific drug discovery and clinical research expertise. At least initially, NZ should concentrate on these niche areas of expertise and not attempt to compete in the areas of drug development where other countries hold an economic or technical advantage; as yet, NZ's industry is too small to attempt to build a fully integrated pharmaceutical industry.

There are several areas where future research could be conducted and build on the findings from this thesis and resulting publications. Further research may include conducting a similar analysis of NZ's drug development industry in 5 to 10 years' time to evaluate whether a viable country cluster has developed, document policy changes that have occurred and assess whether they have produced the desired effects. The number of NZ-discovered compounds could be tracked as a measure of NZ's expertise in drug discovery and the success of these compounds monitored by their progress through the drug development pathway. An increase in the number and success of these compounds may reflect the implementation of specific policies and strategies to support the industry. The number of SCOTT applications should be reviewed annually as an indication of NZ's competitiveness and capacity in clinical research. If the number of applications does not continue to increase, an assessment of whether NZ's capacity has been saturated or whether the pharmaceutical industry is choosing to place these studies in other countries is required. Complementary research could replicate the research methodology developed in this thesis on the industry of another small country or a region of a larger country and compare the results with those obtained in NZ.

In conclusion, the results of this research can be utilised in two ways: to increase the global pharmaceutical industry's awareness of NZ's expertise and to expand NZ's own drug development industry. The pharmaceutical industry is meeting the challenge of its declining profitability by changing its approach to drug development and increasingly outsourcing many aspects of the drug development process. The industry is actively seeking new sources of innovation as well as more effective and efficient methods of drug development. New Zealand's identified expertise, particularly in drug discovery and clinical research, should be co-ordinated by policies to support cluster development, which in turn may enhance local development of NZ-discovered compounds. Further

support could be provided by policy to promote the NZ cluster internationally and particularly to pharmaceutical companies seeking drug discovery innovations and high quality clinical research expertise. The potential value to NZ from two sectors of its drug development industry where it has expertise has been explored. NZ's drug development industry has contributed significant economic benefits and there is the opportunity to increase this further by providing sufficient support. New Zealand's clinical research industry has generated significant and increasing foreign revenue that is higher than the probability-based revenue from the out-licensing of a drug development candidate. Appropriate policy support could ensure that the clinical research revenue continues to grow. New Zealand's medicinal chemistry expertise and innovative culture could benefit from further financial and policy support to maximise its potential in drug discovery. New Zealand has the ongoing challenge of remaining competitive as it faces increasing competition from countries supporting their innovative drug development industries in an attempt to capitalise on the pharmaceutical industry transformation.

Appendix I – Participant Questionnaire

Participant Questionnaire

Section 1 – Personal and Career Information

Name		Position / Title	
Date questionnaire completed	Day	Month	Year
Organisation type	☐ Development Co ☐ Service org ☐ Discovery group		
Gender	☐ Male ☐ Female		
Age (years)	☐ <25 ☐ 25-34 ☐ 35-44 ☐ 45-54 ☐ 55-64 ☐ > 65		
Qualifications (NZ)			
Qualifications (Overseas)			
Country of birth	☐ NZ ☐ Overseas, please specify:		
Percent of time currently spent on drug development projects	%		
Source of skills for DD	% from qualifications	% from job experience	
Number of years experience in DD	years		
Career pathway into DD	☐ Intentional ☐ Accidental		
Specific DD qualifications			
Specific DD training/courses			
Professional organizations you belong to			
Any awards received in DD			

Section 2 - Which of the following have you produced or contributed to in the last 3 years?

	Drug Development Output	Tick if yes	If yes, the number for each
1.	Patents or Intellectual Property	☐	
2.	Peer-reviewed publications	☐	
3.	Conference presentations / posters	☐	
4.	Documents for internal use (e.g. manuals and guidelines)	☐	
5.	Other	☐	

Sections 3 – Personal Capabilities in Drug Development

	Drug Development Capabilities	Tick if yes	If yes, provide competency source	
			Qualification	Job experience
1.	Drug discovery	☐	☐	☐
2.	Chemistry / scale-up manufacturing	☐	☐	☐
3.	GMP manufacturing of API	☐	☐	☐
4.	Formulation	☐	☐	☐
5.	GMP manufacturing of drug product	☐	☐	☐
6.	Package / label drug product	☐	☐	☐
7.	Analytical/stability data	☐	☐	☐
8.	CRF / eCRF preparation	☐	☐	☐
9.	Database / data management	☐	☐	☐
10.	Pre-clinical testing	☐	☐	☐
11.	Safety data management	☐	☐	☐
12.	Statistics	☐	☐	☐
13.	Clinical Protocol development	☐	☐	☐
14.	Clinical trial monitoring / management	☐	☐	☐
15.	Clinical Study Site	☐	☐	☐
16.	Report preparation	☐	☐	☐
17.	Project management	☐	☐	☐
18.	Regulatory Affairs	☐	☐	☐
19.	Bioanalysis	☐	☐	☐
20.	IP management	☐	☐	☐
21.	Other:	☐	☐	☐

Section 4 – Career Satisfaction

	Very unsatisfied	Quite unsatisfied	Neither unsatisfied or satisfied	Quite satisfied	Very satisfied
How satisfied are you with your current role in drug development?	☐	☐	☐	☐	☐
	Very uninterested	Quite uninterested	Neither uninterested or interested	Quite interested	Very interested
How interested are you in continuing your career in drug development?	☐	☐	☐	☐	☐

Section 5 - Any other information about you: _____

_____

Appendix II – Drug Discovery Group Questionnaire

Questionnaire – New Zealand Drug Discovery Groups

Section 1 – Discovery Group Information:

Name of participant	Position in the organisation
	☐ University ☐ CRI ☐ Other:
Name of the group	Location
Areas of discovery research	
Date questionnaire completed	Day Month Year

Section 2 – Information on Compound(s) in Discovery Phase:

If more than two compound(s) expected to enter phase 1 within the next 5 years, use additional pages as appropriate to collect information

Name / identification	☐ Own research ☐ Other source Source of Compound
Stage of discovery	☐ Lead compound ☐ Investigating ☐ Other:
Year expected to enter Phase 1	
Potential indication(s)	

Name / identification	☐ Own research ☐ Other source Source of Compound
Stage of discovery	☐ Lead compound ☐ Investigating ☐ Other:
Year expected to enter Phase 1	
Potential indication(s)	

Section 3 – Funding of the Discovery Project(s):

Tick boxes as appropriate		Please provide details (% of each type; % NZ owned etc)
1. Personal	☐	
2. Private funding within NZ	☐	
3. NZ government grants	☐	
4. Overseas funding	☐	
5. Publicly listed company	☐	
6. Other	☐	

Section 4 – Capabilities for Drug Development:

Please indicate which capabilities you have within your group and collaborators for drug development:

#	Drug Development Activity	Within group	Within network	Comments
1.	Drug discovery / lead compound	☐	☐	
2.	Chemistry / scale-up manufacturing	☐	☐	
3.	GMP manufacturing of API	☐	☐	
4.	Formulation	☐	☐	
5.	GMP manufacturing of drug product	☐	☐	
6.	Package / label drug product	☐	☐	
7.	Analytical/stability data	☐	☐	
8.	CRF / eCRF preparation	☐	☐	
9.	Database / data management	☐	☐	
10.	Preclinical testing	☐	☐	
11.	Safety data management	☐	☐	
12.	Statistics	☐	☐	
13.	Clinical Protocol development	☐	☐	
14.	Clinical trial monitoring and mmgt	☐	☐	
15.	Clinical Study Site	☐	☐	
16.	Report preparation	☐	☐	
17.	Project management	☐	☐	
18.	Regulatory Affairs	☐	☐	
19.	Bioanalysis	☐	☐	
20.	IP management	☐	☐	
21.	Other:	☐	☐	

Section 5 – Qualifications and Experience

Please provide this information to summarise the qualifications in your drug discovery group

Number of full-time equivalent staff			
Indicate the number of people in each of the roles or its equivalent		Highest qualification/s (range)	Number of years discovery research experience (range)
Research Leader			
Group Leader			
Scientist			
Assistant			
Other:			
Other:			

Section 6 – Organisation Knowledge Sharing and Innovative Behaviours:

Knowledge Sharing: Rate your group's performance on sharing of organisational drug discovery & development knowledge:

	Very poor	Poor	Average	Good	Very good
Within the group	☐	☐	☐	☐	☐
With other NZ drug discovery groups	☐	☐	☐	☐	☐
With NZ drug development companies	☐	☐	☐	☐	☐

Knowledge Management: Rate the importance of the following sources to obtain knowledge:

	Not at all important	Not important	Average	Important	Very important
Internal formal training	☐	☐	☐	☐	☐
Internal meeting	☐	☐	☐	☐	☐
Ask work colleagues	☐	☐	☐	☐	☐
External networks	☐	☐	☐	☐	☐
Professional publications	☐	☐	☐	☐	☐
Internet	☐	☐	☐	☐	☐

Innovative Performance: Rate your group's performance compared with the industry on:

	Very poor	Poor	Average	Good	Very good
Having new ideas	☐	☐	☐	☐	☐
Developing contacts with external experts	☐	☐	☐	☐	☐
Making time to work on ideas and projects	☐	☐	☐	☐	☐
Solving problems that caused others difficulty	☐	☐	☐	☐	☐
Project planning	☐	☐	☐	☐	☐
Innovative output	☐	☐	☐	☐	☐
Teamwork	☐	☐	☐	☐	☐
Communication	☐	☐	☐	☐	☐

Section 7 – New Zealand's Drug Discovery and Development Industry

7.1 In your opinion are there any factors that have encouraged the drug discovery and development industry in NZ? ☐ Yes ☐ No. If yes, what are these factors?

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7.2 What factors enabled your organisation to undertake its drug discovery and/or development projects in NZ?

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7.3 In your opinion are there any threats to NZ's drug discovery / development industry?

☐ Yes ☐ No. If yes, what are these threats?

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7.4 What are the main threats affecting your organisation in the next 3-5 years?

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7.5 Are there any other issues specific to your organisation?

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7.6 What advice would you give to other NZ drug discovery and development organisations?

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7.7 What new government policies do you think would further support our drug discovery and development industry?

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7.8 On average, how much is your group spending on drug discovery / development R&D each year?_____

Section 8 – Ranking Questions on New Zealand's Drug Development Industry

Please consider the following 8 possible barriers to the drug development industry in NZ; you may identify a 9th barrier. Then rank the barriers in order of importance for your organisation (i.e. 1 = most important obstacle; 9 = least important obstacle).
☐ Limited funding
☐ Limited local expertise and capabilities / experienced people have moved overseas
☐ Insufficient government policy to support the industry / lack of strategic direction
☐ Difficulty in determining a lead compound
☐ Lack of overall co-ordination between NZ's drug development organisations
☐ Insufficient understanding of the drug development and regulatory processes
☐ Overseas investors want to move the project away from New Zealand
☐ Issues with manufacturing or formulation
☐ Other, please specify:_____

Section 9 – Any Other Comments?

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Appendix III – Drug Development Company Questionnaire

Questionnaire – New Zealand Drug Development Company

Section 1 – Participant and Company Information:

Name of participant	Position in the company
Date questionnaire completed	Day / Month / Year
Name of the company	
Date company formed (or just year)	Day / Month / Year

Section 2 – Information on Compound/s in Clinical Development:

[If more than one compound in clinical development, use additional copies of this page as appropriate to collect information]

Name / identification	Any other names / identifications

Source of the compound in development

Tick 'yes' as appropriate and provide details		Details (e.g. which institution/s or company/s involved)
1. Academic research	☐ Yes	
2. Private research	☐ Yes	
3. Other	☐ Yes	

Potential of the compound in development

Potential indication/s for this compound	
Estimated year of launch in USA	Estimate of potential peak sales for this compound
Other information:	

Section 3 – Clinical Development Information:

Current stage of development of the compound and clinical trial/s completed or underway

Tick 'yes' as appropriate	Provide title of trials conducted in NZ or using NZ-based vendors (for trials initiated after 1st January 2005)
Phase 1 ☐ Yes	
Phase 2 ☐ Yes	
Phase 3 ☐ Yes	

Section 4 – Location of Capabilities Used to for Clinical Drug Development Activities:

Please indicate the location of the following capabilities used for your clinical trials in the last 5 yrs

#	Drug Development Activity	In-house?	NZ Vendor?	Over-seas Vendor?	N/A	Name any external (NZ or overseas) vendor/s used
1.	Drug discovery	☐	☐	☐	☐	
2.	Chemistry / scale-up manufacturing	☐	☐	☐	☐	
3.	GMP manufacturing of API	☐	☐	☐	☐	
4.	Formulation	☐	☐	☐	☐	
5.	GMP manufacturing of drug product	☐	☐	☐	☐	
6.	Package / label drug product	☐	☐	☐	☐	
7.	Analytical/stability data	☐	☐	☐	☐	
8.	CRF / eCRF preparation	☐	☐	☐	☐	
9.	Database / data management	☐	☐	☐	☐	
10.	Pre-clinical testing	☐	☐	☐	☐	
11.	Safety data management	☐	☐	☐	☐	
12.	Statistics	☐	☐	☐	☐	
13.	Clinical Protocol development	☐	☐	☐	☐	
14.	Clinical trial monitoring / mmgt	☐	☐	☐	☐	
15.	Clinical Study Site	☐	☐	☐	☐	
16.	Report preparation	☐	☐	☐	☐	
17.	Project management	☐	☐	☐	☐	
18.	Regulatory Affairs	☐	☐	☐	☐	
19.	Bioanalysis	☐	☐	☐	☐	
20.	IP management	☐	☐	☐	☐	
21.	Other:	☐	☐	☐	☐	

Section 5 – Level of Satisfaction with Vendors:

Please consider all the <u>New Zealand</u> vendors that you used when completing this section:
Please place a '1' in the appropriate box to indicate the primary reason why the NZ vendors were chosen and a '2' in the box corresponding to the secondary reason:

☐ Based in NZ

☐ Cost versus alternatives

☐ Expertise versus alternatives

☐ Recommended by third party / well-recognised in the industry

☐ Other reason, please specify:_____

<u>Satisfaction</u>: How satisfied were you with the performance of this vendor for the following:

	Very unsatisfied	Quite unsatisfied	Neither unsatisfied or satisfied	Quite satisfied	Very satisfied
Level of expertise	☐	☐	☐	☐	☐
Timeliness of completion	☐	☐	☐	☐	☐
Cost	☐	☐	☐	☐	☐
Quality of service provided	☐	☐	☐	☐	☐

Please consider all the <u>overseas</u> vendors that you used when completing this section:
Please place a '1' in the appropriate box to indicate the primary reason why the overseas vendors were chosen and a '2' in the box corresponding to the secondary reason:

☐ Provided expertise not available in NZ

☐ Cost versus alternatives

☐ Expertise versus alternatives

☐ Recommended by third party / well-recognised in the industry

☐ Other reason, please specify:_____

<u>Satisfaction</u>: How satisfied were you with the performance of this vendor for the following:

	Very unsatisfied	Quite unsatisfied	Neither unsatisfied or satisfied	Quite satisfied	Very satisfied
Level of expertise	☐	☐	☐	☐	☐
Timeliness of completion	☐	☐	☐	☐	☐
Cost	☐	☐	☐	☐	☐
Quality of service provided	☐	☐	☐	☐	☐

Section 6 – Drug Development Company Expertise in New Zealand

Please provide this information to cover all company staff (not external consultants)

Number of full-time equivalents					
Indicate which roles they provide		Highest qualification	# years DD experience	% of fulltime	Total time
CEO/GM					
Finance / accountancy					
Project manager					
Study manager					
Clinical research associate					
Clinical research assistant					
Regulatory affairs					
Medical / safety officer					
Other:					
Other:					

Section 7 – Funding of the Clinical Development

Tick boxes as appropriate	Percent funded by
1. Personal	☐☐☐
2. Private funding within NZ	☐☐☐
3. NZ government grants	☐☐☐
4. Overseas funding	☐☐☐
5. Publicly listed company	☐☐☐
6. Other	☐☐☐

Section 8 – Company Knowledge Sharing and Innovative Behaviours:

Knowledge Sharing: Please rate your company's performance on sharing of organisational drug discovery and development knowledge:

	Very poor	Poor	Average	Good	Very good
Within the company	☐	☐	☐	☐	☐
With vendors	☐	☐	☐	☐	☐
With other NZ drug development companies	☐	☐	☐	☐	☐

Knowledge Management: Rate the importance of the following sources for you to obtain knowledge:

	Not at all important	Not important	Average	Important	Very important
Internal formal training	☐	☐	☐	☐	☐
Internal meeting	☐	☐	☐	☐	☐
Ask work colleagues	☐	☐	☐	☐	☐
External networks	☐	☐	☐	☐	☐
Professional publications	☐	☐	☐	☐	☐
Internet	☐	☐	☐	☐	☐

Innovative Performance: Rate your company's performance compared with the industry on:

	Very poor	Poor	Average	Good	Very good
Having new ideas	☐	☐	☐	☐	☐
Developing contacts with external experts	☐	☐	☐	☐	☐
Making time to work on ideas and projects	☐	☐	☐	☐	☐
Solving problems that caused others difficulty	☐	☐	☐	☐	☐
Project planning	☐	☐	☐	☐	☐
Innovative output	☐	☐	☐	☐	☐
Teamwork	☐	☐	☐	☐	☐
Communication	☐	☐	☐	☐	☐

Section 9 – New Zealand's Drug Development Industry

9.1 In your opinion are there any factors that have encouraged the drug discovery and development industry in NZ? ☐ Yes ☐ No. If yes, what are these factors?

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9.2 What factors enabled your company to undertake its drug discovery and/or development projects in NZ?

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9.3 In your opinion are there any threats to NZ's drug discovery / development industry? ☐ Yes ☐ No. If yes, what are these threats?

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9.4 What are the main threats affecting your company in the next 3-5 years?

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9.5 Are there any other issues specific to your organisation?

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9.6 What advice would you give to other NZ drug discovery and development organisations?

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9.7 What new government policies do you think would further support our drug discovery and development industry?

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9.8 On average, how much is your company spending on drug discovery / development R&D each year?

Amount:_____ As a percent of company turnover:_____

Section 10 – Ranking Questions on New Zealand's Drug Development Industry

Please consider the following 8 possible barriers to the drug development industry in NZ; you may identify a 9th barrier. Then rank the barriers in order of importance for your organisation (i.e. 1 = most important obstacle; 9 = least important obstacle).
☐ Limited funding
☐ Limited local expertise and capabilities / experienced people have moved overseas
☐ Insufficient government policy to support the industry / lack of strategic direction
☐ Difficulty in determining a lead compound
☐ Lack of overall co-ordination between NZ's drug development organisations
☐ Insufficient understanding of the drug development and regulatory processes
☐ Overseas investors want to move the project away from New Zealand
☐ Issues with manufacturing or formulation
☐ Other, please specify:_____

Section 11 – Anyone else I should talk with and any other comments?

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Appendix IV – Support Services Organisations Questionnaire

Questionnaire – Support Services Organisation

Section 1 – Organisation Information:

Name of participant	Position in the organisation
Date questionnaire completed	Day ☐☐ Month ☐☐ Year ☐☐☐☐
Name of the organisation	
Date company formed (if applicable)	Day ☐☐ Month ☐☐ Year ☐☐☐☐

Section 2 – Type of Organisation

Tick one box		Please provide details if appropriate
1. Private consultant	☐	
2. University department	☐	
3. Public company	☐	
4. Private company	☐	
5. Hospital (DHB) department	☐	
6. Other	☐	

Section 3 – Funding of the Organisation

Tick boxes as appropriate	Please provide percent of each type
1. Private business	☐☐☐
2. NZ government grants	☐☐☐
3. Overseas funding /grants	☐☐☐
4. Other:	☐☐☐

Section 4 – Services Provided for Drug Development:

Please indicate which of the following services you provide and whether to NZ and/or overseas drug development companies:

#	Drug Development Activity	Tick if yes	To NZ Company/s	To Overseas Company/s	Which companies have you provided this service to?
1.	Drug discovery	☐	☐	☐	
22.	Chemistry / scale-up manufacturing	☐	☐	☐	
23.	GMP manufacturing of API	☐	☐	☐	
24.	Formulation	☐	☐	☐	
25.	GMP manufacturing of drug product	☐	☐	☐	
26.	Package / label drug product	☐	☐	☐	
27.	Analytical/stability data	☐	☐	☐	
28.	CRF / eCRF preparation	☐	☐	☐	
29.	Database / data management	☐	☐	☐	
30.	Pre-clinical testing	☐	☐	☐	
31.	Safety data management	☐	☐	☐	
32.	Statistics	☐	☐	☐	
33.	Clinical Protocol development	☐	☐	☐	
34.	Clinical trial monitoring / management	☐	☐	☐	
35.	Clinical Study Site	☐	☐	☐	
16.	Report preparation	☐	☐	☐	
17.	Project management	☐	☐	☐	
18.	Regulatory Affairs	☐	☐	☐	
19.	Bioanalysis	☐	☐	☐	
20.	IP management	☐	☐	☐	
21.	Other:	☐	☐	☐	

Section 5 - Provision of services to companies overseas:

What percent of your revenue is from companies outside NZ?	%
Where are these companies located (can tick multiple)?	☐ Australia ☐ USA ☐ UK ☐ Other, specify:
Over the next 3 years do you expect this business to:	☐ Decrease ☐ Remain about the same ☐ Increase

Any comments:_____

_____

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Section 6 – Level of Satisfaction with Drug Development Companies:

For the following questions please consider the <u>New Zealand</u> drug development companies that you have provided services to in the last 5 years.

Number of NZ drug development companies you have provided services to: ☐☐☐

Please place a '1' in the appropriate box to indicate the primary reason why you think your organisation was chosen to provide the services and a '2' in the box corresponding to the secondary reason:

☐ Based in NZ

☐ Cost versus alternatives

☐ Expertise versus alternatives

☐ Recommended by third party / well-recognised in the industry

☐ Other reason, please specify:_____

<u>Satisfaction</u>: Please rate your experience of working with the NZ drug development companies on:

	Very unsatisfied	Quite unsatisfied	Neither unsatisfied or satisfied	Quite satisfied	Very satisfied
Level of expertise	☐	☐	☐	☐	☐
Timeframe expectations	☐	☐	☐	☐	☐
Reimbursement provided	☐	☐	☐	☐	☐
Quality of brief for service required	☐	☐	☐	☐	☐

For the following questions please consider the <u>overseas</u> drug development companies that you have provided services to in the last 5 years.

Number of overseas drug development companies you have provided services to: ☐☐☐

Please place a '1' in the appropriate box to indicate the primary reason why you think your organisation was chosen to provide the services and a '2' in the box corresponding to the secondary reason:

☐ Based in NZ

☐ Cost versus alternatives

☐ Expertise versus alternatives

☐ Recommended by third party / well-recognised in the industry

☐ Services provided overseas because expertise was not available locally for that company

☐ Other reason, please specify:_____

Satisfaction: Please rate your experience of working with overseas drug development companies on:

	Very unsatisfied	Quite unsatisfied	Neither unsatisfied or satisfied	Quite satisfied	Very satisfied
Level of expertise	☐	☐	☐	☐	☐
Timeframe expectations	☐	☐	☐	☐	☐
Reimbursement provided	☐	☐	☐	☐	☐
Quality of brief for service required	☐	☐	☐	☐	☐

Section 7 – Drug Development Support Organisation Capabilities in New Zealand

Please provide this information to cover all staff in your organisation who are based in NZ

Number of full-time equivalent staff					
Number of people in the following roles		Highest qualification	# years DD experience	% of fulltime	Total time
CEO/GM					
Finance / accountancy					
Project management					
Study management					
Clinical research associate					
Clinical research assistant					
Regulatory affairs					
Medical / safety officer					
Other:					
Other:					

Section 8 – Organisation knowledge sharing and innovative behaviours:

<u>Knowledge sharing</u>: Please rate your organisation's performance on sharing of drug discovery and development knowledge:

	Very poor	Poor	Average	Good	Very good
Within the organisation	☐	☐	☐	☐	☐
With NZ drug development companies	☐	☐	☐	☐	☐

<u>Knowledge management</u>: Rate the importance of the following sources for you to obtain knowledge:

	Not at all important	Not important	Average	Important	Very important
Internal formal training	☐	☐	☐	☐	☐
Internal meeting	☐	☐	☐	☐	☐
Ask work colleagues	☐	☐	☐	☐	☐
External networks	☐	☐	☐	☐	☐
Professional publications	☐	☐	☐	☐	☐
Internet	☐	☐	☐	☐	☐

<u>Innovative performance</u>: Rate your organisation's performance compared with its peers on:

	Very poor	Poor	Average	Good	Very good
Having new ideas	☐	☐	☐	☐	☐
Developing contacts with external experts	☐	☐	☐	☐	☐
Making time to work on ideas and projects	☐	☐	☐	☐	☐
Solving problems that caused others difficulty	☐	☐	☐	☐	☐
Project planning	☐	☐	☐	☐	☐
Innovative output	☐	☐	☐	☐	☐
Teamwork	☐	☐	☐	☐	☐
Communication	☐	☐	☐	☐	☐

Section 9 – New Zealand's Drug Discovery and Development Industry

9.1 In your opinion are there any factors that have encouraged the drug discovery and development industry in NZ? ☐ Yes ☐ No. If yes, what are these factors?

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9.2 What factors enabled your company to undertake its drug discovery and/or development projects in NZ?

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9.3 In your opinion are there any threats to NZ's drug discovery / development industry? ☐ Yes ☐ No. If yes, what are these threats?

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9.4 What are the main threats affecting your company in the next 3-5 years?

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9.5 Are there any other issues specific to your organisation?

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9.6 What advice would you give to other NZ drug discovery and development organisations?

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9.7 What new government policies do you think would further support our drug discovery and development industry?

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Section 10 – Ranking Questions on New Zealand's Drug Development Industry

Please consider the following 8 possible barriers to the drug development industry in NZ; you may identify a 9th barrier. Then rank the barriers in order of importance for your organisation (i.e. 1 = most important obstacle; 9 = least important obstacle).

- ☐ Limited funding
- ☐ Limited local expertise and capabilities / experienced people have moved overseas
- ☐ Insufficient government policy to support the industry / lack of strategic direction
- ☐ Difficulty in determining a lead compound
- ☐ Lack of overall co-ordination between NZ's drug development organisations
- ☐ Insufficient understanding of the drug development and regulatory processes
- ☐ Overseas investors want to move the project away from New Zealand
- ☐ Issues with manufacturing or formulation
- ☐ Other, please specify:_____

Section 11 – Any Other Comments (and anyone else I should talk with)?

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Appendix V – Stakeholders Questionnaire

Questionnaires – NZ Drug Development Industry Stakeholders

Section 1 – Participant and Organisation Information:

Name of participant	Position in the organisation
Name of the organisation	
Type of organization: ☐ Government agency ☐ Pharmaceutical industry body ☐ Academia representative ☐ Other: _____	
Date questionnaire completed	Day / Month / Year

Section 2 – New Zealand's Drug Discovery and Development Industry

2.1 Has your agency or organisation evaluated NZ's drug discovery and development industry? ☐ Yes ☐ No.

If yes, please summarise what you found, and advise whether a report or reference is available:

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2.2 In your opinion are there any factors that have encouraged the drug discovery and development industry in NZ? ☐ Yes ☐ No. If yes, what are these factors?

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2.3 In your opinion are there any threats to NZ's drug discovery / development industry? ☐ Yes ☐ No. If yes, what are these threats?

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2.4 Do you think that NZ should support its drug discovery and development industry?

☐ Yes ☐ No. If yes, what are new government policies do you think would further support the industry?_____

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Section 3 – Ranking Questions on New Zealand's Drug Development Industry

Please consider the following 8 possible barriers to the drug development industry in NZ; you may identify a 9th barrier. Then rank the barriers in order of importance for your organisation (i.e. 1 = most important obstacle; 9 = least important obstacle).

- ☐ Limited funding
- ☐ Limited local expertise and capabilities / experienced people have moved overseas
- ☐ Insufficient government policy to support the industry / lack of strategic direction
- ☐ Difficulty in determining a lead compound
- ☐ Lack of overall co-ordination between NZ's drug development organisations
- ☐ Insufficient understanding of the drug development and regulatory processes
- ☐ Overseas investors want to move the project away from New Zealand
- ☐ Issues with manufacturing or formulation
- ☐ Other, please specify:_____

Section 4 – Any Other Comments (and anyone else I should talk with)?

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Appendix VI – Publication #1

Lockhart M, Babar Z-U-B, Garg S. 2010. Policy options to support drug development in New Zealand. Health Policy 96:108-117

Health Policy 96 (2010) 108–117

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

Review

Evaluation of policies to support drug development in New Zealand

Michelle Lockhart, Zaheer Ud-Din Babar*, Sanjay Garg

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ARTICLE INFO

Keywords:
Health policy
Drug development
Pharmaceutical industry

ABSTRACT

Objectives: Changes in the traditional model of drug development are creating a potential opportunity for New Zealand's drug development industry. This research evaluates whether New Zealand could utilise some of the policies employed by countries with successful drug development industries.

Methods: A framework to support a drug development industry was developed by taking into account policies that affect the industry. The framework was then used to analyse the types of policies provided by different countries and to postulate six different models that support a pharmaceutical industry.

Results: Countries with a successful drug development industry have identified their strengths, analysed the opportunities in the industry, and have employed consistent and specific policies in support of their industry. New Zealand's policy in support of its drug development industry is most similar to that of the medical research-based model of the UK, Australia and Canada.

Conclusions: New Zealand needs to develop a consistent policy for support of its drug development industry based on identifying and focussing on the competencies where it is internationally competitive. A strong partnership with Australia could capitalise on the strengths of both countries and linkages with other Asia-Pacific countries could further promote the region's capabilities in drug development research.

Contents

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1. Introduction

1.1. Opportunities in the drug development industry

There is a global demand for new medicines, both to treat conditions for which there are currently no effective drug therapies, and to improve the management of diseases for which medicines are available but have limited efficacy and/or cause unwanted side effects. The global pharmaceutical market was estimated to be in excess of US$ 700 billion in 2007, with most of the research and development (R&D) and pharmaceutical innovation occurring in the US, Europe and Japan [1,2]. Pharmaceutical R&D is a lengthy, expensive and risky process that is based on the expectations that the successful drug innovation will provide premium returns once it receives market approvals [3].

Traditionally the majority of new medicines were discovered and developed by pharmaceutical companies based in the US and Western Europe which had the expertise and financial resources from their products already on the market [4,5]. The pharmaceutical industry is unique with R&D expenditure being substantially higher than for other industry sectors [6]. Only about one-third of new drugs are profitable and very few become the 'blockbuster' products (i.e. sales over US$ 1 billion per year) [7] that the industry has sought and in the past, pharmaceutical companies have used mergers and acquisitions in attempts to diversify and enhance their product portfolios [8]. The pharmaceutical industry's profitability may decline due to high-selling medicines coming off-patent, increasing generic competition from Asia [9] and therapeutic areas crowded with competing products [10]. This revenue erosion, leading to lower R&D investment, generates a challenge for the industry to change its traditional approach to drug development. Firstly it is forming alliances and partnerships with the smaller specialist firms and university-based groups with drug discovery innovations as a source for innovations [4,5,10,11]. Secondly there is a focus on reducing the extraordinary costs associated with drug development, by means such as conducting clinical trials in different locations and outsourcing specialised components of R&D projects. Finally the geographic base of the industry is broadening with an emerging Asia-Pacific industry which includes generic manufacture and drug innovation [12].

These factors create a potential opportunity for New Zealand (NZ) to exploit and thereby play a larger role in the global drug development industry, with resulting economic benefits. NZ has the advantages of a strong biomedical research capacity for drug discovery innovations, a resourceful and entrepreneurial society that encourages innovation [13], and a western culture which is conveniently located in the Asia-Pacific region.

1.2. Government policies in support of a drug development industry

Government–pharmaceutical industry relationships are complex and span three major policy sectors: regulatory and health activities controlling safety and efficacy; social policy activities including pricing and reimbursement; and economic development policy influencing R&D activities [14]. Most countries struggle to balance health policies supporting pharmaceutical R&D while meeting the healthcare demands of its citizens within the budgetary constraints imposed. This dichotomy of health policy and industrial policy objectives has not been resolved and it seems that each country attempts to reconcile its cost containment, efficiency, quality and equity objectives in a unique manner [15]. The health policies of some countries (e.g. Australia) try and achieve a partnership between health and industrial policies by having a pharmaceutical policy to support the R&D of medicines while meeting the economic objective of providing medicines at an acceptable cost to the community [14]. In New Zealand, policies to support pharmaceutical R&D are developed and administered by multiple government departments which have resulted in a fragmented policy.

Policies to support a drug development industry are attractive to governments because of the potential benefits they can provide such as wealth creation, employment, international trade and the development of high-technology industries [16]. However the barriers which include the high R&D investment, the knowledge capital required, wage-competition from less well-developed countries and the unpredictable profitability make this investment a high risk proposition [17,18].

As a consequence of this and with the increasing tendency of large multinational pharmaceutical companies to outsource R&D projects including clinical trials, some countries (e.g. India, China) have focused their policies on these lower risk service segments of the industry [18].

Some of the opportunities in the drug development value chain where countries can implement specific policies to develop and promote their capabilities include [19,20]:

- Discovery and development of innovative compounds.
- Production of generic medicines, often using innovative and less expensive methods than the original patented product.
- Applying new drug delivery systems (e.g. once-a-day or controlled release formulations) to existing products to extend their product lifespan.
- Provision of drug development support services.

To exploit the existing climate of change in the industry NZ needs to evaluate which components of the drug development process it can reasonably and effectively compete in and to employ the most appropriate policies to enable this to occur.

1.3. New Zealand's policy for its investment in drug development

NZ has three ministries which can invest in its drug development industry—the Ministry of Research, Science and Technology (MoRST); the Ministry of Economic Development (MED) and the Ministry of Education (MoE). MoRST takes the main responsibility for research policy and investments, while MED and MoE play a secondary role in research direction and funding but may also contribute to New Zealand's policy from a business or education perspective. The Ministry of Health (MoH) provides policies which encompass the quality, funding and provision of medicines, including price regulation by its agency Pharmaceutical Management Agency of New Zealand (PHARMAC).

Through MoRST, NZ is increasing its strategic investment in R&D, is focussing on building relationships in the Asia-Pacific region and has specified that 'the government will continue to support NZ's best biomedical and drug development research' [21]. However NZ's drug discovery and development industry is largely unknown internationally despite the country's world class reputation in medical research [13]. NZ's investment in health research has recently been evaluated and, despite its reputation in specific areas, it was found to be significantly lower than most benchmark countries (i.e. Australia, Canada, Ireland, USA, UK, Netherlands and Sweden) [22].

NZ introduced a R&D tax credit in 08/09, however this was cancelled after one year with a change in government. The success of the tax credit is as yet unknown but may have been of limited value for NZ's drug development companies that did not have revenue-generating products [23]. An OECD review [13] found that in NZ investment strategies have tended towards funding projects rather than building long-term capabilities and enabling the transfer of research results to business. NZ has internationally recognised science and medical capabilities including drug discovery however, despite some initiatives, it does not have a clear strategy for building and funding a drug development industry. Also, the effects of cumulative drug development policies on the pharmaceutical policy of the country have not been studied.

1.4. Objectives

This research was initiated from a wider project to assess New Zealand's drug development industry. The first objective of this paper is to build a framework of policy components by identifying and analysing the various policies (e.g. public health, healthcare, economic and industrial) that countries have implemented to support their drug development industry. This framework will be used to propose policy models within which to categorise each country's strategy. The second objective is to suggest which model NZ fits into and the lessons that NZ may learn from other countries that are successfully building a drug development industry.

The potential benefits of this paper are to provide a possible pathway for NZ policy development targeted to enable it to take advantage of global changes in drug development and gain from the experiences of other countries.

2. Methods

2.1. Search strategy

A literature review was conducted to identify publications relevant to the policies of various countries in support of their drug development industry. Databases researched included Scopus, Google Scholar, Google, EBSCOHost, Science Direct and PubMed. The text words used included health policy, pharmaceutical industry, drug development, clinical research, medical research, pharmaceutical policy, industrial policy, medicines, developed countries, developing countries, generic medicines, pharmaceutical manufacturing and the names of various countries. In addition, online issues of potentially relevant journals (including Australia and New Zealand Health Policy, Health Policy, Technology Analysis and Strategic Management, Research Policy, Journal of Public Health Policy and Health Affairs) were investigated and references of relevant publications tracked. Policy information was also found in government and other agency (e.g. OECD) documents and for some countries this was the main source of information.

From this review a framework was developed to evaluate the various policies of different countries. The framework encompasses the range of different national policy components which could be used to support a drug development industry, and the effects of changes in the pharmaceutical R&D industry. The selection and mix of these policy components varies by country and the policy options that each country considers while developing its overall policy are discussed below. The number of countries that this research could include was too large for this research project and so it has been limited to developed countries and to developing countries in the Asia-Pacific region. Many of the policies in the framework are industrial

Table 1
Summary of framework policies.

Pro public health policies	Industrial policies and policies which support commercial development	Policies with both elements (i.e. promote public health as well encourage the drug development industry)
Pharmaceutical price control policies	Patent protection policies Foreign and private investment policies	Government investment policies Other policies such as supporting education/facilities; encouraging networking and collaboration; country promotion of their expertise

policies in support of developing the industry (e.g. patent protection policies and policies to encourage foreign and private investment), however policies that support public health (e.g. pharmaceutical price control policies) can also influence a country's drug development industry. Finally some policies employed have public health and economic elements (e.g. government investment policies to support specific research such as the Orphan Drug Act). A summary of the policies in the framework is given in Table 1.

2.2. Framework of policy options influencing a drug development industry

2.2.1. Government investment policies

These policies are wide-spread through the developed world and have been particularly effective in developing the pharmaceutical industry in the USA and Western Europe. A widespread government investment involves support of medical research through mechanisms such as academic and research institutes, funding programmes for specific diseases and subsidy of non-commercially viable projects (e.g. the US Orphan Drug Act to encourage research into rare diseases) [5,24]. Other government investment policies include grants targetted to drug development (such as support for innovative projects or specific companies) and R&D tax credit schemes.

2.2.2. Pharmaceutical price control policies

Pharmaceutical price control policies have the goal of limiting a country's spending and on pharmaceuticals and may result in restricted access to certain medicines. Pharmaceutical price control policies may include price-setting, reference pricing, limiting a prescriber's budget, profit controls, and encouragement of generic prescribing and substitution. Some countries allow premium prices for innovative products while exerting price controls on older and less innovative pharmaceuticals [25]. However, countries without price controls may also have reduced access to pharmaceuticals due to lack of affordability or availability [26,27].

There is evidence that reducing prices for pharmaceuticals reduces the strength and innovation of the country's pharmaceutical industry [28]. There appears to be a direct relationship between a country's pharmaceutical pricing and reimbursement policies and the pharmaceutical industry R&D investment in that country. The reasons for this include lower profitability, especially from newer products, lagged cash-flow and therefore less investment in R&D [29]. The USA is an example of a country with no price controls and is the world leader in pharmaceutical development. Some Western European countries are introducing premium prices only for innovative products while instigating cost-containment measures on older medicines. Critics of the price control systems that exist in countries such as Canada and Australia, argue that these policies may lead to multinational companies preferring to move their R&D in other countries [10]. The UK appears to be an exception because it has pharmaceutical price controls but continues to be competitive in pharmaceutical innovation and this may be due to pharmaceutical prices being relatively high for 'me-too' medicines despite price control [10]. Therefore pharmaceutical price control policies involve a trade-off between reduced spending on pharmaceuticals today and the possibility of fewer innovative medicines tomorrow [25].

2.2.3. Patent protection policies

Patent protection policies that affect a country's pharmaceutical industry include those that allow manufacture of medicines still under patent as well as policies that encourage manufacture of generic medicines. The 1995 World Trade Organisation Treaty (WTO) where signatories have to recognize international patents is changing the industries and health policies of countries that previously were free to have their own patent laws (e.g. India and China) [26,28]. The WTO Treaty, with its Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) provides 20 years patent protection calculated from the date of patent filing. A patent awarded to the innovator of a drug product excludes others from making, using, selling or importing the product until the patent has expired.

Pharmaceutical companies may now be more interested in selling their newly patented medicines in developing countries such as India and China that have become signatories to TRIPS because the illegal competition has in theory been prohibited. However the prices they can charge in developing countries may need to be substantially lower than in developed markets which may result in legal 'parallel importing' of the product back into its country of origin at a more competitive price [5,30]. In addition large pharmaceutical companies are investing in the manufacturing capability of these countries such as India and China bringing both economic and technology transfer benefits which may further stimulate local R&D into new medicines [31].

2.2.4. Foreign and private investment policies

Foreign and private investment policies can be encouraged to support specific initiatives of a country's pharmaceutical industry such as specific drug development projects or building manufacturing facilities. These poli-

cies are to encourage foreign investment in a local industry, often because there is insufficient local capital to provide the start for a new industry venture, or because foreign investment will also result in new knowledge being acquired by the local industry (e.g. Singapore [32] and India [19]). Government policies which will encourage R&D investment from foreign sources are those that affect the availability, proximity and cost of specialised researchers and facilities [33].

2.2.5. Other policies

(i) Education and Facilities Policies—many countries (e.g. Canada [22] and Singapore [34]) have policies to encourage higher education and provide the resources in terms of funding, provision of appropriate teaching and research institutions, and encouraging expatriate professionals to return home.
(ii) Networking and Collaboration Policies—encouragement at both national and international levels are important to promote knowledge sharing and to take advantage of knowledge spill-overs [8]. The expertise needed for the development of a specific compound may be held by multiple organisations which can contribute complementary and overlapping information [35]. Countries such as India [36] and Singapore [37] have a policy of encouraging public–private partnerships resulting in joint venture development of innovations from public good research with funding from a large pharmaceutical firm [38].
(iii) Country Promotion Policies—countries such as Australia [39], India [12] and the UK [40] have actively embarked on campaigns to promote their country as a preferred destination for specific pharmaceutical R&D activities. Promotional mechanisms include conference trade displays, journal and magazine advertorials and targeted advertising via email.

3. Results

The framework of policy options was used to analyse the different groupings of policy components provided by various countries in order to support their drug development industries and to then postulate six different general models that they fall into. The government policy models that support a pharmaceutical industry are very diverse and range from 'consistent high investment in research without pharmaceutical price regulation' through to 'no support due to economic constraints'.

3.1. Model 1—leading Innovation in the pharmaceutical industry

The first model has a range of government investments, encouragement of foreign/private investment and other polices supporting the industry, and no price controls on pharmaceuticals. It describes the unique position of the United States (US) as the pharmaceutical industry's leading innovator—the US has invented over half of the new product patents from 1974 to 2003 [5]. In the US policy for government medical and pharmaceutical research funding is independent of policy for the provision and funding of medicines. It has been suggested that if price controls were introduced in the US it is likely that pharmaceutical R&D investments would be reduced. Therefore most of the rest of the world, with various forms of price controls, benefits in health status from the investments of the US pharmaceutical industry [24,41]. The proposed healthcare reforms in the US may have a significant impact on the pharmaceutical industry however those effects cannot be predicted at this time.

Since the 1950s the United States government has had a policy of strongly and consistently investing in medical research mainly through its National Institutes of Health and agencies of the Department of Health and Human Services [22,35]. Two federal funding and support programmes, the Orphan Drug Act 1983 and the Federal Technology Transfer Act 1986 are a result of policy that aims to stimulate private sector investment into areas where the commercial rewards are not attractive. The Orphan Drug Act 1983 encourages development of medicines in orphan indications where the target population is less than 200,000 people in the US. There are generous incentives from this legislation: FDA assistance with protocol design and the registration process, research grants, no patent necessary, 7 years exclusive marketing rights for compounds that are the first in a therapuetic class, and a very large 50% tax credit for clinical research costs [5,24]. The Act has resulted in orphan drug status being granted to 1951 compounds, 325 of which are now registered medicines [42]. It has been suggested that the policies the supported the development of orphan drugs could be applied to stimulate the development of personalised medicines (i.e. those based on specific patient genotypes of disease) [23].

The Federal Technology Transfer Act 1986 subsidises noncommercially viable collaborative research between a federal laboratory and private development. In addition, the Bayh-Dole Act (1986) allows government agencies, such as the NIH, to license knowledge that was discovered in government laboratories and receive royalties from firms that make commercial use of the information [5].

3.2. Model 2—protection of traditional pharmaceutical industry base

This model covers countries that have an established pharmaceutical industry with government support, pharmaceutical price controls but with premium prices for innovative products. This model encompasses countries in Western Europe (e.g. Switzerland and Germany) has mature large pharmaceutical companies that tend to have older products in their portfolios, less pronouced specialisation in their R&D, have failed to keep producing blockbuster products and are increasingly threatened by generic competition as their products lose patent protection [12,43]. As a result, many governments have recently embraced a range of policies to retain the R&D of their local compounds and to protect their established pharmaceutical industry while also trying to attract larger external contract projects. Policies have included focussing

on generic manufacture to assist with cost containment [43], control of public expenditure on pharmaceuticals, and rewarding investment in highly innovative medicines [44].

3.3. Model 3—building on strong scientific and medical research

This model decribes countries (e.g. the UK, Australia and Canada) where government has supported strong science research and funded internationally acclaimed medical research while employing various methods of price controls on pharmaceuticals. However, only the UK has become a significant contributor to the global drug development industry.

Despite the UK's pharmaceutical price regulation scheme (PPRS), the pharmaceutical industry invests BP5000 million per year in the UK compared with government funding of BP1700 per year on medical research. In 2009 the PPRS was updated and agreed to by the government and the pharmaceutical industry in order to improve access to innovative medicines while delivering value for money [45]. It has been suggested that the recent changes may be a disincentive to pharmaceutical companies continuing to place R&D projects in the UK [46]. However this is counter-balanced by the UK's 2006 'Best Research for Best Health' strategy, which aims to meet the needs of the global drug development industry by providing the NIHR as one co-coordinated research organization and streamlined systems allowing clinical research projects to be conducted in a very competitive timeframe. Other goals include the establishment of the NHS as an internationally recognised centre of research excellence and to attract, develop and retain the best research professionals [40].

In Australia health policy focussed on ensuring access to pharmaceuticals and meeting the health policy objectives with public funding of prescription drugs being administered by the Pharmaceutical Benefits Scheme (PBS). In the early 1990s Australia was the first country to require a cost-effectiveness analysis as part of a funding application [14] and Canada followed shortly afterwards.

Australia's National Medicines Policy (NMP) was adopted in 2000 and contains both health objectives (e.g. timely access to quality, safe and effective medicines) and industrial objectives (i.e. maintaining a responsible and viable medicines industry) [47]. In 2001, the NMP was followed up by Australia's Pharmaceuticals Industry Action Agenda where specific goals such as promoting Australia as having the capability to conduct drug development research for multinational companies and doubling Australia's share of the global pharmaceutical industry in the next decade were proposed [48]. In general, Australian policy has relied on incentives and funding programmes to grow pharmaceutical R&D including tax concession on core R&D activities [39].

The effect of NMP supporting the pharmaceutical industry appears to have had some impact with Australia ranked fourth in the OECD for government expenditure on health-related R&D as a percentage of GDP in 2006, and the rate of growth is expected to continue to rise [49]. Currently Australia's drug development pipeline contains over 450 compounds with 189 of these in clinical development. More companies in Australia are taking their medicines to phase III which indicates the success and capabilities in the industry and may also reflect the growing interest from overseas partners entering in collaborative R&D agreements [50]. In addition, Australia is increasingly conducting more early phase clinical research for international pharmaceutical companies [51] and the phase I clinical trial sector now employs over 300 people and has an annual revenue of over AUS$ 50 million [39].

The Canadian government is establishing policies and investing in strategies to foster science and technology-based innovations in the health sector. The National Research Council co-ordinates the initiatives and aims to make Canada one of the top five science and technology R&D countries by 2010. Canada has identified policy areas to support innovation and has increased its funding of R&D, provided generous R&D tax incentives, and has created collaborative institutions to assist with technology transfer of innovations [17]. Canada is also developing linkages with countries in Latin America with the aim of improving access to low cost medicines in both countries [52].

3.4. Model 4—supporting imitation leading to innovation

The fourth model covers countries that also have government investment in the industry and some mechanism of pharmaceutical price control but with the unique feature that the current industry developed from expertise original applied to production of compounds under international patent protection. Some of the more advanced developing countries such as India and China have policies to support the development of their generic pharmaceutical manufacturing to produce high-quality low-cost medicines initially for their own use and later for export. The policies enacted to develop this capability include building education and health systems, investing in the health and scientific skills required, long-term planning and commitment to the industry, and creation of both internal and international research networks [53].

The success of the industry in India has been used as a template for other countries embarking on a similar policy. India's industry arose after it initiated its own Patents Act 1970 which did not recognise product patent protection in drugs and only a new method or process of manufacture could be patented. These changes stimulated the growth in the pharmaceutical industry as firstly the local companies built up tremendous expertise in developing new and efficient processes for manufacturing medicines which were still under patent and then met the stricter regulatory requirements needed to export off-patent drugs to developed countries [26,31]. Since India became a signatory to TRIPS and with the global pharmaceutical industry seeking innovation from external sources, the Indian Government has again taken the initiative with policies to establish research institutes, increase investment, build infrastructure and promote collaborations [36]. India has also realised the economic potential of providing clinical research outsourcing services, building on its established record of quality and speed of conducting clinical trials. As a result many multinational pharmaceutical companies and contract research organisations have become established

Table 2
Comparative analysis of policy models to support a drug development industry.

Policy options framework	Policy models (taking into account industrial and health policies)						
	NZ	1 Leading Innovation	2 Protect traditional pharmaceutical industry	3 Medical research	4 Imitation to innovation	5 Contract manufacture	6 No policy
Government investment							
Medical research	X	X	X	X	X	X	
Drug development projects	X	X	X	X	X	X	
R&D tax credit		X	X	X	X	X	
Pharmaceutical price control							
Price-setting/reference pricing	X		X	X	X	X	X
Premium prices for innovation			X				
Patent protection							
Previously had own patent laws					X		
Encourage generic manufacture					X	X	
Foreign/private investment							
Drug development projects	X	X	X	X	X		
Manufacturing facilities					X	X	
Other policies							
Education and facilities	X	X	X	X	X	X	
Networking and collaboration	X	X	X	X	X	X	
Promote country capabilities	X	X	X	X	X	X	
No policy/no capability							X

in India or formed collaborations with the top Indian firms [12,36] and it is predicted that by 2010 more than 20% of the world's investment in clinical trials will be in India and valued at UD$ 1 billion per year [54].

China's current pharmaceutical manufacturing is almost entirely of generic products and it is predicted to become the second largest producer of generic pharmaceuticals by 2020 [55]. In a similar way to India, China is developing its capabilities to provide both clinical study sites and CRO services in order to be competitive in securing clinical research contracts for the global pharmaceutical industry [56]. China also has local companies that are developing products to meet local health needs; mainly these are treatments for HIV, and vaccines for hepatitis, influenza and HIV [57].

3.5. Model 5—supporting contract pharmaceutical manufacture

This model describes the countries that have chosen policies specifically to encourage multinational companies to set up manufacturing facilities for export markets by providing tax incentives. This model includes both developed countries (e.g. Ireland) and developing countries in the Asia-Pacific region (e.g. Malaysia and South Korea). Being a developed country, Ireland has been particularly successful and in 2004 its pharmaceutical production accounted for more than 11% of GDP [58], however most of the production facilities are owned by multinational companies and Ireland has very few domestic production companies. The large multi-national companies are endeavouring to contain production costs by the use of manufacturing 'centres of excellence' in countries that have attractive business policies and are well-located to service major markets [59].

3.6. Model 6—no policy to support a pharmaceutical industry

The last model is of countries where the investment required to support pharmaceutical innovation is beyond their means, and their dilemma is whether it is more economically viable to import costly medicines or attempt to manufacture them locally [60]. Investment in local medicine production may be considered an attractive policy but in reality there are too many barriers and it is more economical to buy medicines from efficient generic manufacturing countries [59].

4. Discussion

The countries in this comparative analysis provide six very different models of policies that have promoted a drug development industry. In general the different models have arisen from an historical basis, for example on the strength of biomedical research, potential profit from innovative medicines and no price controls, or the need to be able to provide affordable medicines. There are variations in the level of support for some of the policy options between the countries in each of these models, however all countries in the same model have the same focus of policies (Table 2).

NZ does not have the traditional pharmaceutical development industry of western Europe, the process development and manufacturing capability of India and China, the policies to encourage contract manufacturing of Ireland or the extensive and innovative drug development industry of the US.

NZ has consistently funded its medical research community, albeit at lower levels than most OECD countries, has price-regulation for pharmaceuticals through Pharmac, promotes education and provides research facilities. NZ is

attracting foreign investment in specific drug development projects, is increasing its networking and international collaborations, and promoting its capabilities overseas. Therefore, NZ's overall policy in support of its drug development industry is most similar to that of the medical research-based model of the UK, Australia and Canada and it is the policies of these countries that are most applicable for NZ to consider, especially regarding levels of investment in the industry.

The advantages and disadvantages of any model are specific to the characteristics of the country involved. NZ is a small and geographically isolated country with a population of approximately 4.3 million people and so many of the policies employed by the other models may not be appropriate for NZ.

4.1. General guidance for NZ

Although the other policy models to do not apply directly they provide general guidance for potential policies for NZ. Firstly, to be successful policy needs to be consistent and specific in its support of industry. Secondly, rather than trying to build a diverse drug development industry, each policy model has been built on the identification of the country's strengths and analysis of the opportunities in the industry. NZ should identify the competencies where it is internationally competitive and focus on further developing them. Lastly, the most successful countries have amended their policies when needed to respond to changing circumstances in order to capitalise new opportunities, counter new threats and maximise economic gains. With the global drug development industry still in a state of flux, NZ will need to have policies that can rapidly respond to the changing international environment.

The UK has built a robust and successful drug development industry and has recently employed new policies to actively engage with the pharmaceutical industry and meet its needs in order to continue to secure international drug development projects. To examine the UK policy is also important that it takes into account both providing access to medicines to it population through NHS as well as promoting R&D of the pharmaceutical industry. Australia and Canada have also embraced specific policies to support their industries and are beginning to see the rewards of these policy initiatives, though their industries are relatively small compared with the UK. The drug development industry in NZ needs to be more aggressively supported if it is to 'catch up' to that of at least Australia and Canada. For the NZ government to achieve its goal of supporting its best biomedical and drug development research, it will need to significantly and consistently increase funding to levels comparable with these countries.

4.2. Implications for New Zealand's policy

Firstly, NZ needs to evaluate where its capabilities in drug development lie and where it can add value to effectively compete in the global industry. NZ needs to look further than just supporting the development of its innovative compounds—there are significant economic benefits from the provision of drug development services. NZ can capitalize further on its known medical expertise and take advantage of the changes in the global pharmaceutical industry by marketing itself as being able to provide high-quality competitively priced clinical research services.

After identification of NZ's strengths in drug development, appropriate and consistent long-term policies need to be implemented to maximise the potential benefits to NZ. Policies employed by Australia, Canada and the UK that NZ could consider include increasing government expenditure for specific drug development projects, instigating appropriate R&D tax credit schemes to encourage investment, forming stronger links with countries with complementary capabilities, and marketing NZ's competencies globally. The OECD's suggestions of building long-term capabilities, financing research infrastructure and being able to effectively transfer research results to business must be considered.

NZ can cement its pivotal position in the progressive Asia-Pacific region. NZ already has relevant alliances with Australia (e.g. the Australia–New Zealand Biotechnology Alliance) however expanding this to encompass the all innovative pharmaceutical development projects, rather than just those with a biotechnology basis, would be advantageous to both countries. The alliance should also promote the range of drug development capabilities of both countries in order to secure clinical research contracts from the global industry.

Finally strong links of the NZ–Australia alliance with the manufacturing focus of India and China and the emerging medical research base in Singapore would promote the Asia-Pacific region to the global drug development industry.

The advantages of this support include extending the country's pharmaceutical industry knowledge base, the development of NZ-discovered compounds to benefit the health of New Zealanders, and economic returns that could be used to further support research in NZ.

5. Conclusions

The changes in the traditional model of drug development are creating opportunities for NZ, however other countries are also able to take advantage of them.

NZ needs to assess its international competitiveness in the various components of the drug development value chain and implement consistent policies to support further development of its drug development industry.

NZ should expand its alliance with Australia in order to capitalize on the competencies of both countries. Together they should form strong linkages with other Asia-Pacific countries that have strong capabilities in the drug development process and promote the region's expertise to the global pharmaceutical industry in a coordinated approach.

Competing interests

Michelle Lockhart is a PhD student but also provides consultancy advice to some of NZ's drug development companies and other clinical research organisations.

Authors' contributions

ML prepared the manuscript based on her PhD research. SG and ZB supervised her research and participated in its design. All authors read and approved the final manuscript.

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Appendix VII – Publication #2

Lockhart M, Babar Z-U-B, Garg S. 2010. New Zealand's drug development industry – strengths and opportunities. NZMJ 123(1317):52-58

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New Zealand's drug development industry—strengths and opportunities

Michelle M Lockhart, Zaheer U-D Babar, Sanjay Garg

Abstract

Aim Globally the traditional model of drug development is changing and the large pharmaceutical companies are looking externally for innovative compounds, new technologies and cost-effective drug development services.

New Zealand (NZ) can capitalise on its expertise in innovative drug discovery and development but needs to be able to define and promote its capabilities to the global drug development industry. An approach that will enable a ready assessment of NZ's expertise is presented.

Method Interviews will be carried out with key senior personnel from NZ drug discovery groups, drug development companies and organisations that provide a wide range of research and development services. The resulting data will be collated to document current capabilities and expertise, as well as limitations, in NZ's industry and assess their potential for the future. Participants will be asked to identify factors that support and factors that limit their organisation's progress in drug development and to suggest policies that could be implemented to positively influence future performance.

Conclusion A formal assessment of New Zealand's capabilities, strengths and limitations in drug development will aid in the promotion of its expertise to overseas organisations and enhance the economic benefits that could accrue to New Zealand.

Background

The changing model of drug development—The model of drug development is changing. Whereas the traditional approach was that of large pharmaceutical companies developing their own pipeline compounds and focussing on a few blockbuster products, we have now entered an era of partnerships and alliances between big PHARMA and smaller companies and universities the latter being sources of innovative compounds and specialised drug development services. This has resulted in a trend towards personalised therapeutic approaches with niche products that may not provide a high volume of sales but which can, nevertheless, be highly profitable.[1]

This change in the traditional approach to drug development has occurred as the industry adapts to an evolving environment caused by:[1–3]

- The failure of the large pharmaceutical companies to identify sufficient promising new compounds, leading to waning investor confidence;
- The disease categories that require therapeutic innovation (e.g. cancers, neurodegenerative diseases) are less well understood and hence more difficult

to research than disorders that already have a wide range of treatment options (e.g. in cardiovascular and infectious fields);

- Escalating research and development (R&D) costs;
- The wide range of new scientific and technological improvements which make it impossible for one firm to keep up-to-date with all opportunities that they create;
- Current blockbuster drugs coming off-patent and increasing generic competition;
- An increasingly risk-averse regulatory environment which has been exacerbated by safety issues associated with some high profile drugs (e.g. Cox-2 inhibitors); and
- More demanding users who have extremely high expectations of the efficacy, safety and value of their medicines

The costs and risks of drug development—The average capitalised cost to develop a pharmaceutical agent, taking into account costs of discovery, lead generation and failed candidates, has risen with time reaching $US1.24 billion in 2005 dollars.[3,4] The 3 phases of clinical drug development (Phase 1—first pharmacokinetic and safety studies; Phase 2—larger safety and efficacy studies in patients; Phase 3—safety and efficacy studies in large numbers of patients, usually required for drug registration) carry different risks and costs. The largest variation being in the costs of phase 3 as they are most dependent on the therapeutic indication being sought.[5]

Table 1. Clinical development: average (range) cost and chance of success for each phase in a drug's development

Clinical development phase	Average (range) cost ($US)[5]	Chance of success[5,6]
1	15.2 million (9–23 million)	70–80%
2	24.0 million (20–31 million)	30%
3	86.8 million (65–137 million)	80%

Phase 2 (i.e. showing clinical proof of principle) is more expensive and has a much higher risk of failure than phase 1. The Phase 3 programme is the most expensive due to the numbers of patients required to establish both efficacy and safety in the long-term and to obtain data in special populations. In addition to these costs of running the clinical programme there are the costs arising from pre-clinical studies, manufacturing and formulation.

From every 10,000 molecules that are screened, approximately 5 will enter clinical trials and only 20% of these will succeed to the end of phase 3.[6] Even then, regulatory approval is not guaranteed and some compounds are discontinued for reasons including commercial viability and long-term animal toxicity issues.

The opportunity for New Zealand—The uncertainties and changes in the global drug development industry noted above create opportunities for countries with recognised capabilities. New Zealand (NZ) can capitalise on the advantages of a

strong biomedical research basis for drug discovery, a resourceful and entrepreneurial society that encourages innovation,[7] a reputation for conducting world-class medical and clinical research, an acknowledged ability to produce research results "on time", and a comparatively weak dollar which leads to competitively priced drug R&D services.

Potential opportunities available in this new world of drug development include the discovery and development of innovative compounds, production of generic medicines, reformulation and new presentations of existing medicines, and provision of drug development support services.[8,9]

NZ has the potential to add value and effectively compete on a global basis in at least three of these areas:

- The discovery of innovative compounds targetted to treat diseases that currently have insufficient treatment options.
- The development of novel compounds.
- The provision of R&D services to the global drug development industry.

Each of these could bring substantial economic benefits to NZ and the research proposal outlined in brief here is aimed at assessing the viability of these three opportunities.

Though a high-risk enterprise requiring significant financial investment, the discovery and development of a NZ novel compound has the potential to provide significant financial returns to its investors as well as economic and knowledge benefits to all NZers.

NZ's most recent success in this regard is the anti-cancer agent, DMXAA, identified in 1989 at the Auckland Cancer Society Research Centre (ACSRC) and developed under the direction of Professors Bruce Baguley and Bill Denny. The development was complicated and protracted due to lack of funds and expertise in NZ at the time. However, DMXAA, now named Vadimezan, was licensed by Novartis in 2007 and phase 3 trials are underway.

The case of DMXAA highlights some problems and potential benefits to NZ of identifying and developing novel compounds. Much of the clinical development of DMXAA involved NZ clinical sites and the out-license agreement with Novartis included upfront and milestone payments, and royalties on eventual sales. However, in reality, some of these financial returns may be quite limited as the NZ investment has been diluted by larger overseas investment partners and, because of the protracted development process, Vadimezan may well be off-patent by the time it reaches the market.

At $US1.24 billion the cost of drug development is too high for the NZ government and NZ private investor funding even if the costs in NZ are much lower than elsewhere (e.g. by using NZ's Centres of Research Excellence and less expensive local drug development service organisations).

In order for NZ to maximise the returns from its innovative drug discovery and development industry it needs to have access to sufficient capital and to assess the best point in the development process at which to share the risks and costs.

The provision of R&D services (e.g. chemistry, formulation and manufacturing, clinical research and project management) to the global pharmaceutical industry is less profitable than the potential returns from sales of a novel pharmaceutical. However it carries a much lower risk, does not require a large financial investment and can still contribute significant economic returns on a regular basis.

There are already a number of successful but R&D centres in NZ working under contract with large pharmaceutical companies and there seems every reason to build upon the success of these endeavours.

In order to capitalise on its opportunities NZ needs to be able to compete against countries such as Australia, the UK, India and Singapore which are also seeking to attract overseas partners and investors to assist in the discovery and development of novel compounds and to obtain drug development contracts from large pharmaceutical companies. NZ needs to be able to define and promote its drug discovery and development capabilities to the global pharmaceutical industry. This paper outlines research already underway which aims to define those capabilities.

The research approach

Questionnaires based on developed theoretical frameworks will be administered during semi-structured interviews with individuals who have a key role in NZ drug discovery, drug development or R&D organisations. The questionnaires will be used to collect data on drug discovery and development capabilities, industry enablers and barriers, and the potential economic benefit to NZ.

Assessment of capabilities, knowledge management and innovation—Data will be collected to assess the expertise and capabilities of both the participant and the organisation they represent. All eligible drug development companies and R&D support services organisations will be approached to participate. A representative sample of the drug discovery groups will also be taken into account.

For the purposes of this research, a drug development company must be registered in NZ and have conducted at least one clinical trial on a novel compound in the last 5 years. The R&D organisations will include those that provide any of the following services: chemistry, pharmaceutical formulation, analytical methods, toxicology, data management and statistics, clinical research and project management. The drug discovery groups will be those with the potential to carry a compound into human clinical trials in the next 5 years.

The participant information collected to assess the expertise in drug discovery and development will include qualifications, relevant career experience and outputs (such as publications, especially in peer-reviewed journals, and conference presentations), personal competencies, membership of appropriate organisations and any formal recognition of their expertise.[10] Similarly the information collected on the organisations will include their range of drug discovery and development capabilites, qualifications and experience of staff and, where applicable, data on previous and current compounds in discovery and development.

Participants will be asked to compare their organisation's knowledge sharing and knowledge management behaviours both within their organisation and externally with that of their facet of the industry. Based on a knowlegde management questionnaire

developed by Lui and Lui,[11] participants will also be asked to rate the importance of different sources of knowledge (e.g. codified and non-codified information, external and internal sources). Since the process involved in the discovery and development of a new medicine requires extensive knowledge in different specialities distributed across many individuals, knowledge acquisition and sharing is essential.[11,12]

Measuring innovative performance objectively is very difficult because measures such as the number of patents registered or scientific papers published can be affected by the type of organisation. Thompson and Heron[13] adapted seven 'innovator' questions from a broader scope instrument and used this sub-scale as a measure of innovative behaviour in organisations. This sub-scale will be used by participants to rate their organisation's ability to produce new ideas, develop contacts with external experts, make time to work on ideas and projects, solve problems that caused others difficulty, project planning, innovative output, teamwork and communication.

The inter-relationships between NZ drug discovery groups, the NZ drug development companies and the R&D support services organisations used both locally and by overseas companies will be explored. NZ's interconnecting network of expertise will be compiled and assessed in terms of the quality and quantity of expertise, and ability to adhere to timelines and budgets.

Enablers and barriers to NZ's drug development industry—Participants representing the three facets of NZ's industry will be asked to identify the enablers and barriers that have affected their organisation's efforts in drug discovery and development. In addition they, plus government agencies and other industry stakeholders, will be asked for their opinion on which factors have encouraged and threatened NZ's industry as a whole and policies that NZ could implement in order to further support growth of its drug development industry.

Economic benefit to New Zealand—An assessment of the economic benefits that NZ's drug discovery and development industry could provide will be made based on the estimated sales potential of a novel compound discovered and developed in NZ, and on NZ's R&D capability being used by overseas firms.

NZ needs to carefully consider its options for compounds entering clinical development or that have positive data from phase 1 studies. The outcome of the NZ compounds that have entered clinical development in the last 5 years will be considered in order to assess the best time to look for a partner to share risks and costs. Different funding and risk-sharing scenarios will be used to obtain a range of potential economic returns if a NZ-discovered and developed compound reaches the market.

Estimates of the economic benefits that would accrue to NZ through the provision of drug development services to overseas companies will be made. NZ's competitiveness in the provision of these drug development services will be assessed by comparing quotes from NZ companies for standardised services (e.g. investigator fees, hourly rates of personnel associated with clinical research, laboratory tests, ECG costs) with those from equivalent companies in competitor countries such as Australia, the US and India. In addition the cost and time required to obtain the regulatory and ethical approvals to initiate clinical studies will be compared.

Conclusions

The NZ Government invests in science, research and technology with a goal to maximise NZ's potential to conduct excellent and relevant health research and ensure that the economic benefits of health research are captured for NZ.[14] With the current major change in the landscape of new drug development, it is important to asses the potential of NZ to play a much greater role in this eveolving inductry.

The major aim of this project is to calculate the potential economic value of the NZ drug development industry and the feasibility of supporting those facets that could be internationally competitive:

- Drug discovery
- Development of NZ novel compounds
- Provision of R&D services to overseas drug development companies

This formal assessment of NZ's capabilities in drug discovery and development will aid in the promotion of NZ's expertise to overseas organisations and may assist in attracting investors to fund the discovery and development of NZ's novel compounds, thereby reducing the risk to local investors. Both these outcomes will enhance the economic benefits that accrue to NZ from investing in and promoting its industry.

Competing interests: None known.

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Appendix VIII – Publication #3

Lockhart M, Babar Z-U-B, Garg S. 2011. Clinical Trials in New Zealand: Progress, People and Policies. Drug Dev Res 72:229-304

DRUG DEVELOPMENT RESEARCH 72:299–304 (2011)

DDR

Clinical Research Overview

Clinical Trials in New Zealand: Progress, People, and Policies

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Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Competition for clinical trial projects outsourced by the global pharmaceutical industry is increasing with more countries bidding to provide these services. A comprehensive review of the clinical trial landscape in New Zealand was conducted by analysing clinical trial applications, and interviewing senior industry representatives on their expertise, capabilities, knowledge management, and innovative behaviours, as well as the policies and factors that had influenced the development of the industry. The number of clinical trial application approvals increased from 33 in 1989/1990 to 113 in 2008/2009 indicating continued confidence of the pharmaceutical industry in placing clinical research projects in New Zealand. Much of this growth has been due to an increasing number of phase I and II trials as a result of the availability of new purpose-built facilities. The sponsors of clinical trials in New Zealand have changed from predominantly representatives of the pharmaceutical industry to mainly local and overseas CROs. The industry representatives are very experienced with the range of capabilities expected for clinical trials. They prefer informal sources of knowledge acquisition and display innovative behaviours such as solving problems that cause others difficulty, teamwork, and project planning. A large number of factors have encouraged the clinical trials industry in New Zealand including quality sites and data, the western healthcare system, the high incidence of some diseases, and seasonal opposition to Europe and the United States. Respondents suggested policies and strategies to address the increasing threat from global competition. New Zealand has developed significant expertise in clinical research but it should continue to monitor its industry to ensure continued growth. Drug Dev Res 72:299–304, 2011.

Key words: clinical trials; clinical research; policy; expertise; capability

INTRODUCTION

Generally, new medicines have been developed by pharmaceutical companies based in the United States and Western Europe that had the in-house expertise and financial resources from their products already on the market [Mooney, 2001; Schweitzer, 2007]. Currently, there is a change from the traditional "closed" approach to drug development to a new "open" model driven principally by the need for successful and profitable new products. There is considerable interest in any mechanisms that reduce the extraordinary costs of drug development and, as a consequence, the outsourcing of R&D projects to specialised Clinical Research Organisations (CROs) is

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predicted to increase from 28% in 2006 to at least 40% in 2010 [Garofolo, 2010; Kaitin, 2010].

Many of these outsourced projects are clinical trials, with many countries bidding to provide these services to the global industry thereby creating increased competition. However, there is an increasing emphasis for more formalised comparative effectiveness research (CER) to inform funding decisions [Chalkidou and Walley, 2010; Vernon et al., 2010], which will further increase the number and scale of clinical trials required during product development. Countries that are well-known for clinical trial expertise are implementing policies and strategies to remain competitive (e.g., UK's Best Research for Best Health Strategy [Department of Health UK, 2006] and Australia's proposed R and D Tax Credit amendments), while the geographic base of the industry is broadening with Asia-Pacific countries developing clinical trial capabilities [Garofolo, 2010].

In February 2010, the New Zealand (NZ) Government's Health Select Committee initiated an inquiry into improving New Zealand's environment to support innovation through clinical trials. This includes considering ways to improve processes for approvals, co-ordination of the industry, and removal of unnecessary barriers so that NZ can remain a viable option in an increasingly competitive environment. There are many benefits from being involved in clinical studies conducted for the pharmaceutical industry [Brown and Sorrell, 2009; Findlay et al., 2009; Majumdar et al., 2008; Watson, 2006] including:

1. Economic benefits: the pharmaceutical industry pays study sites generously in return for high-quality data and speedy completion of studies, which contributes to improved foreign earnings for NZ.
2. Training benefits: researchers conducting clinical trials refine their research skills from their interaction with the pharmaceutical industry. This leads to a higher likelihood that they will be involved in future trials, which will also assist NZ in retaining these skilled workers.
3. Knowledge benefits: the knowledge acquired from conducting sponsored research can be applied to clinical research undertaken in the public health system, leading to improved clinical care.
4. Researcher benefits: the payments made to study sites for conducting clinical trials are often used to supplement the funding of local research projects, therefore increasing the level of original research carried out in NZ.
5. Participant benefits: it is well documented that patients who participate in clinical trials have better outcomes than those who do not.
6. Health benefits: the combination of the factors above may all contribute to better health outcomes for all citizens.

This report presents original research into the clinical trial landscape in NZ summarising the current state of the industry and the factors that have influenced the industry development.

There are three components to the research:

- An evaluation of the progress and changes that have occurred in clinical trials over the last 21 years,
- An assessment of the expertise and capabilities of the people and organisations working in clinical research, and
- A summary of the policies that have encouraged and hindered the number of clinical trials conducted in NZ, and possible policies that could further support the clinical trial industry.

METHODS

Clinical Trial Trends

Databases of all regulatory approval applications for a clinical trial involving an unregistered medicine were obtained from 1989 to 2009. All databases contained the date when the applications were lodged, and the trial sponsor. For applications lodged after 1 July 1998, the phase of the clinical trial, the expected number of participants in NZ, the number of NZ sites involved, and the expected total number of participants world-wide were also available. The databases were amalgamated, coded, and analysed.

Clinical Trial Expertise and Capability

As part of a wider research project, senior representatives from the majority of NZ's clinical research industry were interviewed. Written informed consent was obtained from all participants and the study had approval from the University of Auckland Human Participants Ethics Committee. Structured questionnaires were used to collect information on participant expertise, and organisation's capabilities, knowledge management, and innovative behaviours. The 36 participants represented specialised service providers (e.g., providing chemistry, manufacturing, formulation, and analytical services), industry consultants who provided advice on clinical programmes and drug development, NZ CROs, clinical researchers from a range of specialities, specialised clinical research facilities for phase I/II and bioequivalence studies, and NZ affiliates of overseas CROs (see Table 1). They participated with the understanding that they and their organisation would not be identified in any reports or publications resulting from the research.

TABLE 1. Summary of Participants Representing NZ's Clinical Research Industry

Participant category	*N* (%)
Specialised service provider	9 (25.0)
Industry consultant	8 (22.2)
NZ CRO	7 (19.4)
Clinical researchers	6 (16.7)
Specialised clinical research facility	4 (11.1)
NZ affiliate of overseas CRO	2 (5.6)
Total	36 (100)

Expertise was measured by the participant's number of years of experience, their qualifications, membership in relevant professional organisations, and drug development output (e.g., peer-reviewed documents), which are accepted measures of expertise [Shanteau et al., 2002]. Participants were asked to indicate their own and their organisation's capabilities using a list provided.

Knowledge management (i.e., knowledge acquisition and sharing) is essential for efficient and effective drug development tasks and problem-solving [Berends et al., 2006; Chataway et al., 2007; Spencer, 2003]. This research asked participants to rate their knowledge sharing within their organisation using a 5-point Likert scale where "1" was "very poor" and "5" was "very good." Based on previous research [Lui and Lui, 2008], participants were asked to rate the importance of a range of six sources of knowledge using a 5-point Likert scale where "1" was "not at all important" and "5" was "very important."

Participants were also asked to rate their organisation on a list of eight innovative behaviours that had been developed by others researching high-technology organisations using a 5-point Likert scale where "1" was "very poor" and "5" was "very good."

Policies Affecting Clinical Trials

The 36 people from NZ's clinical research industry who were involved in the assessment of expertise and capability were also asked open questions on the policies and factors that had influenced the development of their industry, and the policies and strategies that they would recommend to further support clinical trials in NZ.

RESULTS

Clinical Trial Trends

Ninety-eight percent of the 1,492 clinical trial applications involving unregistered medicines that were lodged between 1 July 1989 and 30 June 2009 received regulatory approval to proceed; 1.5% were not approved, and 0.5% were withdrawn or not initiated by the trial sponsor. The total number of trials approved annually increased about 3.5 times from 33 in 1989/1990 to 113 in 2008/2009 and, generally, the number consistently increased from year to year. This result would indicate the continued confidence and interest of the global pharmaceutical industry in the quality of NZ investigators and study sites.

The phase of the clinical trial was available only for applications submitted from 1 July 1998. The proportion and number of phase I trials increased substantially over the period, from 4.3% ($N = 3$) in 1998/1999 to 23% ($N = 26$) in 2008/2009. This is probably a direct result of the opening of several purpose-built phase I/II facilities during this time. The number of phase II also increased from 19 to 36 over the same period, but the percent contribution to the total number of trials remained relatively constant at about 30% per year. With more than 50% of development compounds in phase I and II [Kessel and Frank, 2007], there may be scope to further increase the numbers of these trials conducted in NZ. The number of phase III trials has remained constant but decreased proportionally from 67% ($N = 47$) in 1998/1999 to 45% ($N = 51$) in 2008/2009. There is the expectation that phase III trial participants will continue to receive study drugs after study completion, until they are registered and funded. However, the cost-saving policies of NZ's pharmaceutical reimbursement agency (PHARMAC) have made the reimbursement timeline of new medicines unpredictable. This may have led to a flattening in the number of phase III trials undertaken in NZ by multi-national pharmaceutical companies.

Table 2 provides the number of approved clinical trials and NZ sites taking part in the clinical trials for the first year for which data were available (i.e., July 1998 to June 1999), the most recent year (i.e., 2008–2009), and for the year midway between these two years. It also provides the total number of participants expected to be recruited from those sites, the percent contribution to studies from the New Zealand sites, and the average number of expected participants per site in NZ. The data over this period show an increase in all parameters, most noticeably in the number of participants expected from the New Zealand sites, which trebled over the 11-year period.

However, perhaps the most significant change during the 21-year period was in the sponsors of the clinical trials. In 1989/1990, all clinical trials in NZ involving an unregistered medicine were sponsored by multinational pharmaceutical companies, and usually by their NZ affiliate companies. During the research period, the proportion of these declined but there was an increase in the proportion lodged

TABLE 2. Expected NZ Contribution to Total Study Participants and Number of Participants Per NZ Study Site

	1998–1999	2003–2004	2008–2009
Total number of approved trials involving an unregistered medicine in NZ	70	82	113
Total number sites in NZ	223	219	336
Expected participants in NZ	3,081	4,846	9,682
Expected participants globally	102,877	102,344	132,940
Expected NZ contribution (%)	3.0	4.7	7.3
Expected number of participants/NZ site	13.8	22.1	28.8

by both NZ CROs and overseas CROs (through their NZ or overseas offices). There has also been an increase in the proportion of applications from NZ drug development companies while the proportion of investigator- and institution-sponsored trials has remained at similar levels throughout the period investigated.

Clinical Trial Expertise and Capability

Participants had an average of 18.1 years experience in clinical trials with 80.6% of their skills being obtained through job experience and only 19.4% from their qualifications. Only 16.7% intended to embark on a career in clinical research when undertaking their qualifications but this may be due to the rapidly growing clinical trials industry in NZ. All participants had at least one appropriate tertiary qualification and most were members of a relevant industry organisation.

As anticipated, nearly all respondents (83.3%) had contributed to peer-reviewed documents in the past three years. This is not surprising since preparation and review of clinical protocols, clinical trial applications, clinical study reports, study guidelines, and standard operating procedures are mandatory for clinical trials. The majority of the organisations represented also had capabilities in project management, clinical trial monitoring and management, and regulatory affairs.

Participants rated the informal sources of knowledge (i.e., internal meetings, asking colleagues, using external networks and the Internet) as more important than formal sources (i.e., formal training and professional publications) (Table 3). Participants ranked themselves most highly on the innovative behaviours of solving problems that caused others difficulty, teamwork, project planning, and having new ideas. Less highly rated behaviours were communication, innovative outputs, making time to work on new ideas and projects, and developing contacts with external experts (Table 4).

TABLE 3. Rating Sources of Knowledge*

Sources of knowledge	Mean rating
Internal meeting	4.37
Ask work colleagues	4.23
External networks	4.06
Internet	3.94
Internal formal training	3.71
Professional publications	3.63

*Using a 5-point Likert scale where "1" was "very unimportant" and "5" was "very important."

TABLE 4. Rating Innovative Behaviours*

Innovative Behaviours	Mean rating
Solving problems that caused others difficulty	4.40
Teamwork	4.31
Project planning	4.20
Having new ideas	4.14
Communication	4.09
Innovative output	3.91
Making time to work on ideas and projects	3.83
Developing contacts with external experts	3.80

*Using a 5-point Likert scale where "1" was "very unimportant" and "5" was "very important."

Policies Affecting Clinical Trials

The policies and factors suggested by respondents that have encouraged clinical trials in NZ are:

- The quality, enthusiasm and expertise of the investigators, study sites and CROs.
- Good participant recruitment.
- Western style healthcare system.
- Efficient and sound regulatory and ethics approval systems (including a multi-regional ethics committee).
- English language and western culture.
- High incidence of some diseases in NZ (e.g., asthma, hayfever and gout).
- NZ is seasonally opposite to the northern hemisphere.
- Cost-competitive with other countries that have similar levels of expertise.

An unexpected positive factor is that the policies of PHARMAC, NZ's pharmaceutical funding agency, have generally assisted the number of clinical trials in NZ. The lack of funding of newer medicines for some indications makes NZ a desirable location for clinical research due to its relatively treatment-naive patients. PHARMAC policies have resulted in some multinational pharmaceutical companies withdrawing their clinical research staff from NZ. However, as seen in the

analysis of clinical trial trends, most continued to place clinical trials in NZ through CROs.

The threats to the clinical trials industry concentrated on the increasing competition from overseas, especially from countries that are relatively new entrants into the clinical trials field, and on maintaining New Zealand's competitive edge. Therefore, the policies and strategies recommended by participants to further grow the clinical trial industry in NZ focused on:

1. Mechanisms to improve the time to initiate clinical trials such as setting up a privately funded ethics committee and a reduction in the layers of administration required for setting up clinical trials in public hospital facilities.
2. NZ must maintain its reputation for quality and speed of clinical trials, especially when faced with increasing cost competition from overseas.
3. Some respondents would like NZ to be able to provide formal tertiary qualifications for those employed or planning a career in clinical research.

Limitations of the Research

The results on the trends in clinical trials may not completely reflect what actually occurred because it is not known whether each clinical trial was completed and participant recuitment targets met. Therefore, the results are based on the expectation that the clinical trials were completed as planned. Another limitation is that for the period 1989 to 1998, less information was available for applications (e.g., the phase of the trial was not available and could not be concluded from the information provided).

The limitations on the capabilities and expertise data are because these are self-reported. However, established indicators were used and rating scales were based on previous research by others in similar industries.

The limitations on policies and strategies may be that participants may only be aware of policies that directly affect them and may not appreciate the wider scope of policies that might affect their industry.

DISCUSSION

Our findings are important because this is the first time that a comprehensive review of the clinical trials landscape in NZ has been conducted. We have found that NZ has progressed and developed significant expertise in clinical trials but it is important that it continues to monitor the number and type of clinical trials it conducts. If the industry does not continue to grow, it is important to determine whether this is due to an exhausted capacity and, therefore, making further facilities and resources available should be considered, or is it because other countries have become more competitive. An ongoing analysis of this type will enable NZ to optimise its opportunities to provide these services for the international market, which is projected to show reasonable growth over the coming years.

Threats to its industry include competition from attractive destinations such as India, China, and Eastern Europe, which have larger potential study populations, cheaper cost structures, and higher market potentials. NZ should maximise its competitiveness by implementing strategies to allow it to initiate clinical trials in a timely manner and by maintaining its reputation for quality and efficient research.

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Appendix IX – Publication #4

Lockhart M, Babar Z-U-B, Garg S. 2011. Drug development and research in New Zealand: Policies affecting the industry. Drug Dev Res, published on-line 27 July 2011

DRUG DEVELOPMENT RESEARCH (2011)

DDR

Policy Overview

Drug Development and Research in New Zealand: Policies Affecting the Industry

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Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Many countries employ a range of policies to support their drug development industry. The support is primarily because of the perceived potential benefits from wealth creation, employment, and international trade related to a high-technology industry. New Zealand (NZ) has a growing drug development industry; this article reports on the results of interviews with people representing the industry. The NZ industry reported that government policies that included funding of scientific, medical, and drug development research, a robust regulatory system, and strong patent laws have created a cluster of expertise for specialized drug development services. This is similar to those that have been reported to encourage the biotechnology industries of many countries. Threats to the industry in NZ include insufficient funding, small industry size, insufficient supportive policies, and stakeholders' lack of understanding of the industry. These barriers differ from those of developing countries such as China and India, probably because NZ's industry is built on its scientific and medical research rather than its manufacturing capability. The specific policies requested to further support the NZ industry include increased government investment, improved management of funding, and support for research, education, and career development. Drug Dev Res, 2011.

Key words: drug development; research and development; qualitative; policy; innovation

INTRODUCTION

Despite the high risks and enormous investment needed for drug development, many countries are attempting to build a domestic industry. A viable pharmaceutical industry could reduce their dependency on expensive imported medicines, allow them to capitalize on the potential benefits of this high-technology business, or provide treatments for their population's specific medical needs [Al-Bader et al., 2010; Branston et al., 2005; Frew et al., 2006; Schweitzer, 2007]. A range of policies and strategies are available to influence a country's drug development industry, and countries may be categorized based on the "suite of policies" they employ. New Zealand's is built around its strong scientific and medical research capabilities; it therefore in the same category type as Australia, the United Kingdom (UK), and Canada, but with lower levels of investment. Other policy categories include those built on maintaining the lead in innovation (United States [US]), protection of an existing industry (e.g., Germany), imitation leading to

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innovation (e.g., India), and support of contract manufacture (e.g., Ireland) [Lockhart et al., 2010].

New Zealand (NZ) is a small country in the South Pacific, with a population of only 4.3 million. Its drug development industry is therefore limited compared with other developed countries. In 2008 there were 12 NZ-discovered compounds in clinical development, an increase from one compound in 2001. This rise is considered at least partly due to the increase in government research funding for human therapeutics from NZ$16.3 million in 2000/2001 to $46.1 million in 2006/2007 [NZBIO, 2009]. In 2009, the NZ drug development sector employed almost 900 people and generated revenues of NZ$200 million, providing a positive return on investment for government funding [Moore et al., 2010].

An issue faced by NZ is its levels of both government and business investment in R&D, which are low compared with Organisation for Economic Co-operation and Development (OECD) averages. In 2005/2006, financial year government-financed gross expenditure on R&D as a percentage of GDP was 0.50% compared with the total OECD average of 0.67% [Ministry of Research Science and Technology and New Zealand, 2009], whereas business enterprise R&D investment at 0.49% in 2002 was approximately one-third of the OECD average of 1.6% [Organisation for Economic Co-operation and Development, 2004]. By comparison, Australia was ranked fourth in the OECD in 2006 for government expenditure on health-related R&D as a percentage of the GDP, and the rate of growth since 2000 was second only to Switzerland [Organisation for Economic Co-operation and Development, 2007a]. In 2007, Australia's drug development pipeline contained more than 450 compounds, with 189 of these in clinical development, including 58% in phase II/III trials. More companies in Australia are taking their drugs to phase III, which indicates the success and capabilities in the industry and may also reflect the growing interest from overseas partners to enter in collaborative R&D agreements [McDonald, 2008].

NZ faces additional challenges because of its remoteness from major markets and knowledge centers; however, its society values resourcefulness and creativity, which have allowed it to develop a culture for innovation and specific areas of research excellence [Organisation for Economic Co-operation and Development, 2007b; Smale, 2008]. Furthermore, NZ's small pharmaceutical market size may not make it an attractive destination for pharmaceutical companies considering locations for joint venture R&D centers, such have been set up in Singapore and India.

In 2007 NZ's Ministry of Research Science and Technology (MoRST) specified that "the government will continue to support best biomedical and drug development research" [Ministry of Research Science and Technology and New Zealand, 2007]. In early 2011, MoRST was restructured to provide a new Ministry of Science and Innovation (MSI) as part of a government focus on the economic growth potential of these two areas. Other developments to encourage careers and recognize success in scientific and medical research include the appointment of the Prime Minister's Science Advisor, changes to the government funding of research projects and the Crown Research Institutes (CRIs), and prizes for outstanding scientists [Ministry of Science and Innovation, 2011]. However, it has been suggested that the NZ government is more interested in the efficient use of its drug budget than in supporting innovation by the country's drug development industry [Cumming et al., 2010].

There is tension between the pharmaceutical industry's requirement to maximize its profit and society's requirement to maximize the health of its members; policy-makers need to balance these competing needs [Smith-Merry et al., 2007]. The health policies of some countries (e.g., Australia) try to achieve this balance with the policy objectives of supporting a drug development industry and providing high-quality and affordable medicines [Lofgren and de Boer, 2004]. Recently the US has enacted its Patient Protection and Affordable Care Act to reduce the escalating costs of medicines and to integrate comparative effectiveness research and this may have consequences on pharmaceutical innovation [Spatz, 2010; Vernon et al., 2010]. Some researchers suggest that reducing prices for pharmaceuticals reduces the strength and innovation of the country's pharmaceutical industry [Comanor, 2007; Schweitzer and Di Tommaso, 2005; Sood et al., 2009]. Others propose that the pricing of pharmaceuticals in a country does not discourage the industry from investing there because it takes a global perspective and therefore will conduct development research in different countries from where it expects to obtain its premium sales [Lakdawalla et al., 2009; Thornton, 2007]. This is supported by a study on pharmaceutical R&D in British Columbia [Morgan, 2008] that found that the initiation of reference pricing policies did not result in reduced R&D investment.

NZ's Pharmaceuticals Management Agency (PHARMAC) has has a variable but capped annual budget; therefore, its decision for subsidizing a medicine is more dependent on its relative ranking of medicines that could be funded than its cost-effectiveness. PHARMAC's strategies for managing its budget have resulted in an average annual increase in NZ's drug budget of 2% between 1994 and 2008, and expenditure that is much lower per capita than that of

other OECD countries [Cumming et al., 2010], including Australia, Canada, and the US [Morgan and Boothe, 2010]. However, research has shown that PHARMAC subsidizes fewer new drugs than do Finland, Germany, the Netherlands [Aaltonen et al., 2010], and Australia [Cumming et al., 2010], and that NZ had a low rate of new drug launches during the 1990s, which was related to lower expected prices of pharmaceuticals [Danzon et al., 2005]. These data and other anecdotal evidence have been used by critics of some of PHARMAC's policies and funding decisions [Cumming et al., 2010; MacKay, 2005].

As the global pharmaceutical industry is under increasing pressure to identify and develop effective and profitable new medicines, there is a move away from the traditional closed model of drug development to a more open approach. This is producing a rapid expansion in the level of outsourcing of drug development projects and increasing competition from countries wanting to capitalize on the industry changes [Garofolo and Garofolo, 2010]. Hence there is a need for an assessment of the policies and factors that have influenced the NZ drug development industry development to date and those that could further support it. The potential benefits of this study are to document the situation in NZ, compare it with the experiences of other countries, and discuss policy options that could be embraced to support its growing drug development industry.

Within this context, the specific objectives of this research were to ascertain the opinions of the NZ drug development industry on (1) the policies and other factors that had encouraged the drug development industry to date, (2) the threats to the NZ industry, (3) the policies that the respondents would like to see initiated to further support the industry, and (4) advice for their colleagues in the NZ industry.

METHODS

Potential participants were identified from internet-based searches, industry conferences, journal publications, and snow-balling because a complete database of the industry was not available. To maximize the response rate, participants were approached individually by either personal email or telephone call, whichever was judged to be the most appropriate approach. The first author of this article (M.L.) has 20 years of experience in the industry, which assisted with potential participant identification and the decision of which method to use for the first approach.

Table 1 describes the numbers of potential participants who were identified as being eligible and were approached to be involved, as well as the number of people who consented to participate, by industry category. Participants held senior positions in their organization, e.g., Professor, Chief Executive Officer, General Manager, and Operations Manager.

TABLE 1. Number of Potential and Actual Participants by Category

Category	Total No. identified and a senior representative approached to participate	No. approached who consented to participate
Drug discovery groups	12	12
Drug development companies	12	12
Support services organizations	39	36
Stakeholders	53	46
Total	116	106

One hundred and six (106) senior participants from the following four segments of New Zealand's drug development industry were interviewed:

1. All of NZ's drug development companies developing a new medicine, either a locally discovered new chemical entity (NCE) or novel combination of existing medicines ($N = 12$)
2. All of NZ's discovery groups that expected to have a compound in clinical development within the next 5 years ($N = 12$)
3. The majority (92.3%) of NZ-based support service organizations providing a range of specialized services to the NZ and/or overseas pharmaceutical industry ($N = 36$) (organizations include NZ clinical research organizations [CROs], manufacturers, industry consultants, specialized phase I/II clinical trial units and analytical laboratories; because of the large number of NZ clinical research groups based in hospitals only a representative sample of these were approached to participate)
4. Stakeholders in the NZ industry ($N = 46$) such as government agencies, universities, pharmaceutical industry, those with extensive industry experience who did not fit into the other categories, investors, intellectual property, and legal advisors (see Table 2).

The research data were collected as part of a larger project; the specific open questions to be answered for this research were:

1. In your opinion, what are the policies and other factors that have encouraged the drug development industry in NZ?
2. In your opinion, what are the threats to the drug development industry in NZ?
3. What government policies do you think would further support the industry in NZ?
4. What advice would you give to others working in the drug development industry in NZ?

TABLE 2. Characteristics of the Stakeholder Representatives

Type of stakeholder	N (%)
Government ministries and agencies	9 (19.6)
University representatives (including their commercialization offices)	8 (17.4)
NZ subsidiaries of multi-national pharmaceutical companies conducting research in NZ	5 (10.9)
Representatives with significant industry expertise	5 (10.9)
Investment representatives	8 (17.4)
Intellectual property and legal representatives	5 (10.9)
Other[a]	6 (13.0)
Total	46 (100)

[a]Participants representing an ethics committee ($N = 1$), a District Health Board Research Office ($N = 1$), an industry organization ($N = 1$), and those with specific industry expertise ($N = 3$).

Structured questionnaires designed to collect the data were developed and tested with a sample of 11 participants to check its face and content validity before being administered to the majority of the research participants. Most questionnaires were completed during face-to-face interviews ($N = 95$); however, some were conducted by telephone ($N = 9$) or videoconference ($N = 2$). One researcher (M.L.) conducted the 106 interviews between August 2009 and April 2010. Written informed consent was obtained from all participants after they had the opportunity to read the Participant Information Sheet and ask any questions. The study had approval from the University of Auckland Human Participants Ethics Committee (Approval number 2009/267).

The responses to the open questions were transcribed into a Microsoft Word template document that had been formatted for importation into nVivo software. These qualitative data were examined to identify major themes that were categorized by one researcher (M.L.) to enable analysis using nVivo software. Quantitative data on participant's characteristics were analyzed using SPSS.

RESULTS

Most of the 106 participants were male (67.9%). All held senior positions (e.g., CEO, director, professor, or senior manager) in their organization.

Policies That Have Assisted the Industry in New Zealand

The policies and factors that have encouraged NZ's industry were grouped into the following categories: (1) specific supportive government polices and strategies, (2) factors that have occurred indirectly as a result of government policies, (3) NZ-specific factors, and (4) external factors. The details of these responses are presented and the percentage of respondents who mentioned each policy or factor is provided.

Specific government support included government funding for basic science research in universities and CRIs, grants for medical research, and funding of specific drug development projects (23.6%); strategies to build a knowledge economy with biotechnology as a priority (12.3%); provision of internationally recognized regulatory and ethics systems for clinical research projects and medicines (7.5%); strong legal system and patent protection laws (4.7%); and the policies of PHARMAC (3.8%).

An indirect but encouraging effect of government policies and funding has been the creation of expertise that can provide specialized drug development services both within the universities and in commercial organizations (37.8%). This expertise has been due in part to key individuals with the vision to achieve a particular level of expertise, but has also been assisted by expatriates returning to NZ. In particular, it was mentioned that NZ now has significant expertise in drug discovery, which has led to universities producing spin-out drug development companies. Other results of government policies are NZ's reputation for clinical trials (25.5%), the quality of research in general (24.5%), the commercialization activities of the universities (20.8%), the fact that NZ is less expensive than other countries with a similar level of expertise (12.3%), availability of nongovernment funding (11.3%), and the cluster of collaborating drug development organizations (7.5%).

NZ-specific factors suggested by participants that have encouraged NZ's drug development industry include the Kiwi approach of applying ingenuity to solve problems and an enthusiastic attitude toward innovation (27.4%) and NZ's English-speaking population, Western culture, and style of medical practice (8.5%). NZ's relative geographical isolation provides a unique source of botanicals and biologics to explore for potential new medicines, and an secluded environment for breeding specific disease-free animals (4.7%). Some participants (2.8%) also mentioned that the changes in the global pharmaceutical industry have led to opportunities for NZ as the industry searches for new sources of drug innovations and provision of support services. A phrase that several respondents used to summarize the industry development was that "NZ punches above its weight" in science research, innovation, and creative solutions.

Threats to the Industry

More than one-half of participants (52.8%) specified funding issues as a threat to the NZ industry. This issue was suggested by all categories of participants,

but most commonly by those involved in drug discovery and development who advised that they "had more ideas for innovations than the funding and time to develop them."

Lack of funding was perceived as a threat in itself but was also linked to four other main interlinked themes: expertise issues (31.1%), characteristics and size of NZ's industry (36.8%), government policies (41.5%), and a lack of understanding of the industry (21.7%). Each of these threats comprised a subset of factors, many of which were also affected by one or more of the other main threats thereby making a more complex situation than the policies and factors proposed that have encouraged the industry. External factors mentioned were the current global financial crisis and increasing competition from other countries.

Figure 1 depicts the complex interactions of the factors that threaten NZ's drug development industry. For example, government policies around the level and administration of funding through its various agencies maybe lower than overseas due to a possible lack of government understanding of the potential returns from this funding investment. A better understanding of the industry by funding and research administrators may lead to more supportive government policies and enable sectors of the industry to remain internationally competitive. This point was made particularly by those involved in clinical research where keeping competitive on "time to start" can be critical in securing new projects.

The lack of an economically significant NZ success story to date was suggested to be related to the small pool of expertise in NZ, but also to the small industry size and therefore small number of compounds under development. Another consequence of the small industry is the limited local investment funding available, but that this funding may also be restricted because the local investors may have had little experience assessing the drug development opportunities and so are reluctant to invest in an industry that they did not fully understand. Some respondents suggested that the industry is too fragmented and proposed that better consolidation of the industry would be helpful to overcome expertise issues, improve understanding by the industry and its stakeholders and better promote NZ's expertise overseas.

The cost-saving policies of PHARMAC were mentioned as a threat to the NZ industry by 27.4% of participants. They suggested that the uncertainty of future pharmaceutical reimbursement in NZmade conducting phase III trials in particular of lower interest. Some respondents (8.5%) suggested that the entire drug development programme through to a marketing application was not possible in a country of NZ's size and that NZ should focus on the early development of innovative compounds. The optimal time for NZ companies to consider a partnership, alliance or out-license deal with a larger industry partner should be determined (i.e., before the first clinical trials or at some point in the clinical programme). An industry business model needs to be developed that is appropriate to NZ's circumstances because "the US biotech model won't work here."

Policies Requested to Further Develop the Industry

Those most commonly requested policies were associated with funding. Reinstallment of some form of R&D tax credit was the most frequently mentioned mechanism to achieve increased funds for the industry. Industrial and economic policies were suggested to increase NZ's appeal to multinational pharmaceutical companies, as well as policies relating to the management of government funding of drug development. Other policies to further develop the industry included those to support clinical research; education and career structure to make science and drug development a more competitive career option; encourage investments; and government attitude and commitment to the industry.

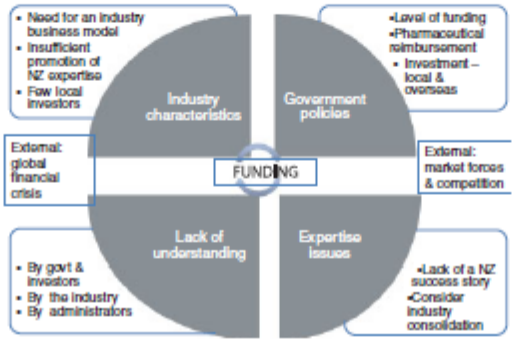

Fig. 1. Threats to New Zealand's drug development industry.

A more general strategy that was suggested was improved collaborations between the NZ drug discovery and development organizations to encourage them to work together. Assistance from government-sponsored central services in areas such as legal issues, regulatory advice and information technology was proposed. Information sharing, especially in areas where NZ's expertise or resources are more limited, could then be improved. Industry consolidation under an umbrella organization may enable more effective promotion of the country's expertise (e.g., as "NZ Inc"); however, several respondents commented that the current competition between the organizations for scarce funding may prevent this from occurring.

Advice to Others in the Industry

The most common expertise and consultancy advice was to involve proven experts in relevant fields as early as possible in the areas of science, management or on company boards and to heed their advice. Other suggestions were to make the best use of consultants and resources available; use local advisors where available but also consider overseas expertise; and employ the "best people available" for the project. Further opinions were to discuss the project with appropriate medicine regulators in the early stages of development, and to cooperate locally and network globally to keep up to date and not become isolated.

Funding advice included having multiple and longer-term funding streams where possible so that milestones could be meet without interruptions to raise more capital, out-license or partner early, and realize that the development costs will be higher than you expect, so allow for contingencies when budgeting.

Strategic advice included having a clear vision of the product being developed; what it will cost to produce; focusing on your nearest term product; and analyzing whether the market both desires and can afford your invention. The importance of having clear "go/no-go" decision points, a well-thought-out business plan should be in place and abandon any project that does not meet the agreed criteria.

General advice was to be organized but flexible, open to new ideas, plan ahead, ensure the highest quality work is done, be realistic about the high risks of drug development, and realize that there are no shortcuts to success.

DISCUSSION

The research participants suggested a range of policies and strategies that could further support and develop the NZ industry. These could also be categoried as "push" or "pull" policies. Push mechanisms are those which fund research and development, and pull mechanisms offer the prospect of financial reward once a product has been successfully developed [Hecht et al., 2009]. Most of the policies suggested by participants were in the push category (e.g., government funding and management, support for science and clinical research). The pull factors include encouragement of private investment, prizes for successful research and pharmaceutical price guarantees for medicines approaching product launch.

A potentially important issue for all countries is "brain drain" or diffusion of skilled human capital that occurs as people are lured overseas by perceived better quality of life or career opportunities [Davenport, 2004]. The importance of the knowledge capital of its returning citizens has been recognized by China as an important catalyst for its emerging drug discovery industry [Zhang et al., 2011]. Policies to encourage skilled people to return home with their global knowledge and contacts was mentioned as a option to encourage further development of NZ's industry. However another strategy is to accept that this diaspora will occur and focus on using it as a resource to gather knowledge and contacts with overseas experts until they are in a position to return to NZ [Davenport, 2004]. For NZ, the contribution of a consolidated and well-connected network of expatriates overseas maybe more cost-effective than incentives to encourage them to return home [Escutia, 2007].

Some countries have recognized the "public-sector bind" of innovative academic scientists whose research results can be applied to the development of new medicines and have attempted reforms around commercialization of academic research [Lehrer and Asakawa, 2004]. The USA's Bayh–Dole Act allowed academic researchers to benefit from their patent filings while not being out-of-pocket because the legal costs were met by their university [Giesecke, 2000; Schweitzer, 2007]. Studies of the reforms of academic R&D in Germany and Japan have suggested that they may not have been sufficiently far-reaching because the largest biotechnology companies are older firms [Lehrer and Asakawa, 2004]. The participants in the NZ research credited the efforts of the commercialization arms of some of its universities as a factor supporting drug discovery and development but suggested that there is scope for further improvement.

An analysis of the inventors of new drugs approved by the USA's Food and Drug Administration (FDA) from 1998 to 2007 found that 8% were discovered by a university and then transferred to a pharmaceutical company and a further 16% were transferred to a biotechnology company. It is suggested that this is due to the high levels of public funding for academic biomedical research [Kneller, 2010]. Others

have found that 153 FDA-approved drugs, vaccines or repositioning of existing medicines for new indications were discovered in public sector research institutions over the past 40 years [Stevens et al., 2011]. These data should be encouraging for NZ's drug discovery scientists, and should influence government decisions on funding levels and other policies affecting its drug development industry.

This NZ research found that the most controversial government policy is funding of medicines through its agency PHARMAC, because it was mentioned as both hindering and assisting NZ's drug development industry. The debate on the influence of PHARMAC on NZ's role as a clinical research destination may continue. However, recent research has shown that the number of clinical trials involving unregistered medicines has grown more than three-fold during the last 20 years [Lockhart et al., 2011]. This result is supported research showing that the number of sites in NZ in 2007 was comparatively high for its population and NZ's growth rate for trials was above that of its traditional competitors, such as the UK, US, Canada, and many European countries [Thiers et al., 2008].

NZ will face increasing competition as a desired location in which to conduct clinical trials. China and India in particular are developing capabilities with well-equipped facilities and highly educated staff; their large populations and market potential are attracting the investments of multi-national pharmaceutical companies [Chataway et al., 2007; Garofolo and Garofolo, 2010; Glickman et al., 2009; Parmar, 2005]. The UK's National Institute for Health Research (NIHR) is dedicated to providing the environment to meet industry needs including rapid review of clinical trial applications, a single point of contact for evaluating the feasibility and patient recruitment for multi-site industry studies and access to the NHS, the world's biggest health service [Department of Health]. Like NZ and the UK, Australia has been reviewing its competitiveness for clinical trials and assessing ways to improve its local research environment. Some of the recommendations of its Clinical Trials Actions Group [2011] (e.g., rapid ethics review and less administration to allow more rapid startup of clinical trials) match those suggested by the NZ industry.

An OECD review [Organisation for Economic Co-operation and Development, 2007b] found that NZ investment strategies have tended toward funding projects rather than building long-term capabilities and enabling the transfer of research results to business. The participants in this research showed agreement with this finding and requested policies to ensure long-term and consistent government funding. Other research also found that public funding tends to be short term and unpredictable and to have insufficient flexibility for drug development projects [Hecht et al., 2009]. A study in Europe showed that biotechnology development performance was linked to a coordination of funding and the use of a competitive peer-reviewed process [Senker et al., 2007]. This information is encouraging for NZ because policy requests from the industry included one funding agency and a transparent review process.

Our results have some similarities with other research of the biotechnology industry of developing countries (Brazil, China, Cuba, Egypt, India, South Africa, and South Korea) [Thorsteinsdóttir et al., 2004]. This is despite our research concentrating on drug development rather than the broader biotechnology industry, and because NZ is considered a developed rather than a developing country. Thorsteiner [2004] found that a key factor for success was that the industry focused on addressing local health needs, for example, Cuba developed the first meningitis B vaccine, and Egypt has produced an affordable recombinant insulin. Other significant factors were long-term funding, coherent policies to support the industry, the leadership of a few key industry individuals, focus of research on niche areas, close linkages between the universities and industry, promotion of collaborations and clusters, and the creation of private firms where there was sufficient venture capital [Thorsteinsdóttir et al., 2004]. These same factors were also identified by the research conducted in NZ, however our research revealed additional factors (e.g., robust regulatory and ethics processes, university commercialization activities and the quality of research) that had supported the industry development.

Other research on the barriers to the biotechnology industry in China identifed the lack of private investment to commercialize the novel products arising from government funded research, international credibility and relationships, timely regulations for intellectual property and research, and information and infrastructure [Frew et al., 2008]. Of these, only the lack of sufficient private investment was considered a hindrance to NZ's drug development industry. Similar research in India reported seven barriers to its biotechnology industry growth [Frew et al., 2007]: poorly coordinated multiple regulatory agencies; shortage of highly trained personnel; public–private partnerships not achieving the desired outcomes; few academic entrepreneurs; requirement for increased foreign investment; need to focus research on domestic medical needs; and the high cost of local distribution. As with China, the barriers in India are different from those in NZ, which is not surprising because the industries of the two countries have different evolved differently. NZ's industry is based on scientific and medical research, whereas the industry in

India originally started with the manufacture of medicines for local use and export.

The barriers to the biotechnology industry development in South Africa [Al-Bader et al., 2009] similarly included a lack of private funding. Other barriers were the sustainability of the country's R&D companies, foreign exchange and intellectual property legislation, and a shortage of highly skilled people. There are similarities between NZ and South Africa—both countries have development companies funded by government and some private investment. However, because of a lack of a sustainable business model, both may sell their IP overseas, thus limiting economic returns and perhaps resulting in the loss of experienced people. Both countries have a limited presence of the multi-national pharmaceutical companies and so have reduced spill-over benefits that could be gained by closer interactions with these companies.

A study of policies affecting the biotechnology industries of 14 Europe countries from 1994 to 2006 [Enzing et al., 2008] found that the most common and long-standing policies were those supporting basic and applied research. The average annual government funding of biotechnology almost doubled between 1994–1998 and 2002–2005; most of this funding (averaging 58% in 1994–1998 and 56% in 2002–2005) was for health applications. More recently implemented policies were those involving academic research and the industry such as encouraging firm creation, business investment and facilitation of technology transfer. It was suggested that these policies could address the issue of Europe being good in science but poor in commercializing its applications. NZ appears to be in a similar position, with its reputation for quality science, but it also its lack of the successful commercialization of a local drug product.

Further research [Enzing and Reiss, 2008] into the policies of these European countries linked success in the biotechnology industry to the high importance given to a broad set of supporting policies. A country's biotechnology performance was measured by a combination of science and commercial indicators and supporting policies were categorized into biotechnology specific policies (i.e., support of the knowledge base, commercialization, and activities such as public debates) and generic policies around the regulation of intellectual property, product quality, and measures to enhance the availability of financial capital. Countries that gave comparable emphasis to specific and generic policies (e.g., Sweden and Denmark) outperformed those that focused only on specific strategies (e.g., Portugal) or that employed mainly generic instruments (e.g., France and Italy). NZ's policies have embraced both specific and generic support, however level of importance afforded them may have been lacking. The reseachers also found that a country's biotechnology performance was influenced by its general economic features. Countries of small economic size but with a high R&D intensity, knowledge intensive labour force and important local R&D companies can be major contributors to the biotechnology field (e.g., Finland and Sweden). This suggests that smaller countries may benefit from improved coordination and strategies to focus on niche areas and NZ should also be able to benefit from its small size.

Collaboration between developed and developing countries has also been studied [Melon et al., 2009]. There are benefits to both countries from these partnerships including lower cost R&D, exposure to new technology and improved access to each other's markets. The US has the highest number of collaborations with India and China, which is likely because of its dominance in the biotechnology sector. Other countries collaborating with developing countries include Germany, the UK, France, and Canada. Despite being a developed country, NZ's industry is probably too small for it to be of interest to a collaboration partner in a developing country however alliances between NZ and other developed countries could be of benefit to both.

CONCLUSIONS

As far as we are aware, this is the first research that encompasses the opinions of almost an entire country's drug development industry and its contribution is therefore unique in that aspect. We found that the central issue is funding policies, especially for science and medical research, drug discovery, and the development of locally discovered medicines. Furthermore, NZ's total level of R&D funding is low compared with OECD countries, and this issue should be addressed, especially as competitor countries continue to increase their investment.

The range of policies employed in NZ may have been broadly adequate but possibly lacking in enough importance to enable success of the sector. There are also niche areas of NZ's industry that would benefit from more specific policy and promotion. There has been growth in the number of innovative, locally discovered compounds entering clinical development in recent years; however, NZ may lack the infrastructure, funding, and expertise to complete the development of a new medicine. Partnerships with countries with more established industries could be beneficial to both parties. NZ's significant clinical research expertise should be supported and the policies requested to maintain its competitive edge in this industry sector should be taken into consideration.

Policies to support education, career development, encouragement of experienced people to return to NZ, and networking with expatriates will be important for the country's industry to remain competitive. Policies to

encourage the pharmaceutical industry to form partnerships with NZ's academia and local firms will also be critical to the country's industry development. Employment of these diverse policies should enable NZ to reach its potential and obtain further benefits from this high technology industry. NZ's unique situation may give an advantage over other emerging and increasingly competitive drug development countries. However, as a much smaller country, NZ needs to focus its industry on niche areas where it has particular expertise or advantages.

A limitation of this research is that it contains only the opinions of the NZ drug development industry; however, the research participants are senior representatives with many years experience in the sector. Further research may include conducting a similar study in NZ in three to five years time to investigate whether the policy recommendations have been implemented and produced the desired effects.

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Appendix X – Publication #5

Lockhart M, Babar Z-U-B, Garg S. 2011. Drug Development in New Zealand – can small country be a cluster? Drug Dev Res, published online 28 November 2011

DRUG DEVELOPMENT RESEARCH 72:1–8 (2010)

DDR

Research Article

Drug Development in NZ: Can a Country Be a Cluster?

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Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT The aims of this research were to assess New Zealand's (NZ) growing drug development industry, and compare it with drug development and biotechnology clusters overseas. This article presents the results of questionnaires administered dutring interviews with 60 senior people representing the industry. It narrates their expertise, knowledge management, and innovative behaviors. NZ's industry comprises highly qualified, very experienced, and motivated people. Their organizations have particular expertise in drug discovery, which has arisen from long-term government support for biomedical research. There is also significant expertise in early-stage clinical development and contract clinical research. Knowledge sharing was rated as better within organizations than externally. The participants gave the highest ratings of their organizations' innovative performance to solving problems that had caused others difficulty, teamwork and having new ideas; they prefer informal methods of knowledge acquisition. These factors may reflect the NZ approach of applying ingenuity to solve problems and preference for casual and internal knowledge sharing. NZ has a hub of drug development activity; however, its size, limited resources, and remoteness from major markets may limit the development of a complete pharmaceutical industry. NZ could be promoted as a unique "country cluster" offering niche areas of expertise especially in drug discovery and clinical research. Drug Dev Res 72:1–8, 2011.

Key words: drug development; policy; expertise; knowledge management; innovation

INTRODUCTION

It is widely accepted that the traditional international model of drug development is undergoing rapid change in an attempt to turn around recent declining profitability [Kaitin, 2010; Smits and Boon, 2008]. The industry is moving from its traditional closed approach to a more open model, and the larger pharmaceutical companies are forming alliances and collaborations with smaller specialist firms and university-based groups with drug discovery innovations [Comanor, 2007; Doran and Henry, 2008; Mooney, 2001; Schweitzer, 2007]. A study of the top 10 global pharmaceutical companies found that their rate of alliance formation increased from an average of 6.3 per company in 1990 to 13.2 in 2005 [Rasmussen, 2010].

More countries are implementing policies and strategies to support their pharmaceutical or biotechnology industries. One of the objectives of Australia's National Medicines Policy is to maintain a responsible and viable medicines industry [Australian Government

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and Department of Health and Ageing, 1999]. The Australian government has recently released a report on initiatives to try and boost the number of clinical trials placed there [Clinical Trials Action Group, 2011]. Through its Policy Research Programme [Department of Health, 2008], the United Kingdom has also specified that clinical research is a priority, and recent changes to the Pharmaceutical Price Regulation Scheme (PPRS) are intended to encourage connections between the pharmaceutical industry and the National Health Service (NHS) [Chalkidou and Walley, 2010; Siva, 2009]. Singapore aims to facilitate biomedical research, promote international collaborations, and create a biomedical hub around its A*STAR (Agency for Science, Technology and Research) research institutes [Agency for Science Technology and Research, 2009]. India is capitalizing on its known skills for competitive generic medicines manufacture, but it is also expanding into innovative dose forms and delivery systems [Chaudhuri, 2007; Singh, 2006] and bioinformatics [Miller et al., 2011]. In addition to national initiatives, regional-level policies are being employed increasingly to stimulate innovation and technology for therapeutics. Policies supported by public funding include improving knowledge transfer, problem-orientated research and increasing the supply of skilled labor [Rosiello, 2007].

As a small country located in the South Pacific, New Zealand is some distance from the bulk of the global pharmaceutical industry. It is similar in geographic size to the United Kingdom and Japan, but with a much smaller population of 4.3 million and a limited drug development industry compared with other developed countries. However, some recent industry growth has been noted; in 2008 there were 12 NZ-discovered compounds in clinical development, an increase from one compound in 2001. This increase is attributed, at least in part, to the increase in government research funding for human therapeutics [NZBIO, 2009]. In 2009, the NZ drug development sector generated revenues of NZ$200million, providing a positive return on investment for government funding [Moore et al., 2010]. The sector employed an estimated 900 people; however, this is low on a per-capita basis (e.g., 5,000 are people employed in the bioetchnology sector in Oxfordshire, United Kingdom, which has a population of 640,000) [Smith and Bagchi-Sen, 2010].

Assessment of Expertise and Capabilities

Expertise is defined as the skills and knowledge that a person has that distinguishes them from less experienced people. The number of years of job-related experience can be as a surrogate for expertise based on the premise that a person could not function as an expert if they were incompetent [Shanteau et al., 2002]. It has been suggested that people working in the pharmaceutical/biotechnology industry need at least 10,000 h (i.e., 5 years) experience to become competent in their area of expertise [Moos and Mirsalis, 2009].

Knowledge Management and Behaviors

The process of pharmaceutical research and development (R&D) requires detailed and extensive knowledge distributed across the many people involved who may be in different departments, companies, and countries [Berends et al., 2006; Spencer, 2003]. Knowledge is classified as either explicit (e.g., from publications or formal training) or tacit (i.e., personal "know-how" that is not formal, and so only available through personal communication). External knowledge is obtained from outside the organization (e.g., from networks, professional publications, and the internet), whereas internal sources of knowledge can include formal training, informal meetings, and asking colleagues [Lui and Lui, 2008]. Knowledge transfer can occur in a structured setting (e.g., project group meetings, conferences, telephone/e-mail conversations), but it can also occur on an informal basis or even unintentionally (e.g., chance meetings, fortuitous introductions) [Berends et al., 2006]. Effective knowledge sharing requires the person to identify what knowledge they lack and to know who to approach to find the information; or for the person with the information to push new ideas and knowledge to someone who may benefit from it [Nonaka, 2007].

Many factors may encourage sharing of knowledge in an organization, including a culture that encourages open communication, a high level of trust among the personnel, promotion of innovation and decision-making, mechanisms for sharing knowledge, management support, and a reward system. Barriers to knowledge sharing include the parties being geographically dispersed, culturally different, and educationally diverse, in addition to concerns about their knowledge being inaccurate or substandard [Rosen et al., 2007; Thompson and Heron, 2006].

Innovative Behaviors

Innovation depends on interactive relationships and active knowledge transfer between different knowledge sources [Spencer, 2003]. There is no consensus on the quantification of pharmaceutical innovation, but it can be measured indirectly using markers such as the number of patents registered or scientific papers published [Morgan et al., 2006].

Cluster Development—Linking Expertise, Knowledge and Innovation

There is increasing interest in creating clusters as the basis of a knowledge-based industry and a potential mechanism for economic growth [Koo et al., 2009]. Clusters can be described as a group of organizations that have diverse and dense ties with each other, and are open to new ideas [Kasabov, 2010]. The benefits of industry and universities being located close together as in a cluster or hub include the cross-fertilization of knowledge whereby academics can gain industry experience and industry gains access to university researchers, especially the "star" scientists [Rosiello, 2007]. Linkages between firms and universities allow greater knowledge spillovers and a higher net social benefit due to less duplication of effort, leveraging of specific expertise and more efficient use of assets [Feldman and Kelley, 2006].

Many factors influence whether and how a high-technology cluster develops from an initial spark, including a strong scientific focus plus an entrepreneurial culture that encourages innovation and is tolerant of business failure. The well-known U.S. biotechnology centers (e.g., San Francisco and Boston) have been typically founded by scientists from leading academic institutions therefore a close association between the industry and academia was unavoidable. The high employee turnover associated with the U.S. clusters contributes to important knowledge transfer between organizations [Rosiello, 2007]. The successful pharmaceutical companies in Switzerland such as Roche and Novartis were based on technology from a preexisting chemical industry [Koo et al., 2009]. In Scotland, the biotechnology clusters in Dundee and Edinburgh are a result of formal knowledge transfer between industry and academia. In the Scandinavian clusters of Stockholm and the Medicon Valley, the existence of supportive infrastructure provided by public research organizations was a dominant factor. Research into the life sciences cluster development in Canada provided evidence that although public sector research institutes are a essential component of a knowledge-based life science cluster, they are not always enough to catalyze the cluster's development. The other factors that were instrumental included a local lead or anchor firm, availability of venture capital and the presence of an established pharmaceutical company [Gertler and Vinodrai, 2009].

Within this context, the aims of this research were to assess the expertise of key informants from NZ's drug development industry, their preferences for knowledge management, and their organization's innovative behaviors. This study would help us to understand the behaviors of NZ's drug development industry and any differences they may have compared with biotechnology and other industry clusters overseas. The results may assist with the further development of NZ's industry.

METHODS

Data on NZ's drug development industry was captured during personal interviews using structured questionnaires.

Study Participants and Organizations Represented

Potential participants were identified from internet-based searches, industry conferences, journal publications and snowballing. Participants held senior positions in their organization, such as Professor and Chief Executive Officer. Table 1 describes the numbers of potential participants who were identified as being eligible and were approached to be involved and the number who consented to participate. In total, 60 senior people (95.2% of those approached) representing the three groups of NZ's industry were interviewed:

All of NZ's discovery groups that expected to have a compound into clinical development for a medical indication in the next 5 years
All of drug development companies registered as a NZ company and developing a new medicine
92.3% of NZ-based support service organizations (e.g., NZ clinical research organizations, Phase I clinical trial units, manufacturers, industry consultants, and analytical laboratories) providing a range of specialized services to the NZ and/or overseas pharmaceutical industry

Data Collected

We collected the participant's number of years experience, their qualifications, membership of relevant professional organizations, awards received, and drug development outputs. Participants were asked whether they had chosen drug development as their specific career, to rate their satisfaction with their

TABLE 1. No. of Potential and Actual Participants

	Total No. identified in NZ and approached to participate	No. who consented to participate
Drug discovery groups	12	12
Drug development companies	12	12
Support services organizations	39	36
Total	63	60

career on a 5-point scale, where "1" was "very unsatisfied" and "5" was "very satisfied," and to rate their interest in continuing their career in drug development on a 5 point scale where "1" was "very disinterested" and "5" was "very interested." Each participant was asked to indicate their organization's areas of capability using a list provided (see Table 2).

Participants were asked to rate the knowledge sharing within their organization and with other NZ drug development organizations using a 5-point Likert scale, where "1" was "very poor" and "5" was "very good." Based on previous research [Lui and Lui, 2008], participants were asked to rate the importance of six sources of using a 5-point Likert scale where "1" was "not at all important" and "5" was "very important."

We collected the number of drug development outputs, and also used an eight question "innovator" scale based on one used previously to measure innovative behavior among 6 United Kingdom high technology firms [Thompson and Heron, 2006]. Participants were asked to rate their organization using a 5-point Likert scale where "1" was "very poor" and "5" was "very good."

RESULTS

Table 2 summarizes the expertise indicators of the participants and the organization's capabilities and therefore provides a summary of NZ's industry. The majority (63.3%) of the 60 organizations are located in Auckland, NZ's largest city, with the remaining organizations scattered throughout seven other cities.

TABLE 2. Expertise of Participants and Capabilities of Their Organizations

	Organization represented			
Expertise of participants	Drug discovery ($N=12$)	Drug development ($N=12$)	Support services ($N=36$)	Total ($N=60$)
Percentage of skills for drug development:				
From qualifications (mean %, range)	30.8 (10–50)	13.1 (0–40)	19.4 (0–80)	20.4 (0–80)
From job experience (mean %, range)	69.2 (50–90)	86.9 (60–100)	80.6 (20–100)	79.6 (20–100)
No. of years experience (mean, range)	24.7 (6–40)	16.4 (8–30)	18.1 (2–40)	19.1 (2–40)
Intended a career in drug development *N* (%)	4 (33.3%)	1 (8.3%)	6 (16.7%)	11 (18.3%)
Member of at least one relevant organization[a] *N* (%)	5 (41.7)	9 (75.0)	17 (47.2)	31 (51.7)
Received an award *N* (%)	5 (41.7)	0 (0)	4 (11.1)	9 (15.0)
Outputs: [3]1 in last 3 y *N* (%)				
Patents	8 (66.7)	10 (83.3)	8 (22.2)	26 (43.3)
Publications	11 (91.7)	8 (66.7)	17 (47.2)	36 (60.0)
Conference presentations	11 (91.7)	11 (91.7)	22 (61.1)	44 (73.3)
Internal reviewed documents	8 (66.7)	10 (83.3)	30 (83.3)	48 (80.0)
Capabilities of their organizations	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Drug discovery	12 (100)	9 (75)	6 (16.7)	20 (33.3)
Chemistry/scale-up manufacturing	12 (100)	6 (50)	4 (11.1)	14 (23.3)
GMP manufacture of API	5 (41.7)	2 (16.7)	5 (13.9)	13 (21.7)
Formulation	10 (83.3)	2 (16.7)	3 (8.3)	10 (16.7)
GMP manufacture of drug product	2 (16.7)	2 (16.7)	3 (8.3)	10 (16.7)
Package/label drug product	3 (25)	2 (16.7)	10 (27.8)	12 (20.0)
Analytical/stability data	8 (66.7)	3 (25)	8 (22.2)	15 (25.0)
Case Report Form preparation	0 (0)	10 (83.3)	17 (47.2)	20 (33.3)
Database/data management	8 (66.7)	7 (58.3)	15 (41.7)	21 (35.0)
Pre-clinical testing[a]	9 (75)	8 (66.7)	8 (22.2)	19 (31.7)
Safety data management	1 (8.3)	6 (50)	15 (41.7)	19 (31.7)
Statistics	5 (41.7)	5 (41.7)	13 (36.1)	19 (31.7)
Clinical protocol development	5 (41.7)	11 (91.7)	22 (61.1)	33 (55.0)
Clinical trial monitoring/management	4 (33.3)	11 (91.7)	19 (52.8)	25 (41.7)
Report preparation	8 (66.7)	11 (91.7)	28 (77.8)	44 (73.3)
Project management	8 (66.7)	11 (91.7)	29 (80.6)	47 (78.3)
Regulatory affairs	3 (25)	9 (75)	19 (52.8)	30 (50.0)
Bioanalysis	6 (50)	4 (33.3)	5 (13.9)	11 (18.3)
Intellectual property management	9 (75)	7 (58.3)	3 (8.3)	20 (33.3)

GMP, good manufacturing practice; API, active pharmaceutical ingredient.

[a]Note that all these are non-GLP, except for one support services organization.

Expertise

Approximately two-thirds of the participants' time was spent on drug development projects with the rest dedicated mainly to management tasks. The participants were highly qualified (57% held PhD or medical qualifications and 85% had a postgraduate qualification), had a mean of 19.1 years experience, and some had received national or professional society awards recognizing the quality and contributions of their work. Most participants (56.7%) were born in NZ; 25% were born in the United Kingdom and the remaining participants were from a range of places, including Australia, Asia, and North America. All participants had a tertiary qualification; 53.3% of participants had only degrees from NZ, 28.3% of participants had only overseas degrees, and 15% of participants had both NZ and overseas qualifications. Most participants had contributed to drug development outputs with patent applications, publications, conference presentations, and the preparation of internally reviewed documents.

Interestingly, the participants showed that the source of their skills for drug development was primarily from job experience rather than their qualifications and this may be a reflection of their length of experience. Most participants did not intend to embark on a career in "drug development" while undertaking their academic qualifications. Participants from the drug development and support services organizations rated their current career satisfaction more highly (mean rating 4.2 for both) than did participants from drug discovery groups (mean 3.8). All participants showed a high level of their interest in continuing their career in their area of drug development (means of 4.5, 4.5, and 4.8, respectively).

The 12 drug discovery groups have 20 distinct discovery programs under way; seven with an identified lead compound and the remainder are investigating potential lead compounds. These groups were located in universities and government-funded research institutes and have obvious capability in drug discovery, but also in associated areas of expertise. The 12 drug development companies have the expected clinical research capabilities. Eight of these companies are developing compounds that are a result of research conducted originally in a university or research institute in NZ; and the remaining companies have compounds sourced from private research. The 36 support services organizations offer a diverse range of specific capabilities that complement those of the drug discovery groups and drug development companies, as well as specialized clinical research activities and clinical trial management. As expected, all organizations have expertise in the general areas of report preparation and project management. However, there is little capability for pre-clinical studies that meet GLP standards and limited capacity for GMP manufacture.

Knowledge Management

Participants from all three organization types rated their internal knowledge-sharing higher than their sharing with other organizations, with 83–100% of participants rating their internal knowledge sharing as "very good" or "good" but only 33–52% rating their external knowledge sharing as "very good" or "good."

Figure 1 shows the percentage of participants in each category who rated the source of knowledge as being "very important" or "important." In general, internal meetings and asking work colleagues were rated the highest with internal formal training being the least important.

The results from the drug discovery groups were different from those of the other two categories in two respects: professional publications were rated as a much more important source of knowledge and internal formal training was rated with low importance by the discovery participants. This difference is probably because the discovery groups are mainly located in universities where publication of data is encouraged and internal meetings are used to disseminate knowledge.

The number of collaborations within the NZ industry, and between the NZ industry and overseas organizations was collected. Nine of the 12 NZ drug development companies each outsourced projects to an average of 3.6 other NZ organizations. In decreasing order of importance, the reasons for the NZ vendor selected was because they were based in NZ, had the expertise required, cost or were recommended by a third party. Each or the 10 of the 12 NZ drug development companies used the services of an

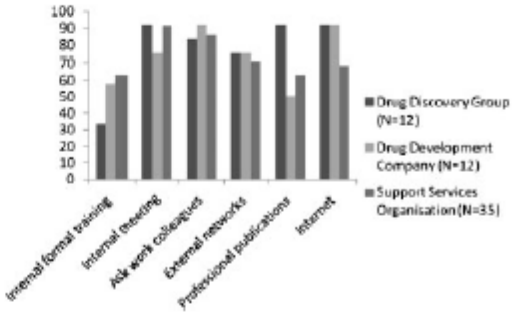

Fig. 1. Percentage of participants rating each knowledge source as "very important" or "important."

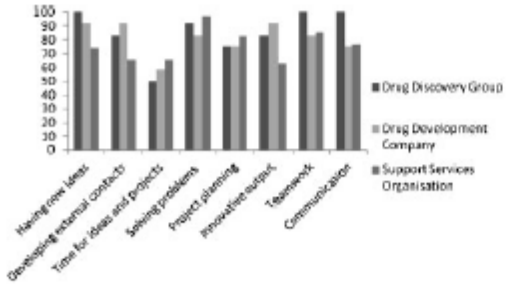

Fig. 2. Percentage of participants rating their organization as "very good or "good" on each of the innovative behaviors.

average of 7.2 overseas organizations. The overseas vendors were selected because there was no suitable expertise in NZ, a requirement to use a vendor based overseas or because a specific overseas vendor was recommended. Twenty-eight of the 36 support services organizations were each contracted to provide their services to an average of 3.4 NZ drug development companies and 29 supplied an average of 12.4 overseas companies. The reasons that the support services companies felt they had been chosen was because they were based in NZ, were recommended by a third party, cost, or could provide the specific expertise required. These collaboration rates are comparable with that of large pharmaceutical companies [Rasmussen, 2010].

Innovative Behaviors

Figure 2 provides the percentage of participants in each category who rated their organizations as being "very good" or "good" on listed innovative behaviors. Overall, ratings were highest for "solving problems that have caused others difficulty," "teamwork," and "having new ideas." This, coupled with the high rate of drug development outputs, confirms the NZ culture of creative innovation and problem solving. The lowest rating was for "making time to work on ideas and projects"; several participants commented that this was because of the time pressures of the other projects they were working on, and that they had more ideas than the time to develop them.

DISCUSSION

This research found that many of NZ's highly qualified and experienced people working in drug development were born and trained overseas, indicating that the NZ has attracted overseas expertise to enhance its industry. This research also identified NZ's specific areas of expertise especially in drug discovery and clinical research. NZ's reported expertise in clinical research is supported by the increase in the number of clinical trials involving unregistered medicines during the last decade [Lockhart et al., 2010b], indicating the global industry's confidence in NZ's capabilities.

The strengths in knowledge creation for drug discovery and early stage clinical development, as evidenced by twenty distinct programs in development, reflects the long-term NZ government policy of investing in scientific and medical research [Lockhart et al., 2010a]. NZ drug discovery teams have had successes in the drug discovery arena. Amsacrine, discovered by the Auckland Cancer Society Research Centre (ACSRC) at the University of Auckland is registered as second-line therapy for acute myeloid leukaemia. ASA404 (previously known as DMXAA, also developed by the ACSRC and out-licensed to Antisoma, was the subject of the biggest drug licensing deal in 2007 when it was acquired by Novartis. In total ACSRC has designed eight anti-cancer drugs that have entered clinical trials with international partners and have further compounds in its pipeline [NZBIO, 2009].

Industrial Research Ltd (IRL), an NZ Crown Research Institute, has also discovered compounds that have reached Phase II clinical trials for leukemia and gout. NZ researchers and companies are also developing compounds for a range of indications, including pain, neuroprotection, diabetes, liver disease, allergic disorders, and wound-healing. Other researchers are developing cancer diagnostics and bioassays to complement the work of NZ's drug discovery and development organizations [NZBIO, 2009]. NZ may not have the resources to develop all of its discovery compounds but it could establish itself as a feeder for the pharmaceutical industry in a similar way to Oxfordshire [Smith and Bagchi-Sen, 2010].

Our finding of preference for internal rather than external knowledge sharing is consistent with New Zealander's inclination for more informal communications and may have been driven by NZ's modest-sized industry and relative geographic isolation. This trait to prefer informal and internal knowledge management practices has been previously reported with the suggestion that it may limit knowledge availability and therefore its potential to be used innovatively [Smale, 2008].

Our finding that NZ's industry exhibits the required strengths in innovative behaviors and problem solving also agrees with earlier research [Smale, 2008] which reported that New Zealanders tend to undertake their innovation projects in silos, exhibit a strong reluctance to give and receive feedback and have a fear of failure. This dichotomy in the NZ entrepreneurial culture which encourages innovation and is open to

TABLE 3. Comparison of New Zealand, Brisbane, and Gothenburg

Outputs (per year)	New Zealand	Brisbane (Australia)	Gothenburg (Sweden)
Population of each country/region within the country	4 million	2 million	1 million
Publications related to their industry	718	861	750
Patents related to their industry	126	60	209

new ideas but exhibits a low tolerance for failure needs to be overcome for the full benefits of NZ ingenuity to be realized.

Despite different methodologies, our results are comparable with similar research of two biotechnology clusters, Brisbane in Australia and Gothenburg in Sweden (Table 3) [Brink et al., 2007]. These two regions and NZ have similarities with a tradition in biomedical sciences and policies of using biotechnology as a focus for a more knowledge-based economy.

A study of industry organizations in Canada found that they are most effective in influencing the success of the industry cluster they represent when used to align the interests and resources of the diverse industry stakeholders, to articulate their common goals and for the pursuit of further resources [Gertler and Vinodrai, 2009]. The industry support organizations of NZ should continue to provide and encourage formal and informal networking occasions to foster the drug development industry in NZ. The challenge is for New Zealanders to overcome their natural preference for informal knowledge sharing with longstanding colleagues and to create new contacts, develop relationships and overcome their reticence for self-promotion. Pharmaceutical companies usually initiate their collaborations [Rosiello, 2007] and therefore need to be aware of the capabilities that NZ can provide so that they can consider NZ when seeking specific expertise.

Our results show that there is a cluster of drug development organizations in Auckland, which includes universities, industry, and a range of service and research providers. There are other pockets of specialized expertise throughout the rest of NZ; however, each is too small to be considered a drug development cluster. A country the geographic and population size of NZ does not have the resources for multiple drug development clusters and we propose that the country's industry be considered as just one cluster, a "country cluster." The importance of the drug development industry is recognized at NZ government level and recent policies have centered on an increasing commitment to science and research with the appointment of a Prime Minister's Science Advisor, increased funding for R&D, including the technology transfer from research organizations to business, and a restructuring of the Ministry of Research, Science and Technology to form a new Ministry of Science and Innovation [Ministry of Science and Innovation, 2011].

CONCLUSIONS

The NZ industry exhibits the drug development industry essentials of expertise, knowledge management and innovative behaviors. NZ's industry comprises highly qualified, very experienced and motivated people. Their knowledge sharing was rated as better within organizations than externally and they prefer informal methods of knowledge acquisition. Their organizations have strengths in solving problems that had caused others difficulty, teamwork and having new ideas. There is increasing international competition for the provision of services to the global pharmaceutical industry; therefore, NZ needs to ensure the development and promotion of its niche areas of expertise.

There is a viable industry spark that could be developed into a life science-based "country cluster." However, based on comparisons of the NZ data with biotechnology and other cluster information, policies will be required to grow this group of organizations into a coherent and globally recognized country cluster. Deliberate strategies are required so that New Zealanders network more effectively both nationally and globally; both industry organizations and government policies will be needed to foster this change. The emerging NZ cluster will need to ensure it is well connected to facilitate collaborations, transfer of complementary knowledge, entrepreneurial skills and management expertise. Finally the development of the country cluster will need strong leadership and will need to ensure that experienced people are retained in NZ.

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Appendix XI – Manuscript #1

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MANUSCRIPT FOR 'DRUG DEVELOPMENT RESEARCH'

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Abstract

The pharmaceutical industry's profitability depends on identifying and successfully developing new drug candidates while trying to contain the increasing costs of drug development. It is actively searching for new sources of innovative compounds and for mechanisms to reduce the enormous costs of developing new drug candidates. There is an opportunity for academia to further develop as a source of drug discovery. The rising levels of industry outsourcing also provide prospects for organisations that can reduce the costs of drug development.

We explored the potential returns to New Zealand (NZ) from its drug discovery expertise by assuming a drug development candidate is out-licensed without clinical data and has anticipated peak global sales of USD350million. We also estimated the revenue from NZ's clinical research industry based on a standard per participant payment to study sites and the number of industry-sponsored clinical trials approved each year. Our analyses found that NZ's clinical research industry has generated increasing foreign revenue which is higher than the probability-based revenue from the out-licensing of a drug development candidate. If provided with appropriate policy and financial support, NZ's discovery and clinical research sectors could provide increased returns to the country.

INTRODUCTION

The pharmaceutical industry is in a state of major change. It is seeking to reverse its declining productivity and increasing research and development (R&D) costs by actively searching for alternative sources of innovative compounds and for mechanisms to reduce its costs (1-3). It has been suggested (51) that the more disciplined and analytical approach to R&D, which included companies benchmarking their outputs with others in the industry, stifled innovation and resulted in drug companies becoming more similar to each other instead of capitalising on their unique skills and expertise. This more regimented approach has not been successful and a return to the industry investing in the higher risk research that produced innovative drugs is required (52). In addition it has been observed that the recent mergers between large pharmaceutical companies appeared to negatively affect the progress of development compounds as the R&D departments integrated and assessed their combined portfolio (305).

The pharmaceutical industry is now trying to procure inventiveness by forming partnerships with innovative academic researchers (2, 51), especially those that can offer expertise in designing molecules of the desired therapeutic class or specific drug candidates (23). The advantages that academia can offer the pharmaceutical industry include having a creative and innovative culture, a source of intellectual capital, less expensive due to lower overheads, a broad range of expertise allowing multi-disciplinary collaborations, and being able to take risks and approaches not possible within the constraints of a pharmaceutical company (58).

The industry is willing to offer substantial upfront and royalty payments to acquire promising drug candidates. In 2005 the total announced payout value by large pharmaceutical companies for all their alliance deals was USD10.8billion, of which USD4.2billion was directed to drug discovery organisations. Note that alliance deal payout values include both the upfront payment and the potential future payments which are dependent on the drug candidate attaining agreed milestones (23). Traditionally large pharmaceutical companies have been more risk averse and have preferred to in-licence late stage compounds (235). An investment when the compound is closer to commercialisation will be more expensive but the uncertainties are lower and the potential commercial value of the product can be more accurately predicted (291). Small and medium size firms are more likely to proceed to phase 2 clinical trials with a compound that will have a higher risk of failing at this stage (33), perhaps lured by the prospect of a more valuable out-licensing deal once clinical proof of principle has been attained. However there is increasing competition and a smaller pool of attractive phase III candidates and therefore earlier stage and even pre-clinical compounds are being acquired (235).

The clinical trial phase of drug development is the most expensive and costs have increased significantly as the number of studies in the average New Drug Application (NDA) has increased from 30 in the early 1980's to 70 in the mid-1990s (57). The pharmaceutical industry is attempting to reduce this expense; one mechanism is to have less clinical trial centres in the US and replacing them with less expensive trial sites in India, South America and Eastern Europe (5).

New Zealand (NZ) is a small country located in the South Pacific with a population of 4.3million. It was ranked 18th on its overall capability to generate innovation in biotechnology (263) and has a recognised culture for innovation (67). NZ has already derived financial benefits from its drug discovery expertise, and has start-up companies undertaking the clinical development of some of its discovery candidates (63). On average over 2000-2009, the human therapeutics sector generated USD31.9million in output, USD71.4million in GDP and 2,000 jobs (including multiplier effects) (306). However, because of the country's size, lack of a strong pharmaceutical industry base and limited venture capital sector, it is unlikely that a NZ company would have access to the capital and the infrastructure to complete the development of an innovative medicine. An assessment of NZ's drug development industry identified specific expertise in drug discovery and clinical research and generated a similar number of publications and patents as the biotechnology industries of Brisbane in Australia and Gothenburg in Sweden (307).

Our research objective was to estimate and compare the potential revenue that could accrue to NZ from the two facets of its drug development industry where it has recognised strengths: (1) from the successful development of a NZ-discovered medicine and (2) from the provision of clinical research services to overseas organisations. The feasibility and sustainability of the contract only research model for discovery, where returns from successful compounds are used to fund further discovery research, are explored. There have been anecdotal reports of the annual value of clinical trials to NZ which range from USD84million in 2004 (244) down to a current NZD25.2million (245). This data implies that NZ's revenue from industry-sponsored clinical trials has been declining, however it is widely acknowledged that no accurate records are available and it is important to estimate its value to NZ.

METHODS

Revenue from the Successful Development of a NZ-discovered Medicine

A hypothetical compound was used, to calculate the potential revenue to NZ of the successful development of a NZ-discovered medicine. This method was chosen because of the confidentiality issues of using an actual development candidate and we do not have access to confidential pharmaceutical industry information. We considered our approach to be valid because the potential value of a compound is dependent on its market potential and the level of risk associated with completing its development. Additionally few pharmaceutical companies undertake potential revenue analyses on their early stage discovery projects because they are dependent on the large number of assumptions made and there is no standard method employed (236).

Our calculations on a hypothetical compound were based on data from previous research (235) which found that the typical upfront payment for a pre-clinical compound is USD6.5million with a further possible USD39million from royalty payments. Typical total deal payouts range from USD65million for a compound with phase I data through to USD220million for a product that has completed phase III. We assumed that the compound was still wholly owned in NZ at the time that the out-licence deal was agreed and that the compound was out-licensed as a lead candidate (i.e. without clinical data) with projected global peak sales of USD350million.

The time to peak sales is influenced by factors including the order of product entry, the quality of the brand and marketing support (237). An analysis of mean worldwide sales for new drugs introduced between 1990 and 1994 found that peak sales occurred around Year 10 from product launch and appreciable sales still occurred at Year 20 (49). Research on new drugs introduced into the UK from 1980 to 2007 (238) estimated a lifetime of 33 years, with peak sales at 17 years. Another analysis of sales from 1981 to 1992 (239) found that mean peak sales were usually achieved within ten years of product launch and noticeable sales still occurred at 20-30 years after launch. An analysis of the effect of entry order on sales for nine indications showed that peak sales of the market leader usually occurred between Year 8 and Year 12 from product launch (240). However research (241) on products introduced in the USA between 1998 and 2008 found that peak sales occurred at five to six years post launch. Note that due to the time delay from product launch until peak sales, data on recently marketed pharmaceuticals is not available,

DiMasi and Feldman (29) used data from the top 50 pharmaceutical firms to determine that the phase transition and clinical approval probabilities for both licensed-in and self-originated compounds first tested in man from 1993-2004 were: phase I-II: 71%; phase II-III: 45%; phase III-NDA: 64%; NDA approval 95%. Therefore the overall probability of a compound being approved for sale of 19% which agrees with the FDA's statistics (30). Other researchers report a wide range of drug development

success rates from 7% to 78%, with the extremely high success provided by hormone therapies (31). Another analysis based on data from 14 companies suggested that the chance of market launch for a product in phase I dropped from 10% in 2002-2004 to 5% in 2006-2008 (32). It is difficult to compare the rates reported due to the use of different data sources, compound types and/or therapeutic areas and we do not have access to all the data available to the pharmaceutical industry. Therefore we used the probabilities suggested by DiMasi and Feldman (29) because they appear to be based on the largest, and one of the most recent, datasets.

Our sales projections were based on the most commonly reported data, although - peak sales at Year 10 after product launch, with sales continuing only to Year 20. Since there are no 'average' sales growth data publicly available to apply to our hypothetical product we used a generally bell-shaped curve of the expected percent of peak global sales for Year 1 to Year 20. This was chosen based on related research by Rasmussen (23) on annual sales growth rates, the knowledge that adoption of new medicines by prescribers generally follows a bell-shaped curve (259) plus personal experience. These percentages of peak global sales for each year were then used to calculate annual sales projections based on peak global sales of USD350million. Annual sales projections were multiplied by the successful phase completion probabilities. We assumed a preclinical out-license deal, and therefore used a 19% overall probability of the compound being approved for sale.

Royalty payments are based on sales profit. We have used an average gross profit of 50% which is the value of sales minus the 'costs of sales' and 'selling and administration costs' (23). This was used rather than the industry's overall profit of around 15% which includes R&D costs because this was accounted for by including a probability of success factor in our calculations. Royalty payments for a compound with no clinical data was estimated to be 10% of profits, i.e. lower than the 12-15% royalties typical for compounds with phase I data (235).

A summary of the assumptions made for our calculation of revenue to NZ are provided in Table 1.

Table 1 - Assumptions for the calculation of potential revenue from drug discovery

Parameter	Assumption	Basis of the assumption
Timing of out-license deal	Pre-clinical (i.e. without clinical data)	N/A
Local ownership when deal agreed	100%	N/A
Upfront payment	USD6.5million	Research by Kessel and Frank (235)

Projected global peak sales	USD350million	N/A
Time of global peak sales	Year 10 after product launch	Data from Danzon and Kim (239), Grabowski (49) and Hoyle (238)
Duration of sales	20 years	Data from Danzon and Kim (239), Grabowski (49) and Hoyle (238)
Sales for Year 1 to Year 20 as a percentage of peak sales	Bell-shaped curve, as described in Table II	Data from Rasmussen (23) and Cook (259)
Probability that the compound is approved for sale	19%	Research by DiMasi and Feldman (29)
Average gross profit on sales	50%	Data from Rasmussen (23)
Royalty payments on sales profit	10%	Research by Kessel and Frank (235)

The out-licence of a promising drug discovery candidate could provide income as upfront and royalty payments for an academic medicinal chemistry centre to expand and undertake more commercially directed research alongside their publicly funded research. We used an average cost of a medicinal chemist or biologist of NZD200,000 (USD168,000) to cover salary, rent, equipment and consumables costs (260).

[Footnote 1 - The following exchange rates (current for 18 July 2011) were used for our research: NZD1.00 = USD0.84 and AUS1.00 = USD1.07].

Revenue from Clinical Research

We estimated the revenue to clinical trial sites performing research for the pharmaceutical industry. The per participant payments to study sites varies widely depending on the phase of the trial and the protocol requirements and are not readily available. However the cost per participant in a clinical trial in the US has been estimated at USD16,000 – USD47,000 (243) (83).

We used an average per participant payment of NZD15,000 (USD12,600) which was confirmed with several NZ clinical research facilities. It is lower than estimates from the US which may reflect the lower costs of labour and services in NZ. We obtained access to the NZ Ministry of Health databases of applications for clinical trials involving unregistered medicines which provided the number of participants expected at NZ sites and the clinical trial sponsor. We applied an average per participant payment for the 2010/2011 year and reduced it by 3% per year going back to the 1998/1999 year (the earliest year for which the relevant data was available).

The revenue to NZ each year from its clinical research activities was estimated by multiplying the number of participants expected from industry-sponsored clinical trial applications each year by the per participant payment for that year. This calculation does not include other trial payments such as set-up fees, ethics application submission, and the costs of the sponsor monitoring and managing the study sites.

RESULTS

Revenue from the Successful Development of a NZ-discovered Medicine

The returns to NZ per year from a compound with peak annual sales of USD350million are provided in Table 2. No adjustments (e.g. Net Present Value) have been made because it was assumed that the returns would be invested back into NZ drug discovery almost immediately to fund further research rather than accumulated for future projects. These proceeds to NZ over the average of 30 years from the out-license deal until sales are negligible, would provide total probability-adjusted returns of USD48.273million. Assuming that only one third was re-invested in building NZ's drug discovery capability an average of USD536,366 per year would fund at least three additional scientists to research drug discovery projects for 30 years.

Table 2 - Revenue from the out-license of a NZ-discovered medicine

Out-license deal after pre-clinical stage	Percent probability of successful completion	Project sales as percent of peak global sales (%)	Projected sales/ milestone payment per year (USDmillion)	Projected profit (50% of sales)	Projected profit multiplied by percent probability of success	Probability-based payments to NZ (USD-million)
Upfront Payment	100	N/A	6.500	N/A	6.500	6.500
Successful Phase I	71	N/A	0	N/A	0	0
Successful Phase II	31.95	N/A	0	N/A	0	0
Successful Phase III and registration dossier submitted	20.45	N/A	0	N/A	0	0
Approval of registration dossier	19.02	N/A	0	N/A	0	0
Year 1 sales	19.02	30	105.000	52.500	9.986	0.999
Year 2 sales	19.02	40	140.000	70.000	13.314	1.331
Year 3 sales	19.02	50	175.000	87.500	16.643	1.664
Year 4 sales	19.02	60	210.000	105.000	19.971	1.997
Year 5 sales	19.02	70	245.000	122.500	23.300	2.330
Year 6 sales	19.02	80	280.000	140.000	26.628	2.663
Year 7 sales	19.02	85	297.500	148.750	28.292	2.829
Year 8 sales	19.02	90	315.000	157.500	29.957	2.996
Year 9 sales	19.02	95	332.500	166.250	31.621	3.162
Year 10 sales	19.02	100	350.000	175.000	33.285	3.329
Year 11 sales	19.02	90	315.000	157.500	29.957	2.996
Year 12 sales	19.02	80	280.000	140.000	26.628	2.663
Year 13 sales	19.02	75	262.500	131.250	24.964	2.496
Year 14 sales	19.02	70	245.000	122.500	23.300	2.330
Year 15 sales	19.02	60	210.000	105.000	19.971	1.997
Year 16 sales	19.02	50	175.000	87.500	16.643	1.664
Year 17 sales	19.02	40	140.000	70.000	13.314	1.331
Year 18 sales	19.02	35	122.500	61.250	11.650	1.165
Year 19 sales	19.02	30	105.000	52.500	9.986	0.999
Year 20 sales	19.02	25	87.500	43.750	8.321	0.832
Total (USDmillion)			4399.000	2196.250	424.227	48.273

Similar calculations using later timings of a licensing-out deal found that the returns to NZ would be 67% higher in total with phase I data and more than two and a half times higher after phase II.
Other analyses were conducted to check the validity and the effects of the following assumptions: peak sales, royalty payment levels, percent probability of approval of the registration dossier, average gross profit on sales and total cumulative sales. A summary of all six analyses is provided in Table 3.

Table 3 - Summary of Sensitivity Analyses

Sensitivity analysis	Detail and total revenue to NZ (USDmillion)					
	Lower end of the range		Original calculation		Upper end of the range	
	Analysis detail	Revenue to NZ (USDmillion)	Analysis detail	Revenue to NZ (USDmillion)	Analysis detail	Revenue to NZ (USDmillion)
Later out-licence deal	N/A	N/A	Pre-clinical	48.273	Post ph I Post ph II	68.347 140.599
Value of peak sales	USD50 million	12.468	USD350 million	48.273	USD1000 million	125.851
Level of royalty payments	8% of sales profit	38.682	10% of sales profit	48.273	12% of sales profit	54.773
Percent probability of approval of registration dossier	10.0%	28.463	19.02%	48.273	30.0%	72.388
Sales profitability	40% of sales value	38.682	50% of sales value	48.273	60% of sales value	54.773
Cummulative sales	USD3294.4 million	37.830	USD4392.5 million	48.273	USD5490.6 million	58.716

Revenue from Clinical Research

The revenue generated from pharmaceutical industry sponsored clinical trials, based on the expected number of participants in pharmaceutical industry sponsored trials and an average per participant payment to study sites provided USD100M in foreign earnings in 2010/2011. The cumulative revenue since 1998/1999 is estimated at USD745M (see Figure 1).

A sensitivity analysis used a lower per participant payment of USD8400 and an upper level of USD21,000 (i.e. similar to that published for US sites). The lower payment produced a return to NZ in 2010/2011 of USD68million and cumulative revenues of USD497milllion since 1998/1999. The upper end of the payment range generated revenue of USD170million in 2010/2011 and cumulative revenues of USD1242million since 1998/1999.

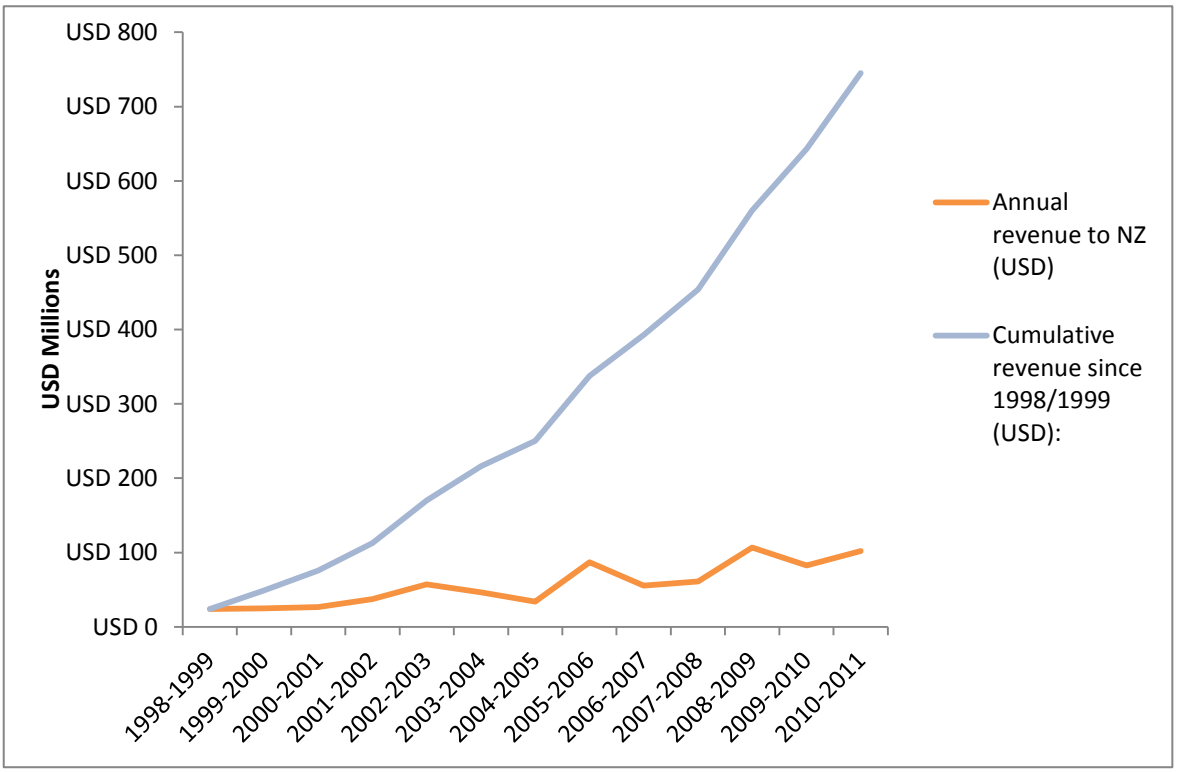

Figure 1 - Annual and cumulative revenue from clinical research

DISCUSSION

Our research methodology could be used by other countries with limited resources to estimate their potential revenues from drug discovery and clinical research and to identify the sectors of drug development where it would be the most beneficial for them to focus their efforts. Countries that have limited resources cannot support a fully integrated pharmaceutical industry which is an expensive and risky enterprise. Instead they should initially focus on their niche areas of expertise (232).

Even though the optimum time for an organisation to out-licence a product is after phase II, data from 2008 suggested that approximately 50% of out-licence deals occurred with pre-clinical compounds indicating that many organisations cannot wait until they have sufficient clinical data (284). Licensing out a drug development candidate is a viable option for an academia-based discovery group that has limited access to funding (291). Another option to maximise academic expertise is through industry partnerships to fund specific research projects; an example of this model is the collaborative research funding and alliance between GSK and Imperial College London Scientists (2).

The revenue from an out-licensed product depend primarily on the peak global sales and the timing of the out-license agreement. The assumptions made for our calculations were based on the

literature, and our predictions maybe limited by the data publicly available, however even the worst case scenario in Table 3 provides some revenue to re-invest into drug discovery research. Our calculations assumed that the compound was still entirely locally owned when out-licensed and has shown that a compound achieving even modest peak global sales (USD350million) has the potential to produce reasonable returns. The returns could continue for 20 years and provide a drug discovery organisation with stable returns to up-scale its drug discovery capabilities, although the scale of revenue will depend on the success of the compounds.

Frequently the contract-only drug discovery model is used as a temporary funding mechanism for the fledgling organisation before expanding into an integrated drug development company (23) with the hope of gaining superior financial returns (232) however our research was to ascertain whether the initial returns would be sufficient to support the first stage of this process i.e. the growth of a drug discovery cluster.

There are several industry factors that should encourage drug discovery groups that are focussed predominantly on small molecule research: (1) the pharmaceutical industry has been downsizing its own drug discovery capability (292); (2) it needs to rapidly increase its discovery output to maintain its profitability (57); and (3) the majority of new medicines continue to be small molecules (293, 308). NZ's research has led to successes primarily with small molecules and many have potential indications in oncology (63). Oncology is an area of global industry focus as indicated by having the highest number of clinical trials from 2005-2007 (294) and is now the therapeutic area with the highest industry investment (32, 134). It is a challenging indication but the industry's interest has been encouraged by increased knowledge of cancer mechanisms and relatively favourable reimbursement opportunities (295).

NZ has been generating significant foreign earnings from its clinical trials industry. Our research calculated that the income accrued from industry sponsored clinical trials of USD100million in 2010/2011 is similar to the upper estimate made of the industry in 2004 (244). It generally increased over the period studied which is contrary to the popular perception that the NZ industry has been in decline. The value of clinical trials in Australia is estimated to be AUS450million per year (USD482million) (301) which is comparable on a per capita basis with NZ. While NZ's size will limit the number of participants and sites it can provide for industry-sponsored clinical trials, it does facilitate rapid review of clinical trial applications through centralised processes. The steady increase in the number of industry-sponsored clinical trials indicates that NZ's capacity for clinical research is not yet saturated. The increase is predominantly due to the rise in the more challenging phase I studies (262),

which is encouraging for a smaller country which is unable to enrol very large numbers of participants into research projects.

These are positive indications for NZ's clinical trials industry and an analysis of its environment to conduct clinical research has been undertaken. A Health Committee Report of the government inquiry (244) has recommended simplifying and speeding up the ethical review process; promoting collaboration between Government departments; development of a national health research action plan and a framework for clinical trial research activities. These recommendations are intended to encourage further growth of the NZ clinical research industry in an increasingly competitive environment. Our research results show some volatility in the revenue from the number of clinical trials placed in NZ and so the recommendations of the Health Committee Report should be carefully evaluated with a view to implementation. Many of the recommendations require policy and process support rather than a high financial investment. The recommendations are similar to those recently proposed to the Australian government (301). Similar initiatives have been undertaken in the UK (188) and emerging clinical trial destinations such as Singapore, India, China and Eastern Europe are also keenly promoting their expertise (1, 214, 242).

CONCLUSIONS

Our analyses have explored the potential value to NZ from two sectors of its drug development industry where it has expertise. NZ's clinical research industry has generated significant and increasing foreign revenue which is higher than the probability-based revenue from the out-licensing of a drug development candidate. Appropriate policy support could ensure that the clinical research revenue continues to grow. NZ's medicinal chemistry expertise and innovative culture could benefit from further financial and policy support to maximise its potential in drug discovery. Out-licensing drug candidates has the advantage of providing an ongoing revenue stream rather than the fee-for-service revenue generated by clinical research, however increasing NZ's income from providing clinical research services would likely require less financial outlay. If provided with further support, both sectors of NZ's drug development industry could provide increased returns and enhance NZ's expertise in these areas.

CONFLICT OF INTEREST

Michelle Lockhart provides consultancy advice to drug development and pharmaceutical companies.

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