Developing the Biomedical Industries in Canada and Australia: An Innovation Systems Approach

Working Paper No. 24

Bruce Rasmussen

Pharmaceutical Industry Project
Working Paper Series

February 2005

Centre for Strategic Economic Studies
Victoria University of Technology
PO Box 14428 Melbourne VIC 8001 AUSTRALIA
Telephone +613 9919 1340
Fax +613 9919 1350

Email: csesinfo@vu.edu.au
Website: http://www.cfses.com

Developing the biomedical sectors in Australia and Canada: An innovation systems approach

Bruce Rasmussen*

Abstract

Canada and Australia both aspire to have a vibrant biomedical sector, but their performance is very different. The paper uses innovation systems theory to search for reasons for these differences. It develops, within a knowledge framework, a set of indicators to measure the dynamic performance of the two sectors. The results suggest that the dynamics of the Canadian biomedical innovation system have been positively reinforcing, while the Australian under performance has been the product of its failure to effectively use the knowledge generated and diffused within the innovation system. The results support the use of the innovation systems approach.

Keywords: innovation systems, performance indicators, alliances, biotechnology

1. Introduction

Canada and Australia have much in common. There is a shared heritage as new world British colonies, similar governmental institutions, living conditions, health and educational standards. Canada is somewhat larger than Australia – its population of about 32m is 160% of Australia's. Both have high living standards although Canada's GDP per capita is marginally higher than Australia's.[1] The countries also share many aspirations. One is to retain their technological edge, as innovative societies, through the commercialisation of their science base.

This is illustrated by the release, within the space of a few months, of innovation strategies designed to enhance the innovation process in each country. In Australia's case, its plan was set out in *Backing Australia's Ability* (DEST 2001), which followed a number of related reports and white papers, and for Canada, the more substantial document *Achieving Excellence* (Government of Canada 2002). Both documents focussed on similar things, strengthening R&D, accelerating its commercial application, and developing and retaining skills. They also emphasised the importance of broader competitive and supportive economic settings. In both cases, the policy initiatives were accompanied by substantial increases in government funding for R&D and associated support programs.

However in terms of their biomedical sectors, Canada seems to have performed much better. For instance in 2002, there were more than three times as many drugs in

* Centre for Strategic Economic Studies, Victoria University, PO Box 14428, Melbourne, Victoria, Australia 8001; tel.: +613-9919-1342; fax: +613-9919-1350, email: Bruce.Rasmussen@vu.edu.au.

This study was supported by funding from the Victorian government and the Merck Company Foundation Program on Pharmaceutical Policy Issues. Thanks are due to Peter Sheehan and Kim Sweeny for their helpful comments on this paper. The enthusiastic research assistance of Alison Welsh is also gratefully acknowledged.

[1] In 2003 the population of Australia was 19.7m compared with 32.2m for Canada. In 2002 GDP for Australia was $525b compared with $934b for Canada (both PPP).

clinical trials in Canada (97) compared with Australia (28). A range of other indicators shows a similar out performance, beyond that which could be simply explained by differences in population.

Can innovation systems theory help to explain the differences in the performance of the biomedical sectors in the Canada and Australia? As Lundvall et al. have pointed out (2002), the notion of innovation systems has become widely used as a framework for comparing the innovation performance of two countries (see for instance, Carlsson 2002; Nelson 1993; OECD 2003). However some of its shortcomings have been noted in recent papers by its original proponents, Lundvall et al. (2002), Carlsson et al. (2002) and to a lesser extent in Nelson and Nelson (2002).

These essentially operational shortcomings arise from the difficulty in modelling the highly complex nature of innovation. As Kline and Rosenberg observed in 1986, 'systems used in innovation processes are among the most complex known (both technically and socially) and the requirements for successful innovation vary greatly from case to case' (p. 276). Models of innovation need to address its many aspects. This includes the nature of the innovation itself – a new product, process or organisation, the uncertainty of its outcomes, its dynamic nature, and the interdependencies of the many organisations that contribute to the innovation process. It is both the complexity of the processes and the difficulty of deciding which aspects can be generalised, that provides the central theoretical challenge.

The attraction of the national innovation systems approach, at least notionally, is that it provides a framework that is sufficiently comprehensive to address the complexity of the innovation process. This includes how the systemic aspects of the innovation system work such as, the routines and dynamics of the technological regime, the interaction of the participants and the nature of the feedback loops.[2] Part of the difficulty of translating this intuitive appeal into more compelling theory is that the innovation system is analytically demanding to model, in part because the underlying forces of the innovation system remain poorly understood in a data deprived environment.

Accordingly for all their shortcomings, well documented case studies can provide a useful insight into the innovation process within an innovation systems framework (Nakicenovic 2004). As Carlsson et al. (2002) suggest:

> In the literature on systems of innovation there has not been much explicit discussion of the function or purpose of each system, nor of what constitutes inputs and outputs of the system. As a result there is not much discussion of the system performance either. (p. 234)

By focussing on the comparative *performance* of the *biomedical* innovation systems of two countries, rather than innovation systems more generally, appropriately defining the system boundaries has clear implications for measuring the relative performance of the two systems. Can the performance of the biomedical system be sufficiently differentiated from that of the rest of the innovation system and can its

[2] There is an extensive literature on the nature of innovation systems in addition to that specifically referred to in the paper including, Lundvall (1992), Freeman (1987), Freeman and Soete (1997), Edquist (1997), Metcalfe (1995), and Nelson (1993).

performance in the two countries be adequately compared? The next section addresses the issues of system definition and performance measurement raised above.

2. Defining a Biomedical Innovation System[3]

2.1 Technology and Product Set

The biomedical innovation system may be regarded as a sectoral innovation system (Breschi and Malerba 1997) and as such is defined both by its underlying technology and product set. The product set includes both final and intermediate stage goods and services. By far the most economically important final stage product is new human therapeutics. This definition is broad enough to include new medicines, diagnostics, and drug delivery systems for human use but seeks to exclude from consideration veterinary, other agricultural and natural resource applications of biotechnology.

The discovery and development of human therapeutics involves a complex set of intermediate goods and services ranging from, scientific instruments and devices to improve the efficiency of the drug discovery process, to advanced information services to manage the vast array of data generated by the drug discovery and development process. Clinical research services are required for the most expensive part of the development process and the manufacturing of biologicals presents particular challenges.

The core technology is biotechnology.[4] There are also a number of complimentary technologies such as the application of information technology to biotechnology (bioinformatics) in which both advanced hardware and sophisticated software is used to generate, manage and analyse the results of the drug discovery and development process. Increasingly nanotechnology (small scale technology) has a place in the biomedical innovation system such as in design of drug development systems, diagnostic devices and instruments.

The geographic boundaries of a sectoral innovation system depend on the characteristics of the system. They may contain firms, which while based locally compete globally, or global firms that compete in regional or national markets. A sectoral innovation system may have certain characteristics that are location specific. As Breschi and Malerba (1997) put it, such systems may have:

> …high degrees of institutional and organisational specificity as a result of historical, path-dependant processes in which the accumulation of idiosyncratic competencies by firms, the working of specific organisations rooted in a country or region and the policies promoted by governments play a fundamental role. (p. 132)

[3] The framework for this section owes much to the suggestions made by Carlsson et al. (2002) towards better defining and measuring the performance of innovation systems. The content of the section reflects an extensive literature on the biomedical sector that includes Arora et al. (2001), Henderson and Cockburn (1996), Henderson, Orsenigo and Pisano (1999), Galambos and Sturchio (1998), Gamberdella (1995), McKelvey and Orsengio (2001), Orsengio (1989) and Sutton (1998).

[4] This can be defined as 'the application of science and technology to living organisms as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services' (from OECD webpage: http://www.oecd.org/document/42/0,2340,en_2649_34537_1933994_1_1_1_1,00.html)

In fact while these local issues are fundamental to explaining the different outcomes of the biomedical systems of Canada and Australia reported on in this paper, it will also be argued that a critical success factor is the degree to which each 'national' system engages with the global industry.

This suggests that the geographic boundary is to some extent endogenous. In order to make inter country performance comparisons, the focus must be on nationally located activities while explicitly incorporating global interactions. This is of special relevance when defining the biomedical 'technological regime' (Malerba and Orsenigo 1993; Nelson and Winter 1982) which while global is one in which the United States has a special role.

2.2 Technological Regime

The concept of technological regime put forward by Breschi and Malerba (1997):

> …is defined by the level and type of *opportunity* and *appropriability conditions*, by the *cumulativeness of technological knowledge*, by the *nature of knowledge* and the means of knowledge *transmission and communication*. [my emphasis] (p. 132)

The biomedical technological regime is one that offers high levels of *opportunity* but at considerable risk. The profits produced by one profitable drug can transform a company from a small start up into a major corporation (e.g. Amgen). More generally however the likelihood of success, even for a drug as it enters human trials is less than 20%.

Appropriability conditions vary between those of final and intermediate goods. Medicines have patent protection for an extended period, up to 20 years, but many intermediate products such as scientific instruments, and specialist computer software will rely on first mover advantage and other market superiorities, even where some form of patent protection is available. This is one of the features distinguishing firms focussing on platform technologies from those developing medicines.

Some aspects of the biomedical *knowledge base* are highly codified (e.g. the chemical composition of a drug), while other aspects of the knowledge base which govern parts of the discovery and product development process are highly specialised and have high levels of tacitness. These differences are important in defining the industry structure (Arora and Gambardella 1994). For instance one of the notable characteristics of the industry is the large number of specialist research-oriented companies linked, both to each other and to large pharmaceutical companies, through alliances (Arora et al. 2001).

Much of the knowledge *transmission and communication* occurs through alliances and networks. For instance pharmaceutical companies can enter into alliances with specialist companies, which reward on the basis of easily codified and measurable outputs such as a successful drug compound (Arora et al. 2001). The specialist developer gains milestone payments and royalties while preserving intact its independence and tacit knowledge base. More difficult to manage are the alliances between specialists in which the tacit knowledge of two or more firms is combined to develop a product. Given the likely divergence between intended and actual

outcomes, the contractual terms are not easy to set in advance. Nonetheless this type of alliance has shown the greatest growth over the last decade, indicating the considerable benefits to be derived from such collaborations (Rasmussen 2004a).

Aspects of the technological regime are location specific. For instance the *cumulativeness* of biomedical technological knowledge, which to a degree is global, has a strong local dimension, such as that embodied in the expertise of particular research institutes or scientific teams. Other aspects of the regime however have a different character, which reflects the dominance of the United States. For instance although each country sets its own *appropriability conditions*, it is those of the United States that largely determine the economic success of any biomedical product. This includes both the patent and product approval processes undertaken by the United States. In essence biomedical products, both proposed and produced by companies domiciled in countries such as Australia and Canada must gain US Patent Office and FDA approval to be economically viable.

2.3 System Dynamics

The dynamics of the biomedical system have several dimensions. The first is the dynamics of the so-called product pipeline, the progression of the final product from discovery to market. The second is that the innovative process for pharmaceuticals has changed radically with the advent of biotechnology and continues to change with the introduction of each new specialist sub-technology, of which bioinformatics and genomics are amongst the most recent. A third dimension is the dynamic interaction of the numerous participants, including universities, pharmaceutical companies, biotechs, venture capitalists and government agencies. As will be argued later in the paper, the effectiveness of this dynamic interaction is important for the performance of the innovation system.

The core of the drug discovery and development process is a linear production model. Before biotechnology, drugs were developed by pharmaceutical companies largely in-house. The advent of biotechnology and related specialist sub-technologies has meant that much of the work now takes place outside the pharmaceutical companies product pipelines in independent specialist firms (Granberg and Stankiewicz 2002). These not only contribute to the development of final product but many are involved in the development of so called ‘platform technologies’. Such technologies are designed to improve the overall capacity and efficiency of the drug development process, e.g. high throughput screening, combinatorial chemistry and gene chips. Integrating the many contributions of such a complex dynamic process involves many feedback loops as success and failure deliver messages to participants about the future prospects of innovative products and processes.

One of the distinguishing features of the biomedical innovation system is that new sub-technologies generally enter the system through start up companies that typically originate from university research laboratories, rather than those of the large established pharmaceutical companies (see for instance, Henderson et al. 1999; Grabowski and Vernon 1994).

As suggested above there is a complex array of participants in the biomedical innovation system. Pharmaceutical companies continue to anchor the activities of

many of the smaller players. They have a key role in supporting the activities of biomedical specialists through collaborations and other alliances as well as being directly involved, not only in the development process, but most importantly in the global distribution and marketing of final products. Universities and research institutes, as the recipients of most of the public funding for research, have a critical role in the holding and developing the basic stock of knowledge. Specialist biotechnology companies are involved in the development and transformation of this knowledge into an array of final and intermediate products and services, often in collaboration with pharmaceutical companies. A range of financial institutions, most notably venture capital companies, but also pension funds and wealthy individuals are involved in financing this transformation. Numerous specialist biotechs provide vital platform technologies to increase the efficiency of the drug development process. Various contract service organisations are available to conduct trials, manufacture and distribute drugs developed by biomedical companies.

Government agencies have a central role, as regulators of the clinical trial process, in providing final product approval for all of the drugs and most other devices produced by the biomedical companies. Government is also active as a supporter of the commercialisation process. In addition to public funding for research, governments in many countries, assist early stage firms to commercialise new discoveries, encourage pharmaceutical companies to partner local firms and provide taxation incentives for investment in R&D. Less targeted government policies may also have an influence on the biomedical system. For instance in Australia, governments have placed emphasis on 'microeconomic reform', which has sought to reduce business costs and deregulate the labour market. Such policies may impact on the cost of conducting research and increase the flexibility of employment arrangements for staff.

2.4 System Performance Measures

Measuring the performance of such a system requires multiple, rather than single measures. Measures are required of the total system performance as well as its components. The key measures of the performance of the biomedical system have been the subject to a deal of empirical research. This literature is well summarised by Noisi (2003). These include measures of the performance of the actors and their interaction with one another and measures of the impact of the institutional and knowledge base. Both system input and output measures are of value in comparing two systems.

As discussed above the biomedical system has a linear product development core and measuring progress of products as they pass down the product pipeline is important in assessing overall performance. Measures relevant to the early stage of the product development process include levels of funding for research, as well as output in terms of scientific publications and patents. Intermediate stage measures include the level of venture capital funding, the multiplicity of collaborations and the number of drugs and other products in various phases of testing. The size of later stage alliance payouts provides an important 'pre-market valuation' of products and technologies. The highest value final products are new medicines, so a critical performance measure is the number of drugs to have gained FDA marketing approval. Finally the size and prosperity of the companies that comprise the innovation system is a further indicator of the value and performance of the biomedical innovation system.

Measures of government support for the innovation system are also relevant to the performance of the system. In addition to public sector funding for R&D mentioned above, this extends to government start up and commercialisation programs and tax incentives for R&D. More difficult to measure is the government's role as a regulator of the IP and product approval environment. As previously suggested the role of the two national governments, Canada and Australia is muted by the dominant place of the US governmental institutions in this process. Companies in both countries rely on access to global markets, the US in particular, for financial viability. Table 1 outlines a possible range of system measures.

Table 1. Possible Biomedical Innovation System Performance Indicators

Knowledge generation	Knowledge diffusion	Knowledge use		
		Early stage	Pre-product	Post product approval
Public R&D on health No. of life science publications No. of biotech patents No. employed on biotech R&D	No. of biomedical technology alliances No. of new start up biomedical companies Value of govt support for diffusion	Business exp on biotech R&D No. of drugs at Phase 1 clinical trial Market value of listed biomedical companies Value of government start up grants	No. and value of drug development alliances No. of drugs in Phase II/III Value of R&D tax incentives Value of alliance payouts	No. of drugs approved No. of other biomedical products at market No. & market value of profitable biomedical companies

Source: Carlsson et al. (2002) and Rickne (2001).

To a significant extent, the empirical measures of system performance are constrained by data availability. The task is made more difficult in this study because the choice is further circumscribed by the need for performance measures of the two countries to be available and comparable over an extended period. Nonetheless the above table of system indicators provides a framework for considering the performance of the two innovation systems.

3. Comparison of the Performance of the Biomedical Innovation Systems for Canada and Australia

This section discusses the comparative positions of Australia and Canada for each of the above factors. It largely draws on data available from secondary sources, except for the work on alliances which has been undertaken by the author.

Table 2 shows the comparative performance of the two systems, Australia and Canada, for a range of indicators grouped under the broad headings used in Table 1 for two three-year periods, 1995–97 and 2001–03 except where noted. The table shows both the value of the indicators for each country and the ratio of the two on a population adjusted basis, except where the low values for Australia render this measure meaningless. The population adjustment is achieved by dividing the ratio of the two indicators comparing Canada to Australia by the ratio of the two populations. The early period, the mid 1990s was selected to coincide with an observed shift in innovation policy in Canada (Rasmussen 2004b). Measures have been compiled over several years to reduce single period volatility. Indicators for the two periods enable some analysis of the dynamics of the two systems to be compared.

Table 2. Biomedical Innovation System Performance Indicators: Australia and Canada

	1995–97*			2001–03*		
Indicator	Australia	Canada	Canada % Aus Pop Adj	Australia	Canada	Canada % Aus Pop Adj
Population (2)	18.3	29.7	100%	19.9	31.6	100%
Knowledge Generation						
Public R&D on health (PPP$m) annual average	501	1050	129%	780	1880	152%
Biopharmaceutical Publications (1)	596	1093	113%	851	1453	107%
Biotech patents issued by USPTO	124	271	135%	239	675	178%
Knowledge Diffusion						
Number of alliances						
University	4	23	355%	10	20	126%
Technology development #	24	123	316%	85	219	162%
Early stage technology development#	9	18	123%	16	55	216%
Early stage drug development#	7	23	203%	14	53	238%
Alliance payouts (US$)						
Early stage drug development#	85	86.9	63%	221	127	36%
Knowledge Use						
Business R&D expenditure						
Health ($PPPm) annual average	205	611	184%	386	1213	198%
Number of alliances						
Late stage technology development	1	5	309%	5	37	465%
Late stage drug development#	1	19	1173%	5	64	805%
Alliance payouts (US$)						
Late stage technology development#	0	225	n.a.	0	1118	n.a.
Late stage drug development#	0	286	n.a.	23	1750	n.a.

Notes: * Except where indicated below:
(1) 1996 and 2001; and
(2) 1996 and 2003.
Technology and drug development alliances with Canadian or Australian firms (excluding universities) as 'developers'. Drug development excludes formulations for alliances that are otherwise unable to be classified as 'early' or 'late' stage.

3.1 Overview of Data Issues

There is a range of data issues that is discussed in more detail in the Appendix. As previously indicated the available indicators are a subset of those suggested in Table 1, being those available on a comparative basis for the two countries. A good deal of emphasis is placed on measures of alliances reflecting the acknowledged importance of alliances in the transfer and commercialisation of biomedical knowledge. Other measures include public expenditure on health R&D as an indicator of government support for biomedical R&D and indicators of research outputs such as biopharmaceutical publications and biotech patents. Indicators of knowledge use include, in addition to those drawn from alliance data, business expenditure on health R&D. Other measures listed in Table 1 such as those measuring the commercial development of the industry such as the number of new companies formed or those

that measure outputs such as the drugs at each stage of the pipeline, are not available on a comparative basis for the two periods.

Data on alliances presented in this paper are extracted from an analysis of the CSES databases based on the Recap database, a specialist biotechnology/pharmaceutical alliance database.[5] Recap classifies alliances by a number of criteria including the type of partner, technologies involved, development stage at signing, disease type and payout size. Two alliance measures are used – the number of alliances formed by Canadian and Australian companies in their role as the developer and the payouts reported for such alliances.

ReCap assigns the alliance parties to one of two roles – 'developer' or 'client'. Generally, the 'client' directs and pays for the work done while the 'developer' undertakes the work and receives payment. Some alliances have high degrees of cooperation, where these distinctions are less clear or where payment is mostly in kind. Some alliances bring together more than one company in the role of client or developer. Nonetheless for most alliances the distinction between the 'client' party and the 'developer' party is clear and Recap classifies the alliance parties on this basis.

The focus of this paper is on the role of the Canadian or Australian company as 'developer' in which knowledge developed or acquired by that company is further generated or used towards the development of a marketable product or service. Although both Canadian and Australian companies are active in the role of 'client', essentially as an 'importer' of overseas technology, this was not viewed as a relevant measure of the process of diffusion or use of locally sourced knowledge. Recap is a global database and makes no attempt to classify alliances by country. The need to identify alliances involving Australian and Canadian companies meant that this was a task was undertaken by CSES.

Alliance payouts are the 'headline' amounts announced at the time of the alliance formation.[6] The size of the alliance as reported, tends to be a total lump sum, incorporating actual upfront payments, as well as contributions contingent on milestone achievements. Generally the announcement of an alliance with a significant payout reflects the fact that the alliance has succeeded in developing a valuable and potentially marketable product. The value of payouts generally increases with the likelihood of FDA approval being achieved. As such it is a better indicator of the value of knowledge use than diffusion.

The classification of alliances in the Recap database enables alliances involved with drug and new technology development to be separately identified. The development of indicators based on alliances formed to further each of these activities was an attempt to differentiate between the roles of biotechs focusing on the development of platform technologies and those working primarily on drug development with particular disease targets in mind. Earlier work has suggested (see for instance Rasmussen and Sweeny 2002) that Australia's performance in the development of

[5] The Recap database used as the source for alliance data collects information on biotechnology and pharmaceutical alliances. For a full discussion of definitions and other aspects of the data sources used for alliances in this paper see the Appendix.
[6] Recorded in ReCap in current US$.

platform technologies, which requires lower levels of development capital, is relatively better than its performance in drug development. As is discussed in more detail in the Appendix, the indicators are not perfect. For instance some alliances are classified as involving both technology and drug development. However the indicators do seem to usefully differentiate between the two roles and appear to confirm the better relative performance of Australian technology companies.

ReCap classifies alliances according to the participating partners – pharmaceutical companies, biotechs and universities (including research institutes). Alliances involving Canadian and Australian universities are considered to be measures of early stage diffusion since they generally involve the transfer of early stage research to the commercial environment, while the drug and technology development alliance indicators are used as measures of development involving only commercial enterprises – either pharmaceutical companies or biotechs.

Where the information is available, ReCap also classifies alliances by 'stage at signing'. The stages are those used to describe the progress of a drug along the development pipeline and include discovery, preclinical, clinical phases I to III, FDA application and approval. This allows the development of indicators of knowledge diffusion compared with its use. For the purposes of developing indicators of 'diffusion' and 'use' the dividing line adopted was entry to clinical trail. Alliances classified post entry to clinical trial are regarded as indicators of 'use' and described as 'late stage' while those in the various stages prior to clinical trial are regarded as indicators of diffusion and described as 'early stage'. Not all alliances are classified according to stage. Over 70% of drug development alliances are classified according in this way while only about 30% of technology alliances are so classified. However of those technology alliances classified by stage, about 80% are classified as 'early stage' – prior to clinical trial. Accordingly the total number of technology alliances is included as an indicator of diffusion, although it is acknowledged that a minority may reflect later stage developments.

3.2 Discussion of Results

Table 2 shows clearly that on a population-adjusted basis the Canadian biomedical innovation system has consistently outperformed its Australian counterpart, and according to most measures, the differences are greatest for *knowledge use*. Over time most of these differences have tended to increase. On the other hand the trends in the differences evident in the indicators of *knowledge generation* and *diffusion* are more mixed with several showing a degree of convergence. This is consistent with the common diagnosis of the Australian biomedical sector which rates its science quite highly but blames poor commercialisation for its under performance (see for instance, DEST 2003; Vitale 2004). This section discusses the indicators of knowledge generation, diffusion and use in more detail.

3.2.1 Knowledge Generation

Standard measures of knowledge generation include the output indicators, publications and patents. This paper uses data on biopharmaceutical publications assembled by Fraunhofer ISI for the OECD. Fraunhofer ISI (2003) and the US Patent Office was the source of biotechnology patents for the two countries. There are a number of relevant input measures of knowledge generation such as public

expenditure on R&D. Table 2 uses the Statistics Canada measure of public expenditure on health R&D for Canada and one developed by Access Economics (2003) for Australia, which has adopted a definition of health R&D expenditure similar to that of Statistics Canada. It encompasses pharmaceuticals as well as other biomedical R&D but may exclude the development of certain biotech platform technologies.

3.2.1.1 Biopharmaceutical Publications

Both countries would claim that their science base is a competitive advantage in establishing a biomedical industry and indeed biopharmaceutical publications is one indicator showing the least difference between the two countries. It is also one in which the gap has closed somewhat with the ratio for Canada to Australia declining from 113% to 107 % between the two periods. However the *Third European Report on Science and Technology Indicators* (European Commission 2003) for the period 1995–99 indicates that Canadian life sciences research is cited more frequently, 8.9 times compared with 6.9 for Australia, indicating perhaps that it is closer to the cutting edge.

3.2.1.2 Biotechnology Patents

The number of biotech patents issued by the US Patent Office by inventor country over the period 2001–03 totalled 239 for Australia compared with 675 for Canada, or 178% of the Australian level on a population adjusted basis. This represented an increase over the earlier period when the ratio was 135%. An analysis of patent data prepared by CHI (Narin et al. 2000) shows, for the period 1994–98, a similar pattern to that of scientific papers. Canadian patents in the pharmaceutical and biotechnology sectors tend to be cited more frequently than Australian ones suggesting that they reflect more valuable technological advances (Narin et al. 2000, p. 24). This analysis concluded that while Australian science is world class, it does not have the same impact as Canadian life sciences.

3.2.1.3 Public Spending on Health R&D

The most comparable measure of public expenditure on biomedical R&D for the two countries is on health R&D. This shows Canada's average annual expenditure for the period 1995-97 was more than twice as high, $(PPP)1050m as Australia's, $(PPP)501m. Despite high growth in expenditure in both countries, this ratio had grown on a population adjusted basis from 129% for the earlier period to 152% for the period 2001-03.

3.2.2 Knowledge Diffusion

The diffusion of biomedical knowledge is particularly complex given the large number of specialist firms contributing to the production of biomedical products. As suggested in this paper and elsewhere (see for instance, Hagedoorn et al. 2000; Orsengio et al. 2001) alliances can play a key role in the diffusion process.

3.2.2.1 Alliances

Table 2 provides data for a range of alliance indicators according to party involved and purpose. Indicators of technology and drug development alliances are those formed by biotechs and pharmaceutical companies. Alliances formed by universities generally reflect an early stage in the diffusion of knowledge from the research labs to

the commercial sector. In the early period the number of alliances reported for universities in Canada was almost six times the level in Australia, 355% on a population adjusted basis. However by the later period this indicator had fallen to 126% largely as result of more active alliance formation by Australian universities. The population adjusted indicator for total technology alliances has also declined from 316% to 162%, so that while Canadian out performance remains, this appears to suggest better relative performance by Australian companies in the later period and is consistent with the Australian perceptions reported earlier. The indicator however for early stage technology alliances suggests a widening gap in performance with the ratio increasing from 123% to 216%, although the low proportion of technology alliances classified by stage may affect the reliability of this measure.

A high proportion of drug development alliances are classified according to 'stage at signing' so the alliance indicators for early and late stage are likely to be more reliable. The ratios of the number of early stage drug development alliances have increased between the two periods from 203% to 238% indicating divergence between the two countries. The indicator of alliance payouts has however moved in the other direction and is also below 100% suggesting out performance by Australian compared with Canadian firms. However the meaning attaching to payout values for alliances at an early stage when the product is a considerable distance from market is questionable and the result may also be affected by the small number of early stage alliances reported with payout values. Accordingly this is probably a less reliable indicator of diffusion than the number of alliances.

3.2.3 Knowledge Use

As set out in Table 1 there is a range of possible measures to indicate performance in the use of knowledge. The key knowledge output measure for the biomedical industry is the number of drugs that receive FDA approval or are at an advanced stage in the product pipeline. While these have been compiled for the recent period and are discussed further below, they are not available for the earlier one. Accordingly this paper focuses on a series of later stage input measures. The production of drugs is extremely expensive (Charles River Associates 2004; Di Masi et al. 2003) and the size of the investment in the drug development process (including related technologies) is a good measure of the expected market value of generated and diffused knowledge actually used in the biomedical production process.

Two measures of this value have been adopted in this paper. One is business expenditure on health R&D and the other is alliance payouts. The expenditure on health R&D captures expenditure on pharmaceuticals and clinical research but may exclude some related biotech R&D. The second measure is alliance payouts.

The value of later stage payouts for drug development and technology alliances are provided in Table 2. Such payouts, especially when sizeable, indicate that the development of the relevant drug or technology has reached a stage where it is both valuable and close to market. The number of late stage technology and drug development alliances is also presented in Table 2 as an indicator of knowledge use.

3.2.3.1 Business R&D Expenditure

The measure of business expenditure on health R&D shows an increasing disparity between Canada and Australia. The ratio of the indicator for Canada and Australia

increased from 184% as the average for the earlier period to 198% for the later period. These ratios reflect very different levels of business support for the industry in the two countries, with the level of business R&D on health for the period 2001–03 averaging $PPP386m p.a. in Australia compared with $PPP1213m per annum in Canada. These differences are even more pronounced for alliance payouts.

3.2.3.2 Alliances

Australia has no late stage payouts recorded for either drug or technology alliances for the period 1995 to 1997, while Canada has $225m and $286m respectively. Australia has only one drug development payout of $23m recorded in the period 2001 to 2003 while Canada has 23 alliances with payouts totalling $1750m. Similarly Australia has no late stage technology alliance payouts while for Canada the total is $1118m for the period 2001 to 2003. This indicates that the Canadian system has attracted a much higher level of support from large pharmaceutical and biotech companies, which perhaps reflects the relative commercial value of the knowledge being transferred within the two biomedical innovation systems.

The numbers of later stage alliances for technology and drug development are both overwhelmingly in favour of Canada. The number of drug development alliances is 8 times the number in Australia on a population adjusted basis for the period 2001-03. The ratio for technology alliances is 465%, representing a substantial difference but a smaller one than for drug development. The ratios suggest some convergence for the number of drug development alliances and divergence for technology between the two time periods, but the gap for drug development remains so large it makes this relatively meaningless.

One possible explanation for this overwhelming difference may be the proximity of the United States to Canada. However the alliance data suggests otherwise. For later stage drug development alliances, the proportion of total payouts recorded for alliances between Canadian biotechs and European pharmaceutical companies for the period 2001–03 was 63% compared with 25% for the United States. The number of alliances was more evenly split with 39% for Europe and 27% the United States.

Another factor is that the number of drug development alliances and value of payouts reflects the number of later stage projects in which to invest. The following data in Table 3 shows the number of drugs at each phase in the clinical trial process for 2002.

Table 3. Drugs in the Pipeline 2002

	Pre Clinical	Phase 1	Phase II	Phase III	Total
Australia	88	13	13	2	116
Canada	246	34	44	19	343

Source: R&D Focus; IMS Health, quoted in OECD (2004).

The drug pipeline for Canada is substantially larger than that for Australia, with about three times as many drugs in total. The difference is most marked at the critical phase III, at which stage the drug is most likely to gain FDA approval, with 19 for Canada compared with only 2 for Australia.

3.3 Possible System Dynamics and Feedback Mechanisms

In the section above in which 'system dynamics' was discussed, three dimensions were identified. One was the dynamics of the product pipeline. A second was the dynamics of changing technology and the third was the dynamics of the interaction of the participants in the biomedical innovation system. Some observations and conjectures about these dynamics are possible from the empirical results. The results suggest that the Canadian biomedical innovation system has been outperforming its Australian counterpart across each of the three areas of knowledge generation, diffusion and use for both periods discussed above. The changing relative position of the two systems across these three areas sheds some light on their respective dynamics.

Relative to Canada, Australia has appears to have closed the gap according to some measures of knowledge generation and diffusion. In biopharmaceutical publications, the number of university alliances and one of the measures of technology alliances, the ratio of Canada to Australia has narrowed indicating that Australia's activities in these early stage areas have grown more rapidly than Canada on a population adjusted basis.

However Canada's dominance compared with Australia in knowledge use in the two periods is undiminished. The indicators of business R&D and alliance numbers and payouts for both technology and drug development alliances are not only heavily in Canada's favour, but the gap appears to be growing.

There are at least two broad explanations for these dynamics. The first is that Australia's biomedical innovation system is simply an immature version of the Canadian system. Support for this view might come from the converging knowledge generation and diffusion measures, indicating relative strength in the activities of the universities, in alliances and publications, and the growing number of technology alliances. Catching up in the indicators of knowledge use, it could be argued, is just a matter of time, while these early stage activities have an opportunity to work their way through the innovation system. However this explanation assumes a simple linear innovation system in which knowledge flows naturally over time from generation to diffusion to use.

An alternative explanation more consistent with the results and the theory of innovation systems suggests that the Australian biomedical sector is suffering from systemic failure and that in contrast Canada is benefiting from significant positive feedback effects. Firstly the indicators are consistent with the dynamics suggested by innovation systems theory in which relatively small differences in certain system inputs can result in large differences in outcomes, arising from the impact of feedback loops and other non linear system dynamics. For both periods, small differences between Australia and Canada in knowledge generation and diffusion appear as significant differences in knowledge use.

In innovation systems terms, the use of knowledge appears to be more effective in Canada than Australia, with business R&D expenditure, and the number and value of later stage alliances substantially higher in Canada. In contrast Australia's efforts in knowledge generation and diffusion appear to be stalling on the point of knowledge

use. It is instructive to observe that Australia's 2001–03 indicators of knowledge generation and diffusion (in Table 2) are of a similar order of magnitude to those of Canada in 1995–97, in yet most of the Australian 2001–03 indicators of knowledge use remain substantially below the Canadian 1995–97 levels. In particular later stage alliances are well below their Canadian levels of six years earlier. Later stage drug development alliance payouts (current dollars) are $23m for Australia for the period 2001–03 compared with $286m for Canada in 1995–97. There are 5 Australian and 19 Canadian later stage drug development alliances for the two periods 2001–03 and 1995–97 respectively.

This suggests that catching up is not simply a question of time but one that requires fundamental issues in the Australian system to be addressed. As previously argued, in an innovation system as complex as the biomedical innovation system, alliances play a central role in integrating the activities of specialists and transferring knowledge to enable new products and processes to be created and this is the indicator which shows the most significant difference.

The financial implications for the innovation system of well-funded later stage alliances, an indicator of *knowledge use*, are likely to be significant, creating positive feedback loops for other financial participants. The magnitude of pharmaceutical alliance commitments would provide domestic capital participants with confidence that exit opportunities were available, reinforcing the inclination of venture capitalists and others to invest in the industry at a somewhat earlier stage. The Canadian biomedical sector has enjoyed excellent support from the business sector with business health R&D around twice the Australian level on a population adjusted basis and with the differential growing.

4. Conclusion

The purpose of this paper has been to apply the theoretical framework provided by innovation systems theory to a comparison of the performance of the biomedical systems of Australia and Canada. An attempt has been made to capture some of the dynamics of the two systems by comparing their performance over the period since the mid 1990s. The indicators were selected to demonstrate the relative performance of the two systems in the generation, diffusion and use of knowledge according to a framework suggested in Carlsson et al. (2002).

The indicators demonstrate that even on a population adjusted basis the Canadian biomedical system has been outperforming its Australian counterpart at least since the mid 1990s. They suggest that this out performance is most pronounced for those indicators measuring the use of knowledge and that this has been evident since the mid 1990s. Further the indicators suggest that this differential in performance particularly with respect to knowledge use has increased between the two periods for which the indicators have been assembled.

This provides evidence to support the proposition that the dynamics of the biomedical systems of the two countries have been consistent with innovation systems theory. In particular the systems appear to be exhibiting self-reinforcing feedback mechanisms in which relatively small differences in the generation of knowledge lead to significant differences in the success with which it is used.

Appendix: Data Sources

Public R&D on Health is by funding source and includes funding by federal, provincial and universities. R&D expenditure on health is sourced for Australia from Access Economics (2003) and an ABS special data request for 2003. The Australian series has been structured to be comparable with the Canadian data and may include some non-biotech related R&D expenditure on pharmaceuticals The Canadian data was sourced from Canada: Gross domestic Expenditures on R&D in the health field 1988 to 2003 Statistics Canada 88F0006XIE-No. 014. The measures of purchasing power parity where derived from the OECD PPP indices available at http://www.oecd.org/dataoecd/61/56/1876133.xls

Business R&D expenditure on health is from the same source as that for public R&D expenditure on health discussed above. An alternative measure available from the Canadian Biotechnology Use and Development Survey (see Statistics Canada Cat No 88F0006XIE2003005) for estimates of biotech R&D on human health had no counterpart in Australia and accordingly could not be used. The measures of purchasing power parity where derived from the OECD as above.

Bio pharmaceutical publications are sourced from data assembled by Fraunhofer ISI for the OECD. (Fraunhofer ISI 2003.) Biotech patents are those issued by the US Patent and Trademark Office for Class 435 Chemistry: Molecular Biology and Microbiology for inventor country and available from the US PTO website http://www.uspto.gov. This is the indicator used by Allansdottir et al. (2002) in their study of European biotechnology industry.

The data source for alliances is the speciality alliance database established by ReCombinant Capital (ReCap) in 1988 and accessible at www.recap.com. It attempts to collect comprehensive, worldwide alliance information from press releases, SEC filings and company presentations. The information is limited to those alliances that are announced publicly and the details that those announcements contain. This may mean that the more commercially sensitive information is withheld or not reported until there are some positive results. However public disclosure rules generally require listed companies to announce information which is price sensitive. In other cases companies find it in their interests to release information about alliances as a sign of progress towards their strategic goals. For this reason it can be expected that information about most significant alliances is released and therefore available to ReCap. Because of the nature of the source material e.g. SEC filings, it can take an extended period (up to 12 months) for alliances to be listed on ReCap. Accordingly listings for the most recent period can be incomplete.

Alliances in ReCap are broadly defined and include asset purchases and acquisitions as well as partnerships that involve collaboration, licensing, joint ventures, joint development, distribution, marketing and manufacturing. Data on transactions classified as company mergers and acquisitions or primarily asset sales involving whole businesses were excluded from the analysis on the basis that they were not alliances as generally defined in the literature (OECD 2001).

Most of the alliances in the database involve biotechs, pharmaceutical companies and universities (including research institutes), but also include a small number of 'non-medical' organisations, which were excluded from the analysis.

Data on drug development alliances were compiled from alliances classified according to disease type. This includes a very small number of alliances involving diagnostic devices on the basis that their development is often closely associated with drug development. In addition

their exclusion would have no material impact on the results. Similarly technology alliances are those classified by technology. Most of the technologies listed are platform technologies such as screening or drug class technologies such as monoclonal antibodies. Two listed technologies, 'generics' and 'in licensed' did not seem appropriate and were excluded.

As discussed in the body of the paper alliances were classed as 'early' or 'later' stage on the basis of their classification by ReCap at 'stage on signing'. However alliances classified as 'formulations' were excluded on the basis that they could not be properly classed according to stage.

References

Access Economics, 2003. Exceptional Returns: The Value of Investing in Health R&D in Australia. Report to Australian Society of Medical Research (AMSR), Sydney.

Allansdottir, A., Bonaccorsi, A., Gambardella, A., Mariani, M., Orsenigo, L., Pammolli, F., Riccaboni, M., 2002. Innovation and competitiveness in European biotechnology. Enterprise Papers No. 7, Enterprise Directorate-General, European Commission, Luxembourg.

Arora, A., Gambardella, A., 1994. The changing technology of technological change: General and abstract knowledge and the division of innovative labour. Research Policy, 23, 523–532.

Arora, A., Fosfuri, A., Gambardella, A. 2001. Markets for Technology: The Economics of Innovation and Corporate Strategy. MIT Press, Cambridge, Mass.

Breschi, S., Malerba, F., 1997. Sectoral innovation systems: Technological regimes, Schumpeterian dynamics and spatial boundaries. In Edquist, C. (Ed.), Systems of Innovation: Technologies, Institutions and Organizations. Thomson Learning, Stamford, Conn.

Carlsson, B., (Ed.), 2002. Technological Systems in the Bio Industries: An International Study. Kluwer Academic, Boston.

Carlsson, B., Jacobsson, S., Holmen, M., Rickne, A., 2002. Innovation systems: Analytical and methodological issues. Research Policy, 31, 233–245.

Charles River Associates, 2004. Innovation in the Pharmaceutical Sector. Study undertaken for the European Commission, ENTR/03/28, London.

Department of Education, Science and Training (DEST), 2003. Mapping Australian Science and Innovation: Main Report. Canberra, available at: http://www.dest.gov.au/mapping/

Department of Education, Science and Training (DEST), 2001. Backing Australia's Ability: An Innovation Action Plan for the Future. Canberra, available at: http://backingaus.innovation.gov.au/default2004.htm

DiMasi, J., Hansen, R., Grabowski, H., 2003. The price of innovation: New estimates of drug development costs. Journal of Health Economics, 22, 151–185.

Edquist, C., (Ed.), 1997. Systems of Innovation: Technologies, Institutions and Organizations. Pinter, London.

European Commission, 2003. Third European Report on Science and Technology Indicators 2003. Luxembourg.

Fraunhofer ISI, 2003. Bibliometric Data. SCI via STN, OECD, Paris.

Freeman C., 1987. Technology Policy and Economic Performance: Lessons from Japan. Pinter, London.

Freeman, C., Soete, L. 1997. The Economics of Industrial Innovation. MIT Press, Cambridge, Mass.

Galambos, L., Sturchio, J.L., 1998. Pharmaceutical firms and the transition to biotechnology: A study in strategic innovation. Business History Review, 72, 250–278.

Gamberdella, A., 1995. Science and Innovation: The US Pharmaceutical Industry During the 1980s. Cambridge University Press, Cambridge.

Government of Canada, 2002. Achieving Excellence: Investing in People, Knowledge and Opportunity: Canada's Innovation Strategy. Prime Minister's Office, Ottawa, available at http://www.innovationstrategy.gc.ca/gol/innovation/site.nsf/en/in04135.html

Grabowski, H., Vernon, J., 1994. Innovation and structural change in pharmaceuticals and biotechnology. Industrial and Corporate Change, 3, 435–449.

Granberg, A., Stankiewicz, R., 2002. Biotechnology and the transformation of the pharmaceutical value chain and innovation system. Research Policy Institute, Lund University, Sweden.

Hagedoorn, J., Link, A., Vonortas, N., 2000. Research partnerships. Research Policy, 29, 567–586.

Henderson, R., Cockburn, I., 1996. Scale, scope and spillovers: The determinants of research productivity in drug discovery. Rand Journal of Economics, 27, 32–59.

Henderson, R., Orsenigo, L., Pisano, G., 1999. The pharmaceutical industry and the revolution in molecular biology: Interactions among scientific, institutional and organizational change. In Mowery, D., Nelson, R. (Eds.), Sources of Industrial Leadership: Studies of Seven Industries. Cambridge University Press, Cambridge.

Kline, S., Rosenberg, N., 1986. An overview of innovation. In Landau, R., Rosenberg, N. (Eds.), The Positive Sum Strategy: Harnessing Technology for Growth. National Academy Press, Washington DC.

Lundvall, B., 1992. National Systems of Innovation: Towards a Theory of Innovation and Interactive Learning. Pinter, London.

Lundvall, B., Johnson, B., Anderson, E., Dalum, B., 2002. National systems of production, innovation and competence building. Research Policy, 31, 213–231.

Malerba, M., Orsenigo, L., 1993. Technological regimes and firm behaviour. Industrial and Corporate Change, 2, 45–71.

McKelvey, M., Orsengio, L. 2001. Pharmaceuticals as a sectoral innovation system. Paper prepared for the ESSY Project (European Sectoral Systems of Innovation), November.

Metcalfe, J.S., 1995. Technology systems and technology policy in an evolutionary framework. Cambridge Journal of Economics, 19, 25–46.

Nakicenovic, N., 2004. Transitions to new technologies. In IAASA TNT 2004 Research Plan. International Institute for Applied Systems Analysis (IIASA) A–2361 Laxenburg, Austria, available at (December 2004): http://www.iiasa.ac.at/Admin/OSR/RP2004/tnt.pdf?sb=2

Narin, F., Albert, M., Kroll, P., Hicks, D., 2000. Inventing our Future: The link between Australian patenting and basic science. Report to the Australian Research Council, CHI Research, available at: http://www.arc.gov.au/pdf/00_02.pdf

Nelson, R., 1993. National Innovation Systems: A Comparative Analysis. Oxford University Press, New York.

Nelson, R., Nelson, K., 2002. Technology, institutions and innovation systems. Research Policy, 31, 265–272.

Nelson, R., Winter, S., 1982. An Evolutionary Theory of Economic Change. Belknap Press, Cambridge, Mass.

Niosi, J. 2003, 'Alliances are not enough explaining rapid growth in biotechnology firms', *Research Policy*, vol. 32, pp. 737–750.

Organisation for Economic Cooperation and Development (OECD), 2004. Study on the National Innovation System in the Spanish Biopharmaceutical Sector. Sectoral Case

Studies in Innovation: Pharmaceutical Biotechnology, DSTI, OECD, Paris, available at: http://www.oecd.org/document/29/0,2340,en_2649_34273_15709661_1_1_1_1,00.html

Organisation for Economic Cooperation and Development (OECD), 2003. Biotechnology Update. No. 12, March, Internal Coordination Group for Biotechnology, OECD, Paris.

Organisation for Economic Cooperation and Development (OECD), 2001. Biotechnology Statistics in OECD Member Countries: Compendium of Existing National Statistics. Working Party of National Experts on Science and Technology Indicators, Paris.

Orsenigo, L., 1989, The Emergence of Biotechnology. Pinter, London.

Orsenigo, L., Pammoli, F., Riccaboni, M., 2001. Technological change and network dynamics: Lessons from the pharmaceutical industry. Research Policy, 30, 485–508.

Rasmussen, B., 2004a. Innovation and industry structure in the biomedical industry: Some preliminary results. Paper presented at the Merck Company Foundation Program on Pharmaceutical Policy Issues, Policy Conference 2004, Lafayette Hill, Pennsylvania, 1–2 March, also Pharmaceutical Industry Project Working Paper No.17, February, CSES, Victoria University, Melbourne.

Rasmussen, B., 2004b. The biomedical sectors in Australia and Canada: Comparative policy analysis. Pharmaceutical Industry Project Working Paper No. 22, July, Centre for Strategic Economic Studies, Victoria University, Melbourne.

Rasmussen, B., Sweeny K., 2002. Development paths for Australian biotechnology firms. Pharmaceutical Industry Project Working Paper No. 8, September, Centre for Strategic Economic Studies, Victoria University, Melbourne.

Rickne, A., 2001. Regional characteristics and performance: Evidence from biomaterials firms. In Carlsson, B. (Ed.), New Technological Systems in the Bio Industries. Kluwer Academic, London.

Sutton, J., 1998. Technology and Market Structure: Theory and History. MIT Press, Cambridge, Mass.

Vitale, M., 2004. Commercialising Australian Biotechnology. Australian Business Foundation, Sydney.