Value creation and investor performance of the Australian drug development biotech sector

by

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ABSTRACT

Australia has long been lauded as a biotechnology leader and consistently been ranked in the top five biotechnology nations worldwide, based on the *Scientific American Worldview* biotechnology scorecard. For the first time, this thesis seeks to objectively measure the performance of the Australian biotech sector.

This has required addressing and resolving several long-standing definitional problems around what biotechnology is and what biotech firms are. In examining and ultimately resolving these problems, the thesis makes several conceptual contributions, which form Part A of the thesis. Part B then uses the definitions and the performance metrics developed in Part A to address the research question: *Do Australian drug development biotech firms create value and deliver attractive investor returns?*

Part A first examines the definitional chaos that has surrounded the biotech industry. To break through the conceptual/definitional roadblock, I focus on those firms engaged in the most prevalent and important application of biotechnology, which is pharmaceutical drug development. Using business model, value chain and market lenses, I derive a comprehensive new definition for drug development biotech firms, which I call 'DDB' firms. DDB firms (DDBs) are defined as technology-agnostic, pre-commercial intermediaries in the pharmaceutical value chain, whose market is the demand from pharmaceutical firms for new drug pipeline. I refer to this as the 'Pre-commercial Intermediary' (PCI) view of the biotech firm.

The PCI view frees the biotech firm definition from any specific technology definition and breaks the nexus with commercial-stage firms, the inclusion of which in industry datasets has long confounded firm performance and biotech industry analysis. I also use the PCI conception as a springboard for redefining all biotech firms, merging the concept of 'dedicated biotechnology firm' (DBF) and outlining a classification schema for various types of DBF, based on industrial focus.

I tackle the problem of performance measurement for biotech firms, armed with the PCI view and with a focus on DDBs. I explore the notion of 'pipeline value' (PV) and its relationship to the established metric, enterprise value (EV). I develop a novel value creation metric, which I call VCR, calculated as growth in PV over time, minus the cash cost of delivering that growth. The notion that value growth occurs when candidate drugs progress in the drug development pipeline has long been appreciated. However, that value creation performance can be represented as a measurable construct, VCR, is a new idea.

An important principle underpinning the PCI view and VCR is that investor returns are a critical consideration for DDBs. Unlike profitable commercial firms, DDBs are generally loss-making and rely largely on the willingness of investors to continue to fund a loss-making business in pursuit of the

intangible value created by the progress of candidate drugs, which is realised as capital growth. Without attractive capital returns that are aligned to the level of risk, investors will not invest in DDBs. VCR represents one measure of a DDB's efficacy and efficiency in moving candidate drugs forward, but it is not a direct measure of investor return. Therefore, I introduce share price (SP) growth as an important established measure of performance, with investor return calculated as the compounded annual growth rate, equivalent to the internal rate of return (IRR) from the investment.

In Part B, I apply these performance metrics to the Australian public DDB sector. I use the 15-year period from 2003 to 2018 as the assessment period and identify 40 ASX-listed DDB firms for performance analysis, based on pre-stated inclusion and exclusion criteria. The results clearly show that the Australian DDB sector failed to create value over the 15-year period, as measured by VCR. Further, the average IRR from a portfolio of the 40 firms over the 15 years was negative (-6.2%), with the portfolio investor losing half their principal over the period. I discuss possible reasons why so many Australian DDBs failed and identify several strategic missteps. I also introduce the concept of the 'Red Queen', a factor that seeks to capture the time-sensitive nature of drug development.

The results do not support the belief that Australia is a global biotechnology leader, at least based on drug development. Compared with the US, the Australian DDB sector is small and weak. In 2018, the sector comprised 38 firms with a total market capitalisation of $4.8 billion, equivalent to 3% of the US sector value; moreover, the Australian average firm value was only 13% (one eighth) of the US average firm value.

Using data from the performance analysis, I conclude that VCR has validity as a predictor of IRR performance and potential utility as a short-term measure of firm performance, as it embeds investor- and management-relevant factors, such as candidate drug progress and efficient use of investor funds.

In the final chapter, I present the limitations, implications and conclusions of the research. Important implications for theory, policy and practice are discussed. The chapter closes with the conclusions and a summary of the contributions of the research. A primary contribution of the research is that – for the first time – it answers the question: Do Australian drug development biotech firms create value and deliver attractive investor returns? Based on this research, the answer is "no".

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Peter Molloy

DECLARATION

This PhD thesis:

- Contains no material that has been accepted for the award to the candidate of any other degree or diploma.

- To the best of the candidate's knowledge, contains no material previously published or written by another person, except where due reference is made in the text of the examinable outcome.

- Discloses the relative contributions of the respective workers or authors where the work is based on joint research or publications.

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List of Abbreviations and Definitions

ASX	Australian Securities Exchange; the main Australian stock market
Big biotech	A biotech firm that has evolved from a pre-commercial intermediary to a commercial enterprise that generates at least US$1 billion in revenues
Big Pharma	Large multinational pharmaceutical firms
Biologics	Biologics or biologic drugs are defined as drugs that are derived from biological sources and comprised of at least 42 peptides (protein subunits); they are distinguished from 'small molecule' drugs
Biopharmaceutical & Biopharma	Biopharmaceutical technically refers to biologic drugs that are the product of bioprocessing techniques, but increasingly has been used to refer to all drugs; and its foreshortened variant 'biopharma' frequently is used to refer to all firms in the drug development value chain
BPCI	US Biologics Price Competition and Innovation Act (BPCI Act) of 2010 that conferred 12 years of commercial protection on biologic drugs in the US
BR	Burn rate; the annual operating cash outflow for a biotech firm
CEO	Chief executive officer
CSIRO	Commonwealth Scientific & Industrial Research Organisation, Australian PRO
DBF	Dedicated biotechnology firm; the definition of a biotech firm as first expounded by Powell; also referred to as the 'Powell definition'
DCF	Discounted Cash Flow analysis; projection of the commercial cash flows from a drug, discounted by a cost of capital interest rate, the development costs to reach approval and the risks associated with each development stage
DDB	Drug development biotech firm, defined as an independent, R&D-intensive, pre-commercial enterprise born after 1976 that primarily creates value as an intermediary in the pharmaceutical value chain
DDC	Drug development commercialisation firm – a commercial stage firm that started life as a DDB
DXB	Diagnostic development biotech firm; a pre-commercial DBF focused on development of IVD and other diagnostic products for human (and animal) use
EV	Enterprise value; equals MV + market value of debt – cash and equivalents

FDA	US Food and Drug Administration
FIPCO	Fully-integrated pharmaceutical company; business that undertakes all aspects of drug development and commercialisation
GFC	Global financial crisis of 2008-2009
GMO	Genetically modified organism; a common application of biotechnology is to insert genes into plants, bacteria or other organisms to modify genetically-expressed characteristics and create what are referred to as GMOs
IRR	Internal rate of return; a technique for calculation of the annualised return on investment from a stock or portfolio
IVD	*In vitro* diagnostics; diagnostics, usually in the form or kits, that are used to detect disease states in humans (and animals)
MDB	Medical device development biotech firm; a DBF focused on development of medical devices for human (and animal) use
MV	Market value of a public firm
NBT	The journal, *Nature Biotechnology*
NME	New molecular entity; a previously untested drug
NPV, rNPV	Net Present Value and risk-adjusted Net Present Value; most widely used technique for valuation of candidate drugs; based on DCF
OECD	Organisation for Economic Co-operation and Development
OECD paradigm	View of biotechnology as a set of techniques and technologies that is unrelated to industrial application
PAB	'Promissory aspirations for biotechnology'; the drive to see the successful industrialisation of biotechnology and creation of a Utopian bioeconomy
PCI view	Pre-commercial intermediary view: where biotech firms are conceptualised as exclusively pre-commercial participants in an industrial value chain
Phase 1 trial	Drug trial in healthy human volunteers to establish safety and maximum tolerated dose
Phase 2 trial	Drug trial in a small number of patients to establish the safe and effective dose of a drug and to demonstrate efficacy in the target disease
Phase 3 trial	Drug trial in a sufficiently large number of patients to confirm safety and

	efficacy prior to filing for marketing approval
Pisano definition	Biotech firm definition as elaborated in *The Promise, the Reality, and the Future of Biotech*, a book by Gary Pisano, and explained in Chapter 5
PV, PVG	'Pipeline value' (PV), for pre-commercial public firms, is equivalent to enterprise value (EV) and for DDBs is calculated as the market value of the firm minus cash reserves; PVG is the growth in PV over time
R&D, RDE	R&D refers to research and development; RDE refers to R&D expenditure
rDNA	Recombinant DNA; DNA created by recombination of genetic material from different sources, creating novel genetic sequences
RNA	Ribonucleic acid; a single-stranded form of DNA that carries genetic information
Red Queen	A concept proposed in Chapter 10 that recognises the time-sensitivity of DDB drug development
RTB	Research tools biotech firm; DBF focused on developing devices, techniques and equipment that can help researchers elaborate disease pathways, identify drug targets and otherwise assist research in various fields
Small molecule drug	Drug that is the product of synthetic chemistry or derived from natural sources, and not comprised of peptides or other biological material
SI	Number of shares on issue by a firm at any time
SP	Share price of a public firm
Swinburne DBF Dataset	A database, developed at Swinburne University of Technology, consisting of data for all Australian biotech firms from 2003 to 2014
TA/TAQ	TA is the technology asset that a firm leverages to develop drugs; TAQ is its quality or potential for valuable drug development, as discussed in Chapter 7
UCSF	University of California San Francisco
US	United States of America
VC	Venture capital or venture capital firm, depending on context
VCR	'Value creation' measured as PVG, minus BR (the annual operating cash cost)

Part A: Conceptual Foundations

Chapter 1. Overview

1.1. Background

My experiences working in the biotechnology and pharmaceutical industry have given me perspectives and insights that have contributed significantly to both the conceptual foundations developed in Part A of this thesis and the direction of the empirical research in Part B. Therefore, in order to explain my frame of reference and motivation for this thesis, I would like to describe those experiences, perspectives and insights.

Soon after graduating from the University of Melbourne in 1976 with a Bachelor's degree in science, I moved to Adelaide, where I completed a Master of Business Administration degree at the University of Adelaide. I also started work with an Australian pharmaceutical firm, FH Faulding & Co Ltd (Faulding), which had its headquarters in Adelaide. During my 12 years working for Faulding, I was fortunate to work in a variety of management roles and to be exposed to a wide range of disciplines and ideas. Initially, I worked as a product manager, responsible for the marketing strategy of several brands and product categories within the company's pharmaceutical division, including prescription drugs, hospital products and retail pharmacy medicines. After five years, at the age of 29, I became the general manager of that division and for four years, oversaw a period of growth and development of the business. During my nine years in the pharmaceutical division, I launched or helped launch 20 products in Australia and executed eight licensing deals with international firms, mostly to acquire new products or technologies.

In 1987, Faulding acquired a controlling interest in a US-based drug development biotech firm and moved me to Boston, where I became the chief operating officer and acting CEO. This was my first experience working with what people referred to as a 'biotechnology' company. Two years later, Faulding also acquired a scientific equipment distribution business in Melbourne and moved me back to Australia to become its general manager.

I left Faulding in 1990 and moved to Sydney as the managing director of the Australian subsidiary of an international pharmaceutical company, Pharmacia. I worked in that role for five years and for three of those years, was enrolled as a part-time PhD (management) candidate in the Graduate School of Business at the University of Sydney. Since my days as a product manager at Faulding, I had become keenly interested in product positioning and the drivers of market evolution in the pharmaceutical industry, so this was the focus of my early PhD research in Sydney.

After Pharmacia merged with a US-based pharmaceutical company, Upjohn, I moved back to the US as vice-president for international strategic marketing for the merged entity, which became known as Pharmacia & Upjohn. This role saw me responsible for strategic planning for the company's extensive drug portfolio across 23 countries. This move caused me to suspend (and ultimately to terminate) my PhD candidature at Sydney University.

In 1998, I left Pharmacia & Upjohn and returned to Australia, where I was offered and accepted the role of CEO of a Melbourne-based biotech firm, Florigene, which was using genetic engineering to manipulate the colour and other characteristics of flowers, with the primary goal being to produce a 'blue' rose. This was my first exposure to a biotech business outside the pharmaceutical industry and it gave me some valuable insights into how different the value chains can be for applications of biotechnology in different fields or industries.

Approximately 18 months later, Florigene was sold. I then moved back to the US as the CEO of another biotech company, SLIL Biomedical Corp, based in Madison Wisconsin. This company was a small private (not publicly traded) drug development biotech business engaged in discovering and developing new drugs to treat cancer. In contrast to Florigene, my experiences in this biotech firm were highly aligned with the pharmaceutical industry and I started to appreciate the important role of dedicated biotech firms as suppliers of new drugs to large pharmaceutical companies.

As CEO, my principal responsibilities were to secure funding from investors to support the company's ongoing R&D program and to do licensing deals with pharmaceutical firms for the company's candidate drugs in development. When I left SLIL in 2002, the company had one cancer drug in human clinical studies, two pharmaceutical licensing deals in place and sufficient funding for 18 months. While the firm was loss-making throughout, its valuation doubled over the period, based on investment pricing.

In 2002, I was recruited as the managing director and CEO of another drug development biotech firm called Biota Holdings Ltd (Biota). This was an Australian ASX-listed (public) biotech business that was developing new drugs for viral diseases, such as influenza, the common cold, HIV and hepatitis C infection. Born in 1985, Biota was Australia's first and oldest ASX-listed drug development biotech firm. While Biota had its headquarters in Melbourne, it also had substantial R&D operations in California, where I was based. Part of the rationale for a US-based CEO for an Australian company was that the company saw pharmaceutical partnering as crucial to future value creation by the firm. With virtually all the major pharmaceutical firms having their headquarters or global partnering functions in the US, it was essential to be close to the 'market' for partnering deals.

During my three years and six months at Biota, the R&D team successfully moved forward several programs from the discovery stage into preclinical development and some into human clinical

studies. We also executed several valuable pharmaceutical partnerships around these programs. At all times, Biota saw itself as an intermediary in the pharmaceutical value chain, developing drugs to a point where they could be licensed to pharmaceutical partners. Despite the fact that Biota consistently made losses over the period, the market value of the company grew from $30 million to around $300m. The fact that small, loss-making biotech firms can create significant investor value without ever launching a product, generating sales or making a profit is an important idea that is at the core of the conceptual foundations of this thesis.

After leaving Biota in 2006, I continued to live in the US until 2010, when my wife and I moved back to Australia. From 2006, I worked as a consultant to several biotech firms and as a non-executive director for firms, including an Australian drug development biotech firm and an Australian pharmaceutical business. The drug development biotech firm, Viralytics, was developing novel drugs to treat cancer. During my six years on the board of that company (2008-2014), the company developed a clear strategic plan focused around moving the drug candidate forward to a point where a pharmaceutical deal could be consummated and the company sold in the process. Ultimately, this occurred in 2018, when Viralytics was acquired by the pharmaceutical giant, Merck, for US$ 394 million (approximately $500 million). This experience reinforced the notion that drug development biotech firms do not need to become commercial or even survive in order to be successful. This is another core idea in the conceptual foundations of this thesis.

In 2012, I co-founded Firebrick Pharma Pty Ltd, which is a private drug development firm focused on the treatment of respiratory viral infections; I remain chairman of that firm. In 2016, I co-founded and became managing director and CEO of Race Oncology Ltd, an ASX-listed pharmaceutical firm focused on cancer treatment; I remain CEO of that firm.

As a CEO, strategy consultant and non-executive director, I developed or helped develop numerous strategic plans for biotech firms. In so doing, it became clear to me that the traditional strategic planning frameworks did not apply to, and did not work for, drug development biotech firms, because such businesses rarely sold products, generated revenues or made profits; further, they rarely had any significant tangible assets or competition in the traditional sense. Yet, these consistently loss-making biotech firms could attract substantial investor funds and build large market valuations. In 2016, along with Professor Les Johnson at Swinburne, I published a paper describing the unique nature of drug development biotech firms and how they were strategic planning ‘orphans’ (Molloy and Johnson, 2016), because none of the existing strategy framing models worked for these firms. The fact that drug development biotech firms did not fit the established strategic planning models, suggested to me that they were different to most enterprises. It seemed there was an opportunity to build a new conception of these biotech firms and ultimately to develop strategic planning tools that worked.

In 2014, I commenced as an Adjunct Teaching Fellow at Swinburne University of Technology in the Faculty of Business and Law and delivered a lecture to post-graduate marketing students on the topic of 'Marketing in Life Sciences'. In July 2015, I enrolled as a part-time PhD student.

1.2. Motivation

In considering a PhD, my initial motivation was to complete the research project that I had started at Sydney University some years earlier, in the field of pharmaceutical market evolution. However, with guidance from Professors Johnson and Gilding, and considering my more recent biotech experiences, my research interest shifted to the topic of measuring the performance of drug development biotech firms.

Setting aside for the moment the question of how one defines a biotech firm – a key issue I try to address in this thesis – the genesis of my interest in the topic was the observation, as an industry insider, that Australian biotech firms seemed to consistently fail. When I joined Biota in 2002, it was considered to be the leader in the sector, but after its market value peaked between 2006 and 2009, its share price and value plummeted, never recovering. I saw the same pattern with numerous other ASX-listed biotech firms involved in drug development. They created high investor value expectations only to disappoint and abruptly lose most of their value, with very few rising again. In fact, looking back over the history of the biotech sector in Australia, there had not been a single flagship drug development biotech firm that had consistently built value and gone on to become a 'big biotech'. This was in contrast to the US, where flagship big biotech companies abounded – Genentech, Amgen, Gilead, Celgene and the list goes on.

This observation was at odds with the often-expressed view by politicians and local biotech industry supporters that Australia 'punches above its weight' in medical research and as a biotech innovator. However, no research-quality analysis of the performance of Australian biotech firms had ever been conducted to substantiate or counter this view. Therefore, undertaking such a project seemed to offer an important and novel contribution. I felt it could lead to a better understanding of the causes of the failures that appeared to prevail in Australia and potentially contribute to strategy or policy changes that might avert such failure in the future. I also felt that these insights might prove useful in other countries, especially outside the US.

This line of research thinking, however, opened a Pandora's Box of conceptual challenges. Let me outline the key ones:

(1) To measure the performance of a biotech firm requires one to define what a 'biotech' firm is, but there is no consensus in the literature as to what constitutes a biotech firm. Confounding the problem is the fact that there is no consensus about what 'biotechnology' is; as a result,

virtually any SME with almost any technology orientation can call itself, or be counted as, a biotech firm.

(2) Even if one can arrive at an acceptable definition of a biotech firm, how does one measure the performance of such firms, when the vast majority of these businesses are loss-making enterprises that cannot be evaluated using standard financial metrics? Most biotech industry performance reports appear to ignore the problem and include enough revenue-generating firms in their datasets to make financial metrics measurable (albeit not meaningful) at an aggregate level.

(3) The literature on performance measurement for biotech firms is extensive, but of limited value, because the datasets co-mingle a wide array of firms under the heading of 'biotech'; as a result, performance analyses generally have had to resort to non-specific performance surrogates, such as 'R&D effectiveness' or 'innovation performance', which may have no clear relationship to organisational performance goals. However, when the definition of a biotech firm is vague and the aggregates purporting to represent the biotech industry comprise diverse business with diverse or unclear goals, it is not surprising that performance measurement is a difficult task.

The challenge of unravelling this Gordian conceptual knot appealed to me, because it came with great possibilities: Not only might one be able to measure, for the first time, the performance of biotech firms, but it could create a new and integrated conception of a biotech firm that could open up new tracts of fertile research. It could also have significant implications for the management of biotech firms and for government policy aimed at fostering a healthy biotech sector, both in Australia and elsewhere.

1.3. Part A: Conceptual foundations

The first part of the thesis (Part A) lays the conceptual foundations on which my proposed re-conception of the biotech firm is built. Part A first addresses the definitional issues and uses the most important and prevalent application of biotech – drug development – as a springboard to elaborate a new definition for biotech firms.

In so doing, Part A presents a review the literature across several relevant fields: (a) the history and definition of biotechnology and biotech firms, (b) the history of the representation and measurement of the biotech industry, (c) the literature on performance measurement for biotech firms, and (d) the literature on pipeline modelling for drug development biotech firms. The analyses and conclusions of each of these literature reviews are melded into a redefinition of the biotech firm and distilled into several conceptual contributions. Because of the stepwise development of ideas in Part A, it was not

feasible to have a single 'literature review' chapter. As a result, there are multiple literature reviews, each conducted under their respective headings and chapters in Part A.

Chapter 2 reviews the history and definition of biotechnology, discussing how its promissory aspirations for creating a new bioeconomy and a Utopian 21st century have contributed to a pervasive "definitional dysfunction" (Miller, 2007, p. 58). Chapter 3 describes the history and definition of the biotech firm as the unit of analysis for research and the emergence of the DBF (dedicated biotechnology firm). Chapter 4 continues the conversation around the definition of the biotech industry and the industry datasets that have been used for research. Chapter 5 seeks to reconceptualise and redefine the biotech firm, using the dominant application of biotechnology, drug development, as a springboard. From this emerges the definition of the drug development biotech firm or DDB, which becomes the focus of the current research.

Chapter 6 reviews how performance is measured for biotech firms. Chapter 7 brings Part A to a close. It proposes a novel, improved performance metric for DDB firms, called 'value creation (VCR). It also proposes a general model describing the interplay between VCR and the firm's internal rate of return or IRR.

The main conceptual contributions in Part A are summarised below. One of the important contributions is the development of the concept of the drug development biotech firm, which I have abbreviated to 'DDB' firm. Since starting my research, I have published one paper discussing the DDB concept and its importance for strategy development and have a second working paper (to be submitted for publication) that discusses performance assessment for biotech firms. The ideas in these papers are embedded in the conceptual foundations section of this thesis.

The DDB concept is an extension of the definition of a biotech firm offered by Pisano in his well-known book: *Science Business: The Promise, the Reality, and the Future of Biotech* (Pisano, 2006b). Pisano defined biotech firms as firms founded after 1976 that applied biotechnology for the purposes of drug discovery and development. In an important conceptual leap, he ignored the problem of defining exactly what 'biotechnology' was and instead, adopting a business frame of reference (rather than a technology one), he simply defined it as any modern technology, including biology, chemistry, medicine and computer science, that contributed to drug development. This technology-agnostic view was in contrast to the 'purist' view of biotechnology, which sought to restrict the definition to genetic engineering, biologic drugs and a handful of other biology-based technologies, generally in line with the definition offered by OECD. The importance of this is discussed in Part A.

While not integrated into his definition, Pisano (2006b, p. 143) also observed that biotech firms acted as intermediaries in the pharmaceutical value chain: "Biotechnology firms are like middlemen in a

R&D supply chain: they take on projects at early stages, develop them to some point, and then license (resell) them to pharmaceutical companies for further development."

This observation was aligned with my own experiences in managing biotech firms and provided a key insight that helped me build a comprehensive new definition of biotech firms that sees such firms, not only as technology-agnostic (like the Pisano definition), but as exclusively pre-commercial firms that create value as intermediaries in an industry value chain. I refer to this idea as the 'pre-commercial intermediary' (PCI) view of the biotech firm and I believe it represents a valuable contribution to future thinking about biotech firms.

The DDB is the most prevalent and important type of biotech firm under this view. According to my definition, DDB firms are independent, pre-commercial enterprises born after 1976 (the year that the first DDB appeared) that operate within the pharmaceutical industry as R&D-focused intermediaries in the pharmaceutical R&D value chain. Their market is the pool of demand from pharmaceutical firms for new drugs to in-license from these DDBs. Their unique business model (R&D intermediary), value chain (pharmaceutical R&D) and market (licensing demand) are what define DDBs as biotech firms and separate them from all other businesses.

Using the three parameters – business model, value chain and market – as defining characteristics, I distinguish DDBs from all other so-called 'biotech' firms. Importantly, from a performance evaluation perspective, they are distinguished from 'big biotech' firms and other commercial-stage biotech businesses, which are firms that were mostly born as DDBs, but over time have migrated to become pharmaceutical businesses that compete with other pharmaceutical firms for prescription demand. They also compete as buyers in the market for drug licenses from DDBs.

The term 'big biotech' implies a sales threshold of US$1 billion. However, there are numerous smaller commercial-stage firms that have yet to reach the big biotech sales threshold, but are actively commercialising drugs and are no longer DDBs. To capture all such commercial firms and distinguish them from DDBs, I elaborate the concept of 'drug development and commercialisation' firm, abbreviated to 'DDC' firm. Under that conception, big biotech is simply a special case of a DDC that has achieved a sales threshold.

Like their Big Pharma cousins, DDCs are commercial firms that seek to maximise sales and profitability in the long-term. Therefore, they can be evaluated largely based on traditional financial metrics. My contention is that DDBs, which are pre-commercial, seek to create value in other ways and cannot be evaluated by such financial metrics. Distinguishing DDBs from DDCs is an important conceptual contribution of the thesis, because for the first time, it points to the critical distinction between pre-commercial and commercial-stage firms for strategy, research and performance purposes.

Despite the observation that biotech firms are 'middlemen', Pisano's definition failed to embrace the pre-commercial imperative in defining a biotech firm. As a result, his dataset for performance evaluation co-mingled pre-commercial and commercial firms and he concluded that the industry has performed poorly, based partly on sales and profit performance. I believe that the historical co-mingling of pre-commercial and commercial firms in industry datasets has been a primary barrier to understanding and measuring the performance of biotech firms, because it generally leads to performance assessments based on sales and similar financial performance metrics.

The unstated assumption seems to be that those biotech firms that have not yet generated revenues aspire to do so, and therefore, revenues are a valid measure of the maturation and performance of the industry. I argue against this and note that the transition of DDBs to DDCs is an extremely rare event and virtually non-existent outside the US. By aggregating DDBs and commercial firms, those reporting on the so-called biotech 'industry' may obtain some familiar and readily-obtainable measures of financial performance, but these measures are irrelevant to the vast majority of DDBs and other pre-commercial biotech firms in the dataset.

Overall, I argue that the biotech 'industry' as historically conceived and reported is illusory. I further argue that the illusion is born out of an apparently unblinking desire to demonstrate the industrialisation of modern biotechnology, regardless of business model, value chain or market considerations. I refer to this as the 'promissory aspirations for biotechnology' or 'PAB' phenomenon and argue that the PAB force has led to considerable definitional dysfunction and hampered effective performance analysis for biotech firms.

I further argue that it becomes evident that DDBs are very different businesses to commercial firms and can create substantial value regardless of their lack of sales and profitability. Using DDBs as a springboard, I then propose a comprehensive new definition for any biotech firm as: A research-intensive, pre-commercial firm born after 1976 that utilises a range or mix of technologies to create value in an industry value chain. This is essentially the definition proposed by Pisano (2006b), but unlike the Pisano definition, it is not limited to drug development and *is* limited to pre-commercial firms. Although the most prevalent and important (based on market value) type of biotech firm is the DDB, it represents one type of dedicated biotech firm (DBF). Other types are identified in Part A and a classification schema and nomenclature are suggested. This classification schema represents another contribution.

I also compare my proposed biotech firm definition with the widely-researched concept of 'dedicated biotechnology firm' or DBF. With certain specific limitations on the DBF definition – principally that all DBFs should be pre-commercial firms – the DBF concept and my proposed biotech firm concept are equivalent and can be used interchangeably. That being the case, DDBs would be considered one type of DBF.

Specifically limiting DBFs to pre-commercial firms allows me to disaggregate biotech industry datasets into strategically meaningful subsets suitable for performance assessment. However, performance measurement represents its own conceptual challenge, because as already discussed, biotech firms generally cannot be evaluated based on financial metrics. This has meant that I have had to develop a new performance metric that is strategically relevant for DDBs (and likely other DBFs), which I refer to as 'value creation'. This is elaborated also in Part A and summarised below.

Briefly, for a DDB, the value of the firm is comprised of the value of its primary tangible asset – normally its cash reserves – plus the value of its primary intangible asset – its drug development pipeline. This 'pipeline value' or 'PV' entraps the aspirations of investors for the realisation of future tangible value by the firm; this may take the form of a monetisation event, such as a pharmaceutical alliance that generates substantial license fees and royalties, or an outright acquisition of the DDB at a substantial premium to its current market value. In essence, investors are betting that the intangible PV will be converted into a tangible asset, such as cash, which will be returned to investors. Naturally, these aspirations must be tempered by the risk, cost and time of achieving the monetising deal. In this way, the PV can be thought of as the risk-adjusted net present value (rNPV) of the drug pipeline.

DDB firms generally have few tangible assets other than cash. Given that $1 of cash has a market value of approximately $1, for public DDB firms at least, the PV can be calculated as the market value (MV) minus cash (C). In most cases for DDBs, this value is arithmetically equivalent to a widely-used metric in professional investment circles, called 'enterprise value' or 'EV'. However, because the EV technically refers to the acquisition value of a firm and can refer to commercial firms, I prefer to use the term 'pipeline value' or PV in the context of DDBs, where the firms are pre-commercial and the primary intangible asset is the candidate drug pipeline.

As indicated above and for public DDBs, the PV can be thought of as the rNPV attributed by investors to the firm's drug development pipeline at a specific point in time. This valuation is subject to rapid change in response to signals and narratives from the firm about the progress of the drug development pipeline. The most common way for a DDB to grow its PV is to advance a candidate drug from one phase of drug development to a more advanced phase. This signals to investors that development risk has been reduced and the drug is potentially one step closer to a pharmaceutical deal. However, the PV concept is not restricted to clinical trial progress. The aspirational value of future monetary gain for investors could be increased by the firm's receiving licensing revenues.

For performance measurement of DDBs, I propose the concept of 'value creation', which I abbreviate to 'VCR'. Positive VCR or value creation occurs when the DDB efficiently grows its PV. I make the case that the growth must be *efficient* for value creation to occur, in that the increase in PV needs to be of greater value than the cash cost of producing it. When VCR is positive, the share

price and MV of the firm typically increase. The obverse is that when a candidate drug (CD) fails to move forward in a phase of drug development or fails terminally and is abandoned, the PV drops significantly and negative VCR (value destruction) occurs.

I propose that VCR, measured as the growth in the PV over time, minus the cash cost (operating cash burn rate, BR) of delivering that growth, is a useful performance metric for public DDBs. The notion that value growth occurs when CDs progress in the drug development pipeline has long been appreciated, but the idea that DDB performance can be represented quantitatively as VCR is a new idea and another conceptual contribution of this thesis. VCR is used as an important metric in the empirical research in Part B.

The other performance metric I use in Part B is less novel, namely, the internal rate of return (IRR) for investors in a public DDB stock. The IRR is the compound annual growth rate in the share price adjusted for share splits or consolidations. In this research, IRR is calculated for each DDB and the overall DDB sector, based on a set of assumptions and methodology that is comprehensively described in Chapter 8 of Part B.

I also introduce the concept of 'technology asset' (TA) value. This is seen as a broad-based, qualitative and idiosyncratic evaluation of the value of a firm's technology as a platform for successful drug development, where 'success' – in the PCI view – is defined as pipeline value growth towards a pharmaceutical deal. Finally, in Figure 6 in Chapter 7, I present a general model of the relationships between TA, VCR and IRR, which may be a basis for future research.

1.4. Part B: Empirical research

Part B of the thesis seeks to measure the performance of DDB firms in Australia using the concepts developed in Part A. The research question that this thesis addresses is: **Do Australian drug development biotech firms create value and deliver attractive investor returns?**

The focus is on public (ASX-listed) DDBs, because all the metrics are readily available for calculating VCR and IRR. Private firms are not amenable to such analysis. The impact of limiting the dataset to public firms is discussed in Chapter 8 and Chapter 10. In summary, public DDB firms appears to be strongly representative of the overall DDB sector, public and private.

Part B first defines the public DDB sector in Australia and traces the history of the listed DDB sector from its inception in 1985 through 2018. I use the 15-year period from 2003 to 2018 as the period over which performance of the sector is assessed. The rationale for this is discussed and alternative time periods are later discussed and assessed in Chapter 10 and Chapter 11. For performance assessment, I identify 40 ASX-listed DDB firms, based on pre-stated inclusion and exclusion criteria in Chapter 8.

Chapter 9 presents descriptive statistics and performance results for the whole DDB sector and for each of the 40 DDB firms. The results clearly show that the Australian DDB sector has failed to create value over the 15-year period. Further, the average IRR from the sector over the 15 years has been negative, indicating that public DDBs in Australia were an exceptionally poor investment. At the end of the 15-year period, a portfolio of the 40 firms that represented a total investment of $40,000, had a value of only $19,724, representing a loss of 51% of the invested principal. This translated to a portfolio IRR (annual compounded loss) of -6.2%. Based on VCR, the sector did not efficiently create pipeline value. The public DDB sector grew its pipeline value (PV) by $1.59 billion; however, it burned $2.85 billion in investor cash to produce that growth, yielding a negative VCR of -$1.27 billion, which represented value destruction, not value creation.

Of the 40 firms evaluated, only 10 (25%) had positive VCRs, with only five (13%) producing VCRs greater than $100 million each. Nine firms (30%) produced positive IRRs, but the highest was only 8.5%. Thirty-one firms (78%) produced negative IRRs for the period.

Chapter 10 discusses the results in detail. To assess whether changing the terminus year from 2018 might alter the results, I also tested each of 2014 through 2017 as terminus years for the portfolio analysis. The VCR was not improved by changing the terminus year – in fact, in 2015, 2016 and 2017, it was far worse. Also, the overall IRR was worse for all years other than 2018, which was a relatively positive performance year for the sector.

Chapter 10 also provides a detailed analysis of the performance of 12 firms that had the most influence on the overall results. Two firms – Clinuvel and Viralytics – are seen as the most successful DDBs, based on VCR and IRR. Clinuvel generated $662 million in cumulative VCR over 15 years and produced an IRR of 7.2%. Viralytics was acquired in 2018 for $500 million, producing cumulative VCR of $357 million over 11 years and IRR of 7.2%. A third firm, Starpharma is seen as relatively successful, producing VCR of $284 million over 15 years and IRR of 6.2%. Clinuvel and Viralytics are discussed in detail in the chapter, in order to distil possible reasons for their success.

Given the poor performance of the DDB sector overall, the chapter also discusses the likely impact on overall investor sentiment towards DDB and biotech. Highlighted in this discussion is the 2013-2014 ‘train wreck’ that saw a procession of high-profile failures. Individual firm analyses pointed to several possible strategic errors, which I refer to as ‘market definition’ failure, ‘commercial focus’ and ‘profit means success’ orientations, and a concept called ‘Red Queen’ failures. Each of these is described in detail and defined in the chapter.

Potential causes of the sector-wide failure are also discussed, including lack of cash and poor TA (technology asset) quality and attendant low R&D productivity. The discussion brings into question

the overall quality of Australian drug discovery and development technology, the role of venture capital firms and the role of the ASX in contributing to sector performance.

Chapter 10 closes with a validation of VCR as a performance metric, using IRR as the valid comparator. The rationale and limitations of this approach are discussed. In conclusion, VCR seems to have validity as a measure of firm performance, because it is highly-correlated with and predictive of long-term IRR; moreover, it embeds factors that are highly relevant to investors, such as growth in pipeline value and efficient use of investor funds.

The final chapter, Chapter 11, presents and discusses the limitations and implications of the research. The first section discusses the limitations under several headings: Concepts and constructs, methodology, dataset exclusions and other limitations. The second half of the chapter outlines the implications of the research for theory, policy and practice.

1.5. Contribution

In summary, the major contributions of the research are both conceptual and empirical. The conceptual contributions in Part A are:

1. The unravelling of the definitional morass around biotechnology, biotech firms and the biotech industry.

2. The reconceptualisation of biotech firms as pre-commercial intermediaries (PCI) and the definition of the DDB and recommendation that it become an important unit of analysis for DBF research. Out of this has also come a refinement of the definition of the DBF and a classification schema for DBFs.

3. The conceptualisation of value creation for DDBs and the creation of a new performance metric for DDBs and potentially all (pre-commercial) DBFs, called VCR.

4. The development of a general model of the interplay between VCR and IRR, along with the introduction of the concept of TA quality as an important driver of value creation potential.

Empirical contributions (related to the research question) in Part B are:

5. A primary contribution of this research is that, for the first time, it addressed the question: Do Australian drug development biotech firms create value and deliver attractive investor returns? Based on this research, the answer to that question is “no”. For the 15-year period from 2004 to 2018, the Australian DDB sector failed to create value, based on VCR, and failed to generate attractive investor returns, based on IRR. It also failed to produce a commercial ‘anchor tenant’ on which to build a sustainable sector in the future.

6. The research has allowed definition of the possible reasons for the failure, including strategic mistakes by firms, the role of VCs, the role of the ASX and the quality of Australian drug development technology.
7. The thesis also identifies important implications of the research for theory, policy and practice and suggests new avenues for research based on the concepts and research results.

In both the conceptual and empirical parts of the thesis, not all of the ideas and conclusions presented are exclusively derivative of the literature or the empirical data. In some chapters, notably 10 and 11 , it was not possible for me to completely set aside my industry experiences and focus on the data or the literature as the sole basis for all ideas and analysis. I believe this is reasonable, as it helps fill in some of the gaps without necessarily resulting in overreach. I also hope that it makes for a richer and more interesting thesis.

Chapter 2. Defining biotechnology

2.1. Introduction

As will be apparent from the literature review, there is no clear definition for 'biotechnology' or a 'biotechnology/biotech' firm. Yet having a clear and conceptually sound definition for a biotech firm is essential to research into the performance of such firms, since without it, one cannot unambiguously define the pool of firms for which performance is to be assessed. Moreover, without a clear conceptualisation and definition, it may be impossible to determine the appropriate performance criteria. This chapter examines these issues and sets the stage for a redefinition of the biotech firm.

My conceptualisation of biotech firms – the unit of analysis for this research – relies on a decoupling of firms from technology. To avoid ambiguity, I intend to use the term 'biotechnology' (the noun) to apply to technologies and the term 'biotech' (the adjective) to apply to firms and aggregates of firms, as in a biotech firm or the biotech industry.

Many authors have used the terms interchangeably and used both terms as adjectives to describe a firm or industry. However, where the distinction has been made between 'biotechnology' and 'biotech', it has been generally accepted that the former refers to techniques or technologies and the latter to firms (O'Neill and Hopkins, 2012).

2.2. History of biotechnology

In a paper entitled, 'The evolution of the word 'biotechnology', Kennedy (1991) summarises the history of the term. He reports that it was first used in a 1919 German publication by a Hungarian agricultural economist, Karl Ereky. The context was large-scale agricultural activities and the term was used to describe the integration of biology with technology in pig farming.

According to Kennedy (1991), a second reported usage was in 1947 to describe the development and use of machines to aid human beings. A third usage was in 1962, when the *Journal of Microbiological Technology and Engineering* changed its name to *Biotechnology and Bioengineering*, with the term 'biotechnology' referring very broadly to all aspects of the use and control of biological systems (Kennedy, 1991).

However, these usages were incidental compared to the extensive use by scientists, governments, investors and the public after the early 1970s, when recombinant DNA and related technologies first emerged. According to one author, the first modern day use of the term can be attributed to the *Wall Street Journal*, which used it in the early 1970s to describe the breakthrough work in recombinant DNA by two scientists, Stanley Cohen and Herbert Boyer (Loffler, 2002).

However, according to Smith (2009), the term originated in US government circles to assuage concerns about 'genetic engineering', with the term 'biotechnology' deemed to be more palatable than 'genetic engineering'. Whatever, the origins of the term itself, it is important to try to understand how modern-day biotechnology is defined.

'Modern biotechnology' initially referred to recombinant DNA and genetic engineering, which were the primary industrial breakthroughs emanating from the work of Cohen and Boyer (O'Neill and Hopkins, 2012; Verma et al., 2011). The term 'modern' was added to distinguish it from broader-based conceptions of biotechnology that viewed biotechnology, not as revolutionary science starting in the 1970s, but as a biological continuum with deep historical roots, as described by Hilgartner (2015, p. 676):

> Alongside the notion of revolution, the discourse on biotechnology also features an opposing frame that stresses continuity with the biological and historical past. Thus, supporters of biotechnology sometimes downplay its novelty, defining it inclusively (e.g., as the harnessing of biological agents to provide goods and services) and portraying it as merely the latest twist on age-old methods of plant breeding, animal husbandry, and brewing.

Adopting this broader, *inclusive* conception of biotechnology, some authors distinguish modern biotechnology from 'ancient' biotechnology and 'classical' biotechnology. Ancient biotechnology has been defined as pre-1800 technology that includes domestication and breeding of animals, agriculture, food preservation, cheese-making, brewing and a host of other technologies. Classical biotechnology has been defined as those biology-related technologies developed from the 1800s through the mid-twentieth century; these included Mendelian genetics, the discovery of nucleic acid and the chromosome, the discovery of bacteria and the development of the first vaccine and antibiotics (Amin et al., 2011; Verma et al., 2011).

The abstraction of biotechnology as an evolving set of techniques that spans the ages may have some scientific, social and historical utility, but I believe it contributes to the confusion and ambiguity about what 'biotechnology' means, which is discussed in detail below. For the purposes of this research, when using the term 'biotechnology' I will be referring only to modern biotechnology.

2.3. Defining biotechnology

From a basic science perspective, the roots of modern biotechnology lie in the work of Watson and Crick in elucidating the structure and role of DNA (Lecocq and Looy, 2016; Powell et al., 1996; Verma et al., 2011). However, it was the later work of Cohen and Boyer that gave rise to the first real application of that science, in the form of recombinant DNA (rDNA), and seeded the birth of what is considered to be the first biotech firm, Genentech (Burrill, 2014; Downs and Velamuri, 2016; Lecocq and Looy, 2016; Oliver, 2001; Powell and Sandholtz, 2012; Zucker and Darby, 1997). Given that

biotechnology is generally considered 'applied' science, rather than basic research (Stockwell, 2017), most argue that the arrival of rDNA was the birth of modern biotechnology. In that regard, the period between Watson-Crick and Cohen-Boyer might be considered its gestation period.

Recombinant DNA involves the use of enzymes to excise a gene sequence from one bacterial cell and insert it into another. The recipient cell then divides, producing multiple copies of the DNA containing the gene and producing the protein coded for by that DNA (Briggle, 2012). In 1982, the US FDA approved the marketing by Genentech of human insulin produced in such genetically modified bacteria (Briggle, 2012; Greenwood, 2014).

A second important technology emerged in 1984, with the development of PCR (polymerase chain reaction), which automated the sequencing of DNA, allowing more rapid identification of genes and the proteins for which they coded (Briggle, 2012). Another important biotechnology was monoclonal antibodies or 'Mabs' (Liebeskind et al., 1996), which are synthetic antibodies or antibody fragments with an affinity for specific antigens (proteins). This led to the development of new molecular diagnostics and drugs that have employed the high target-specificity of Mabs.

Others biotechnology developments have included gene therapy, stem cells, *In vitro* fertilisation (IVF) and a range of other technologies (Greenwood, 2014). Modern biotechnology is increasingly integrated with information technologies, so 'biocomputing' (use of organic systems for information processing) and 'bioinformatics' (use of computers in drug development) are now considered to be biotechnology, at least by some definitions (Briggle, 2012). Indeed, the exponential growth of computing technology and the ongoing integration of IT and biotechnology (Loffler, 2002) doubtless will give rise to new types of biotechnologies in the future. It is this indefatigable march of technology on multiple fronts that makes biotechnology a constantly evolving concept, for which boundaries are (and must be) fluid.

Since modern biotechnology first appeared in the 1970s, its meaning and usage have gone through several evolutions (Kennedy, 1991; O'Brien, 1991; Walsh et al., 1995). That evolutionary process left in its wake a multitude of definitions (Bauer, 2005; Miller and Young, 1987; Oliver, 2001; Smith, 2009), along with confusion and ambiguity about the meaning of biotechnology. However, the term 'biotechnology' was always destined to have an elastic and evolving meaning. Any definition intended to reflect relevant current technologies is going to expand and change as technologies mature and new rafts of technology emerge (Kennedy, 1991).

However, as early as 1987, Miller and Young (1987, p.28) observed: "Defining the terms 'biotechnology' and 'genetic engineering' isn't an easy task, since the terms don't represent natural groupings of processes or products. They connote something different to individual commentators, journalists, organizations, congressional staffers and members of the public. The terms are

ambiguous, the source of much confusion and little advantage, and we would do well to return to more specific and descriptive terms."

Scientific usage of the term 'biotechnology' peaked in the mid-1980s and decreased thereafter, suggesting that over-usage, incorrect usage and a broadening definition of the word had limited its scientific value (Kennedy, 1991). It has been suggested that it may also reflect the rapid adoption and widespread use (and misuse) of the term by the public, business, investment community and governments in the late 1980s (Kennedy, 1991).

Little has changed since then, at least with respect to arriving at any clear definition of biotechnology. Smith (2009, p.5) noted: "There is also a considerable danger that biotechnology will be viewed as a coherent, unified body of scientific and engineering knowledge and thinking to be applied in a coherent and logical manner. This is not so."

In a scathing critique of what he described as the "terminological chaos" around the use of terms like biotechnology and a related term, biopharmaceutical, Rader (2008, p. 747) lamented: "Criteria for what is biotechnology and biopharmaceutical are unfixed, subjective, adaptable to the needs of the moment, presumed to be continually evolving and rarely defined."

More recently, Briggle (2012, p.301) observed that biotechnology remains a term "with contested boundaries informed by conflicting visions" and Hilgartner (2015, p. 676) stated that "Defining biotechnology poses challenges, for the word is less a tightly defined, technical term than a loose umbrella category, or even a slogan, that conveys – sometimes simultaneously – visions of unbounded progress and unregulated tampering with nature."

Others also have lamented the *sloganisation* of biotechnology, arguing that it has become little more than a buzzword co-opted by small technology-focused companies to provide a high-tech allure that appeals to investors (Kennedy, 1991; Rader, 2008). Some even argue the term should be avoided altogether (Miller, 2007).

Against this background, it is not surprising that there have been many definitions of biotechnology. In 1990, it was reported that there were more than 40 definitions in use, just in Europe (O'Brien, 1991). In 2009, Smith identified nine broad ways in which biotechnology had been defined (Smith, 2009), reproduced below as Table 1:

Table 1 Selected definitions of biotechnology

A collective noun for the application of biological organisms, systems or processes to manufacturing and service industries.
The integrated use of biochemistry, microbiology and engineering sciences in order to achieve technological (industrial) application capabilities of microorganisms, cultured tissue cells and parts thereof.
A technology using biological phenomena for copying and manufacturing various kinds of useful substances.
The application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services.
The science of the production processes based on the action of microorganisms and their active components and of production processes involving the use of cells and tissues from higher organisms. Medical technology, agriculture and traditional crop breeding are not generally regarded as biotechnology.
Really no more than a name given to a set of techniques and processes.
The use of living organisms and their components in agriculture, food and other industrial processes.
The deciphering and use of biological knowledge.
The application of our knowledge and understanding of biology to meet practical needs.

Based on a review of the literature, I identified at least five prominent government or institutional definitions of biotechnology. These 'official' definitions are summarised in Table 2:

Table 2 Official definitions of biotechnology

Organisation	Biotechnology is…	References
OECD	The application of science and technology to living organisms, as well as parts, products and models therefore, to alter living or non-living materials for the production of knowledge, goods and services.	(Chojnacki and Kijek, 2014; Friedrichs and van Beuzekom, 2018; OECD, 2005)
United Nations (UN)	An application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.	(Nicolau and Santa-María, 2015)
Office of Technology Assessment (OTA)[1]	Any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses	(O'Neill and Hopkins, 2012)
Convention on Biological Diversity (CBD)	Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.	https://www.cbd.int/kb/Results?q=biotechnology
European Federation of Biotechnology (EFB)	The integration of natural sciences and organisms, cells, parts thereof, and molecular analogues for products and services	(Smith, 2009)

All these official definitions have the same basic theme: biotechnology is about making useful products (or processes or services) by using living organisms (or their components and derivatives). The OECD definition is subtly broader than the rest, in that it extends the output to 'knowledge' as well as products and services. However, including 'knowledge' could be interpreted as extending the

[1] The OTA closed on September 29, 1995. During its 23-year history, OTA provided Congressional members and committees with analysis of the complex scientific and technical issues of the late 20th century (www.princeton.edu/~ota/)

scope of biotechnology beyond applied science to basic science, in contrast to the generally-held view that biotechnology is only applied science (Stockwell, 2017).

Regardless, all of the official definitions are very broad, which is not surprising given that the only way to address the ambiguity and uncertainty around biotechnology is to have a sufficiently broad definition to accommodate all possibilities. However, for these same reasons, broad definitions can be widely interpreted. Moreover, in their attempt to be all-inclusive, they fail to differentiate modern biotechnology from ancient and classical biotechnology.

In a critique of the OECD definition, which equally might be levelled at all of the official definitions, Miller (2007, p. 58) states that the definition encompasses "not only most biomedical R&D and commercial activity that involves laboratory animals or humans but also virtually all of agriculture, baking that uses yeasts, and the production of fermented beverages and foods – ranging from beer and yogurt to kimchi (a traditional Korean dish of fermented chili peppers and vegetables). The use of such a broad definition is destined to yield worthless results."

Obviously, it is not the intention of OECD and other organisations to report beer-brewers and bakeries as biotechnology firms. However, the enduring failure to properly resolve the definition of biotechnology has apparently left little choice than to adopt the broad, inclusive position.

While the broad definitions dominate official definitions of biotechnology, there are those that have attempted to define biotechnology in narrower terms (Briggle, 2012). In reviewing the literature, I also believe that they can be further usefully classified by whether a broad or narrow frame of reference has been applied. I have sought to summarise these in Table 3 below:

Table 3. Frames of references for definitions

Frame of reference	Type of definition	Examples
Broad definitions		
Biotechnology is part of a long biological continuum that spans the ages	Ancient (pre-1800), classical (1800-1950) and modern biotechnology (post-DNA discovery)	(Briggle, 2012; Hilgartner, 2015)
Biotechnology is not just a collection of techniques, but manipulation of biology	Broad, abstract single definitions such as 'manipulation of living organisms or their parts in order to provide desired outcomes'	(Briggle, 2012); includes OECD and most other official definitions
Biotechnology is what member companies (biotech firms) are doing	Biotechnology 'harnesses cellular and biomolecular processes to develop technologies and products	Biotechnology Innovation Organisation (BIO)

	that help improve our lives and the health of our planet.'	www.bio.org/what-biotechnology
Narrower definitions		
Biotechnology is a collection of specific techniques	OECD list-based definition	(Friedrichs and van Beuzekom, 2018; van Beuzekom and Arundel, 2006)
Biotechnology is applied biology not basic science of biology	Biotechnology is applied biology to develop tools to solve human problems	(Stockwell, 2017)
Biotechnology is a modern revolution	It is limited to rDNA and post-rDNA technologies	(Woollett, 2012)
Biotechnology is the integration of IT, engineering and biology	Biotechnology includes bioinformatics and nanotechnology	(Erbas and Memis, 2012; van Beuzekom and Arundel, 2009)
Biotechnology is bioprocessing	It is about manufacturing products from living organisms using bioprocessing	(Rader, 2008)
Must involve transformation by a biological process and be made of biologically-derived components	Defines biotechnology by exclusion of techniques considered 'not biotechnology'	(Stockwell, 2017)
Pisano: Biotechnology is any technology used for drug development	Includes medicine, chemistry, biology and computer science, all exclusively aimed at drug development	(Pisano, 2006b)

For the purpose of gathering biotechnology statistics and in an attempt to be both inclusive and narrow or specific, OECD offers a 'list' definition of biotechnology in addition to its broad single definition (OECD, 2005). The list definition specifies what techniques or technologies qualify as biotechnology. These are shown in Table 4.

Table 4. OECD list-based definition of biotechnology techniques

DNA/RNA: Genomics, pharmacogenomics, gene probes, genetic engineering, DNA/RNA sequencing/synthesis/amplification, gene expression profiling, and use of antisense technology.
Proteins and other molecules: Sequencing/synthesis/engineering of proteins and peptides (including large molecule hormones); improved delivery methods for large molecule drugs; proteomics, protein isolation and purification, signalling, identification of cell receptors.
Cell and tissue culture and engineering: Cell/tissue culture, tissue engineering (including tissue scaffolds and biomedical engineering), cellular fusion, vaccine/immune stimulants, embryo manipulation.
Process biotechnology techniques: Fermentation using bioreactors, bioprocessing, bioleaching, biopulping, biobleaching, biodesulphurisation, bioremediation, biofiltration and phytoremediation.
Gene and RNA vectors: Gene therapy, viral vectors.
Bioinformatics: Construction of databases on genomes, protein sequences; modelling complex biological processes, including systems biology.
Nanobiotechnology: Applies the tools and processes of nano/microfabrication to build devices for studying biosystems and applications in drug delivery, diagnostics, etc.

According to OECD (2005, p. 1):

> The provisional single definition of biotechnology is deliberately broad. It covers all modern biotechnology but also many traditional or borderline activities. For this reason, the single definition should always be accompanied by the list-based definition which operationalises the definition for measurement purposes.

Tellingly, OECD notes that the list functions as an 'interpretative guideline' and that the list is only 'indicative rather than exhaustive' (van Beuzekom and Arundel, 2009). Moreover, they note that it is expected to change over time as biotechnology evolves and have recently proposed a list of qualifying technologies (Friedrichs and van Beuzekom, 2018). In collecting data from member countries, while stipulating that the list definition should be applied in determining whether an activity qualifies as 'biotechnology', OECD also offers an 'Other' category to accommodate technologies not on the list that might be deemed to biotechnology by member countries.

While these definitional gymnastics attempt to accommodate both the inclusive view of biotechnology and the need for greater specificity, they fail comprehensively, according to Miller (2007, p. 58), who described the OECD biotechnology statistics as "An egregious and recent example of definitional dysfunction" and "attempts to survey biotechnology regulations and other developments in OECD countries were repeatedly stymied by inconsistent definitions – even when countries were asked to use a specific one". The data published by OECD in their 2006 report were collected using different and incompatible definitions of biotechnology (Miller, 2007). Indeed, OECD itself acknowledges in the report that not all contributing countries used the same definitions for biotechnology (van Beuzekom and Arundel, 2006, p. 7):

> The OECD list-based definition, or close variants, were used in surveys in 15 countries, but different definitions of biotechnology were used in the other 11 countries: 7 studies limit biotechnology to ''modern'' or third-generation biotechnologies that are similar to the OECD list-based definition in practice, 2 studies use mixed definitions that include second generation biotechnologies (Japan and South Africa), and 2 do not define biotechnology, but leave it to the survey respondent to decide if their firm is active in biotechnology. As the latter two studies cover Denmark and Sweden, a large majority of the respondents are likely to interpret biotechnology as modern biotechnology.

Miller (2007, p. 59) observes:

> This chaotic state of affairs brings to mind the old computer saying, 'Garbage in, garbage out'. The data in the OECD report are garbage.

The response to this critique from the authors of the OECD report (Arundel et al., 2007) did little to assuage the concerns raised by Miller. Rather, it seemed to defend OECD's diligence in collecting their data, while confirming their difficulty in getting all member countries to use a consistent definition. Overall, it acknowledged the definitional problem.

2.4. Promissory aspirations for biotechnology

When modern biotechnology first appeared, it promised a bounty of new drugs and devices to detect, treat and prevent disease, along with pest-resistant crops to feed the world, biofuels to replace depleting fossil fuels, and other innovations that would transform society and spawn a utopian 21st century for humankind (Petersen and Krisjansen, 2015; Stefanec, 2011; Verma et al., 2011). It also promised a new 'bioeconomy' that would deliver a new engine of industrial growth in first world countries, along with the health and environmental benefits.

I suggest that biotechnology was too big a promissory prize not to be co-opted, used and ultimately misused by a range of parties – governments, non-government agencies, industry associations, consultants, firms, investors and academic researchers. I believe that this phenomenon has had a

substantial influence on the way in which biotechnology and the biotech industry has been viewed and reported. As I seek to untangle the definitional knots that have confounded performance assessment of biotech firms and the biotech industry, I will refer to this phenomenon several times. To that end, I propose the term, 'promissory aspirations for biotechnology' or 'PAB', as a descriptor that captures this blinkered drive to see biotechnology succeed.

Possibly one of the most blatant examples of the PAB force is OECD's collection of statistics on the application of biotechnology across its member countries, one major purpose of which seems to be to demonstrate and measure the degree of industrialisation of biotechnology, regardless of business models, value chains or markets. The fact that the data have been described as 'garbage' (Miller, 2007) has not stopped OECD continuing to collect them.

Further, OECD seems so committed to PAB that it has not been impeded by the lack of consensus about the definition of biotechnology. It periodically just amends its list definition to reflect an expanding menu of technologies (Friedrichs and van Beuzekom, 2018).

2.5. Conclusions

Over the last three decades, the definition of biotechnology has been so pulled, stretched and distorted that no-one really knows what it means. It remains an elastic term about which there is no consensus, but plenty of confusion and ambiguity. Where definitions exist, most tend to be so abstract and broad as to be useless for demarcation of the term's boundaries. Some have offered narrower definitions, but these have not been widely adopted or become the seeds for any definitional consensus.

Against this background, it is hard to imagine that the term's application as an adjective to describe firms or an industry – as in the 'biotech industry' – would lead to anything other than more confusion and misuse. However, driven by PAB, it was inevitable that many parties would want to see and promote the industrialisation of biotechnology and report on the biotech industry. I examine this phenomenon in the next chapter.

Chapter 3. Emergence of the DBF

3.1. The founding era

In this chapter, I examine the early history of the industrialisation of modern biotechnology, the emergence of the dedicated biotech firm (DBF) and the establishment of what has become known as the biotech industry. Burrill (2014, p. 21) provides a comprehensive history of the discovery of rDNA that gave birth to the biotech industry. He describes the historic meeting at a conference in Hawaii in 1972 between Herbert Boyer, a professor of biochemistry at UCSF and Stanley Cohen, a professor of medicine at Stanford University:

> The two had been working on complimentary [*sic*] projects and combined their efforts to develop a method for isolating genes and DNA fragments and reproducing them. Boyer's lab had identified an enzyme that cut precise DNA fragments that coded for the production of specific proteins. Cohen had developed a method for inserting DNA fragments into bacteria cells. The process they developed for recombinant DNA essentially allowed a scientist to place DNA from higher organisms into bacteria or other cells and harness these cells as factories of desired proteins.

The rDNA discovery was published a year later in 1973. While this discovery was the first example of modern biotechnology, it was a second partnership between Boyer and a venture capitalist, Robert Swanson, which actually gave birth to what is generally considered the first biotech firm, Genentech, three years later in 1976. Burrill (2014, p. 21) describes the genesis of that partnership:

> Robert Swanson, a venture capitalist who became convinced of the commercial potential of recombinant DNA, had been cold calling leading scientists in the field to see if they believed the technology was ready to be commercialized. While each agreed the technology had commercial potential, they told him it was at least a decade or two away. When he reached Boyer, not realizing the University of California, San Francisco (UCSF) scientist codeveloped the technique for recombinant DNA, and told him he wanted to start a company based on the technology…the two entered a partnership that would lead to the formation of Genentech in 1976. By the time the Swiss pharmaceutical giant Roche completed its acquisition of Genentech in 2009, the company was worth $100 billion, more than any pharmaceutical company at the time.

Most authors agree that Genentech was the first biotech firm and therefore, that the industry started in 1976 (Downs and Velamuri, 2016; Marks, 2014; Pisano, 2006b). However, some regard another biotech firm in the San Francisco Bay Area, Cetus, which was established in 1971, as the first biotech firm (Powell and Sandholtz, 2012).

It has been argued that because Cetus initially was focused on finding microorganisms for industrial applications, rather than modern biotechnology, Genentech qualifies as the first genuine biotech firm (Oliver, 2001). The fact that Genentech also developed the first biotechnology product to reach the market, human insulin, and ultimately came to be worth more than US$100 billion, probably adds to the appeal of nominating Genentech as the founding biotech firm. Later, Cetus did embrace rDNA and was responsible for one of the other major technical breakthroughs in biotechnology, which was the development of PCR (polymerase chain reaction), a technique to sequence DNA (Oliver, 2001). In the current research, I will use 1976 as the starting year for the industry, in line with Pisano (2006b) and most other authors.

Many firms followed in Genentech's footsteps in the late 1970s, with the first wave of new biotech start-up firms not restricted to the San Francisco Bay Area. In the Boston area, Biogen and Genzyme were formed. Like the Bay Area firms, these also sprung up out of local universities, namely MIT, Harvard and Tufts University (Burrill, 2014). In 1978, Hybritech sprung up in the San Diego area in the same way and later seeded a multitude of new firms in that region. Indeed, virtually all of the first wave of pioneer biotech firms were co-founded by or maintained strong linkages with academic researchers at local universities in these three locations (Zucker and Darby, 1996).

1980 was an important year in the first decade of the US industry. In October of that year, there was Genentech's historic IPO (Initial Public Offering), as described by Shimasaki (2014c, p. 282):

> The stock went for sale on the NASDAQ exchange at $35 a share, and within hours the share price reached $89 before closing at the end of the day at $71.25. Genentech raised $35 million that day.

However, there were key regulatory events in 1980 that preceded the Genentech IPO and doubtless added investor interest in the stock. One was the *Diamond v. Chakrabarty* patent decision that permitted the patenting of man-made organisms and the passing of the *Bayh-Dole Act* that encouraged universities to license scientific breakthroughs for commercialisation. These are expansively described by Burrill (2014, pp. 24-25):

> The case of Diamond v. Chakrabarty examined the question of whether genetically engineered organisms could be patented. Ananda Chakrabarty was working for General Electric when he developed a bacterium that would break down oil and could be used to clean oil spills. The U.S. Patent and Trademark Office rejected the Chakrabarty applications saying living organisms could not be patented. A patent appeals court overturned that decision, saying the fact that something is living is irrelevant to the question of patentability. Sidney Diamond, the commissioner of the patent office, appealed the decision to the U.S. Supreme Court, which

> ruled in a 5 to 4 decision that the Chakrabarty's bacterium did not naturally occur in nature and was, in fact, the invention of a man and therefore capable of being patented.
>
> That same year, the Patent and Trademark Law Amendments Act, commonly known as the Bayh-Dole Act, changed the rights surrounding intellectual property created through federally funded research. Until then, the government retained control of all patents resulting from federally funded research and licensed it out on a nonexclusive basis…The new law established a policy for federally funded research that allowed universities, small businesses, and other recipients of research funding to retain the intellectual property they created with government-funded research and have the rights to license it. This allowed universities to become a critical source of biotechnology innovation that industry could then work to commercialize.

Mowery et al. (2001) undertook an empirical assessment of the impact of the Bayh-Dole Act and reported that it was associated with a dramatic growth in patenting by US universities, along with an explosion in the number of technology licensing and transfer offices at universities, the latter growing from 25 in 1980 to 200 in 1990 (Mowery et al., 2001). However, they note that the Bayh-Dole Act was only one of several factors behind increased patenting and licensing activity, including the *Diamond v. Chakrabarty* decision and an overall increase in biotechnology research activity. They also note that the period was accompanied by a broad, positive shift in US policy towards strengthening of intellectual property rights, which elevated the economic value of patents and facilitated licensing (Mowery et al., 2001). One way or another, at the end of its first decade, the biotech industry in the US was poised for an exciting future.

Another key event that drove the excitement about the commercial potential of biotechnology was the first licensing deal between a biotech firm and a Big Pharma company. Prior to Genentech's development of recombinant (synthetic) human insulin, diabetics had to be treated with insulin derived from animals, but it caused allergic reactions in many patients. The new recombinant human insulin overcame these problems. In 1978, two years after the founding of Genentech and with the new insulin still in early development, the company executed a landmark licensing deal with Eli Lilly for rights to the product, as described by Pisano (2006a, p. 117)

> In return for the manufacturing and marketing rights to recombinant insulin, Lilly would fund development of the product and pay Genentech royalties on its sales. This agreement knocked down one of the chief barriers to new firms' entering the pharmaceutical business: the huge cost ($800 million to $1 billion in today's dollars) over the long time (ten to 12 years) generally required to develop a drug.

Prior to the advent of biotech firms, drug development had only occurred in large pharmaceutical firms (Big Pharma) under a 'FIPCO' or 'fully-integrated pharmaceutical company' model (Downs and Velamuri, 2016; Shimasaki, 2014b), with all phases of drug development carried out within the

Big Pharma firm. The Genentech-Lilly deal showed that a biotech firm could participate and create value as a participant or intermediary in the pharmaceutical drug development pathway, without undertaking marketing and sales.

Another way to view this is that the Genentech deal showed that drug development could be a value-creating proposition in its own right. Moreover, the deal provided proof-of-principle that biotech firms dedicated to drug development could create substantial investor value without needing to market a final product. Downs and Velamuri (2016, p. 19) put it this way:

> [the deal] showed would-be new biotech entrants and venture investors that intellectual property (IP) could be packaged and sold independently of having a final product. This key event thus ignited an explosion of thousands of new biotechnology firms which have in turn driven hundreds of new biotechnology derived therapies to market approval.

Four years later in 1982, Lilly gained approval for and launched Genentech's synthetic insulin, which grew to become a blockbuster drug. This further proved, not only that biotechnology could lead to a marketable drug, but that biotechs could participate in the commercial rewards of drug development, extending their value proposition for many years into the commercial phase of a drug's life via royalties on sales. By 1994, twenty-five biotechnology-based drugs had been approved by the FDA (Powell et al., 1996).

3.2. The DBF: Birth of a new business model

Genentech provided the blueprint for an entirely new business model that became the foundation for the biotech industry (Pisano, 2006a). Pisano (2006a) describes it as a model for monetising intellectual property and identifies three key elements to the model:

- Technology transfer from universities, spinning out (creating) new biotech firms to house the technology, rather than selling it to established companies;
- Venture capital and public equity markets that provide funding at critical stages for the new biotech firm;
- A deal-making market in which biotech firms license (or sell) their intellectual property to established pharmaceutical firms in exchange for funding and licensing revenues.

From Big Pharma's perspective, the Genentech-Lilly deal was also the first time that a Big Pharma firm had effectively outsourced part of its drug discovery and development to a biotech firm (Pisano, 2006b). Since then, outsourcing by Big Pharma of drug R&D to small biotech firms has become the norm, affirming the value of the biotech business model, creating a symbiotic relationship between pharma and biotech, and spawning thousands of new biotech firms keen to make deals with pharma (Burrill, 2014). These firms now make up the biotech 'industry'.

A name was needed for the new biotech business model. Powell et al. (1996) referred to the new US biotech firms as 'dedicated biotechnology firms' or DBFs. While not explicitly stated, these DBFs were *dedicated* in the sense that they focused on R&D rather than commercialisation. Instead of having global sales and marketing organisations with an R&D group in tow, like their large pharmaceutical cousins, they created value by focusing on R&D and outsourcing the sales and marketing activities through licensing arrangements with large pharmaceutical companies. The term 'DBF' therefore sought to capture the new business model pioneered by Genentech and by the mid-1990s, the term was well-established in the literature (Walsh et al., 1995).

Most researchers see the DBF primarily as a US phenomenon (Momma and Sharp, 1999; Walsh et al., 1995). Momma and Sharp (1999, p. 267) state:

> In the United States, the agent of mediation has become the dedicated biotechnology firm (DBF)—small companies, mostly founded by, or affiliated with, brilliant scientists, operating at the cutting edge of research, and, in themselves, pushing forward the frontiers of science as they explore the opportunities for commercialisation (Zucker and Darby, 1995). Innately Schumpeterian in nature (namely a 'swarming' of new firms motivated by the prospect of temporarily high monopoly profits to be gained from exploiting a radical innovation), the industrial dynamics do not always follow this model.

Schumpeterian economic theory posits that innovations, led by entrepreneurs, disrupt the otherwise circular flow of economic activity. As the innovations demonstrate success and profitability, other entrepreneurs follow or 'swarm' (Cooke, 2003). Further, innovations in one field, such as pharmaceuticals, may trigger innovations in related fields, such as diagnostics and research tools. Whether or not the emergence of DBFs is truly Schumpeterian is debatable (Cooke, 2003), but the phenomenon did appear to exhibit the 'swarming' feature, which has been used to contrast the successful creation of the US biotech industry with other countries. The contrast between the US and other countries with respect to the biotech industry, and the global dominance of the US in that regard, is an important theme and conceptual foundation for the current research. The forces that drove this dominance are discussed in detail in a separate section.

Powell et al. (1996, p. 123) sought to restrict the definition of DBF to human biotech and exclude all firms other than those engaged in the development of therapeutic and diagnostic products for human use:

> Many researchers…treat the wide array of biotechnology companies as comparable. In contrast, we intentionally restrict our attention to only those for-profit firms engaged principally in human therapeutics and diagnostics, hereafter referred to as dedicated biotech firms, or DBFs. We are persuaded that the therapeutics sector is driven by a different research

> agenda and operates within a distinctive regulatory regime. We intentionally omit firms engaged only in agricultural, veterinary, or bioremediation activity and exclude peripheral companies that produce only equipment, materials, or test kits for the industry.

Apart from the research and regulatory distinctions, they also noted the political and public perception factors in excluding agricultural and veterinary biotechnology. In the US, while there was considerable public opposition to genetically altered food and animals, there was a generally positive view towards developing a new cancer drug (Powell et al., 1996).

In addition to restricting DBFs to therapeutics and diagnostics, Powell later stated (Powell et al., 2005) that while DBFs can be public or private firms, their definition excluded biotechnology-focused subsidiaries of larger firms. Powell et al. (2005, p. 1148) asserted that autonomous decision-making was a key feature of DBFs:

> We exclude organizations that might otherwise qualify as DBFs, but are wholly owned subsidiaries of pharmaceutical or chemical corporations…Our rationale for excluding both small subsidiaries and large, diversified chemical, medical, or pharmaceutical corporations in the DBF database is that the former do not make decisions autonomously, while biotechnology may represent only a minority of the activities of the latter. Their exclusion from the primary sample of DBFs eliminates serious data ambiguities.

The DBF has been widely used as a unit of analysis in research studies. These include studies comparing the evolution of the biotech industry between countries (Momma and Sharp, 1999; Moustakbal, 2014; Yagüe-Perales et al., 2013), assessing the role of alliance formation (Farag, 2009; Niosi, 2003; Oliver, 2001; Quintana-García and Benavides-Velasco, 2005), analysing geographic clustering and network phenomena (Gilding, 2008; Moodysson and Jonsson, 2007; Quintana-García and Benavides-Velasco, 2005; Rosiello and Orsenigo, 2008; Whittington et al., 2009), and examining relationships with venture capital funds (Kolympiris et al., 2011).

However, some studies did not adhere to the Powell et al. (1996, 2005) definition of the DBF, notably the exclusion of all applications other than therapeutics and diagnostics. Many DBF studies included (or failed to exclude) those firms engaged in other applications of biotechnology, such as medical devices, digital health, agricultural, veterinary, environmental and other biotechnology (Kolympiris et al., 2011; Moodysson and Jonsson, 2007; Moustakbal, 2014; Niosi, 2003; Oliver, 2001; Quintana-García and Benavides-Velasco, 2005).

More recently, Yagüe-Perales (2013, p.20) distinguished DBFs as ‘makers’ of new products or processes, while others are seen as ‘users’:

> The national statistics offices usually make a distinction between dedicated biotechnology firms (DBFs), and users of biotechnology. The first ones are research intensive firms producing

> new processes or products (genetically modified animals, bacteria or plants, human tissue, proteins, etc.) on the basis of this set of new technologies. The second ones are environmental, food, forest, pharmaceutical, mining, or other companies that use biotechnology processes or products in their operations.

Moustakbal (2014, p.67) added that DBFs should have biotechnology as their predominant activity:

> Further, we focus on dedicated biotechnology firms (DBFs) defined by OECD (2005, 2009) as: 'A biotechnology firm whose predominant activity involves the application of biotechnology techniques to produce goods or services and/or to perform biotechnology R&D'.

Particularly in Europe, the term 'new biotechnology firm' or NBF has sometimes been used instead of DBF to refer to entrepreneurial, early-stage, biotech firms (Diestre and Rajagopalan, 2012; Ireland and Hine, 2007; Liebeskind et al., 1996; Mang, 1998; Momma and Sharp, 1999; Peters et al., 1998; Shan and Visudtibhan, 1990). Momma and Sharp (1999) seemed to use the terms interchangeably, but also sought to distinguish NBF from DBF, with the latter purported to reflect a mostly US phenomenon characterised by a more aggressive business model, where the goal was to evolve into a FIPCO or big biotech (Momma and Sharp, 1999). In the context of pharmaceutical drug development, Mang (1998, p. 231) distinguished NBFs from established firms:

> Two types of firms have participated in the development of biopharmaceuticals: biotechnology start-up firms and established pharmaceutical companies. Since the mid-1970s, hundreds of new biotechnology firms (NBFs) have been formed to pursue commercial R&D opportunities spawned by recent advances in the biotechnological sciences.

A combination term, 'new dedicated biotech firm' or NDBF, has also been used (Lecocq and Looy, 2016). However, it is unclear from definition or context how this differs from DBF or adds value beyond the DBF concept.

Finally, the term 'new biotechnology enterprise' or NBE has also been used for biotech firms (Zucker and Darby, 1996; Zucker and Darby, 1997). The NBE was seen as a broader conception that included both independent biotech firms (NBFs) and biotechnology-focused subunits or subsidiaries of established companies, the latter referred to as 'new biotechnology subunit/subsidiary' (NBS).

In Europe, the distinction also has been made between different applications of biotechnology based on a colour coding system, where firms engaged in human health or bio-medical applications are referred to as 'red' biotech, in contrast to agricultural applications that are 'green', environmental 'grey' and industrial 'white' (Bauer, 2005; Chojnacki and Kijek, 2014; Farag, 2009; Mietzner and Reger, 2009; Shimasaki, 2014a). Recently, 'yellow' biotech was added to cover insect applications (Vilcinskas, 2013), and one study referred to 'rainbow' biotech to capture applications involving

cross-over between different colours, such as using plants to produce therapeutic proteins and vaccines (Gartland et al., 2013).

Focusing on red biotech firms, I found inconsistencies in the definitions applied. In many cases, red biotech was restricted to firms engaged in the development of diagnostics and therapeutics (Chojnacki and Kijek, 2014; Farag, 2009) and therefore consistent with the Powell definition of the DBF. However, in one study where both terms are used, DBF was seen as a broader term embracing all the colours (Chojnacki and Kijek, 2014). In another, red biotech included veterinary applications (Mietzner and Reger, 2009). In a major recent analysis of the European biotech industry, Ernst & Young limited red biotech to pharmaceuticals and diagnostics that were products of living organisms and manufactured via recombinant technology, thereby excluding firms developing small-molecule drugs (Ernst & Young, 2014). Another study defined red biotech firms even more specifically as those using gene therapy, genetic testing, pharmaceuticals and medicines, reproduction and IVF, human genetics, human genome and xeno-transplantation (Bauer, 2005). In one case, 'bioinformatics' was added as an additional biotechnology application, while retaining the colour designations for the other categories (Amin et al., 2011).

I have prepared a table that summarises the range of definitions for biotech firms (Table 5).

Table 5. Summary of definitions for biotech firms

Firm name	Definitional features	References
Original DBF (the 'Powell DBF')	Mainly US phenomenon Restricted to human therapeutics and diagnostics 'Dedicated' = focused on R&D not commercialisation For-profit firms Typically founded by university-affiliated scientists Swarming, Schumpeterian	Powell et al. (1996)
	Autonomous: independent enterprises, not subsidiaries	Powell et al. (2005)
DBF variations	Includes medical devices, digital health, agricultural, veterinary, environmental and other biotechnology	Moodysson and Jonsson (2007), Kolympiris et al. (2011), others
	'Makers' of new products/processes: genetically modified animals, bacteria or plants, human tissue, proteins; distinguished from 'users'	Yagüe-Perales (2013)
	Predominant activity must be: (a) application of biotechnology to produce goods or services and/or (b) performance of biotechnology R&D	OECD definition, Moustakbal (2014)
NBF	'New biotechnology firm' Entrepreneurial, early-stage, biotech firms	Multiple studies
	'New' in that they were not previously established	Mang (1998)
NBE	'New biotechnology enterprise' includes both autonomous firm (NBFs) and new biotech-focused subsidiaries of established companies (NBS)	Zucker & Darby (1996, 1997)
Red biotech	Part of colour-coded classification based on application field: Red, green, grey, white, yellow, rainbow	Multiple studies
	Equivalent to Powell DBF: Limited to human health or bio-medical, restricted to pharmaceuticals, diagnostics	Chojnacki & Kijek (2014) Farag (2009)
	Further limited to pharmaceuticals and diagnostics that are products of living organisms and manufactured by recombinant technology	Ernst & Young (2014)
	Includes veterinary applications	Mietzner (2009)
	Pharmaceuticals and medicines, further limited to those using gene therapy, genetic testing, reproduction and IVF, human genetics, human genome and xeno-transplantation	Bauer (2005)
	Includes bioinformatics	Amin et al., 2011

3.3. Challenges in defining a biotech firm

I see several challenges in attempting to define a biotech firm: First, if biotech firms are generally considered to be independent firms that engage in the research and development of products based on biotechnology (Liebeskind et al., 1996; Oliver, 2001), then there is a fundamental problem in that there is no consensus around what biotechnology is or what technologies might qualify.

Second, even if qualifying biotechnologies could be clearly defined, then how much biotechnology does a firm need to engage in, in order to qualify as a biotech firm? Should it be a dominant activity? If so, how is the activity level measured? Does one include established commercial firms that also engage in substantial biotechnology R&D?

These questions have not been adequately addressed in the literature to date. Some have sought to address the first point by being very specific about qualifying technologies. For example, Liebeskind et al. (1996) limited biotechnology to rDNA, Mabs and protein engineering; Zucker and Darby (1997) stipulated that only those firms developing biologics, as distinct from small-molecule drugs, qualify as biotech firms for industry analysis. Clearly, one of the problems with such an approach is that different researchers may choose different sets of qualifying technologies.

A second problem is that it requires a detailed understanding of each firm's R&D programs to make an assessment as to whether they are applying qualifying technologies. Any such assessment then needs to be applied to the dataset offered for an analysis and all non-qualifying firms carefully screened out. This makes practical application of a qualifying technology approach extremely cumbersome.

OECD has sought to resolve the second problem of 'how much is enough' by including all firms using biotechnology to *any* extent and then applying a complex classification structure. First, OECD defined a biotech firm as "a firm that is engaged in biotechnology by using at least one biotechnology technique (as defined in the OECD list-based definition of biotechnology techniques) to produce goods or services and/or to perform biotechnology R&D. Some of these firms may be large, with only a small share of total economic activity attributable to biotechnology" (van Beuzekom and Arundel, 2009, p. 10).

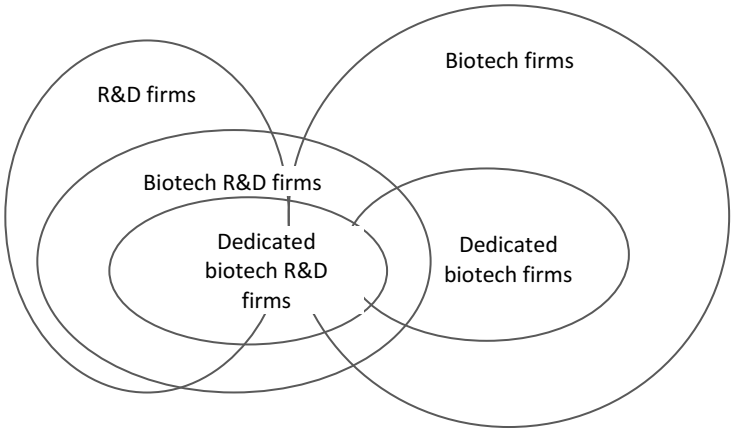
Therefore, according to OECD, any firm that uses – to any extent – any one of their long list of qualifying technologies, qualifies as a biotech firm. Within that broad definition, they identify two sub-groups:

1. Dedicated biotechnology firm: defined as a biotechnology firm whose predominant activity involves the application of biotechnology techniques to produce goods or services and/or to perform biotechnology

2. Biotechnology R&D firm: defined as a firm that performs biotechnology R&D. Dedicated biotechnology R&D firms, a subset of this group, are defined as firms that devote 75% or more of their total R&D to biotechnology R&D.

These definitions are supported by a Venn diagram that seeks to explain the overlap and differences, the key components of which are represented here in Figure 1.

Figure 1. OECD definitions of biotech firms



Adapted from OECD Biotechnology Statistics 2009, p. 10

Whether based on the written definitions or the diagram, the classifications are ambiguous and extremely difficult to comprehend. It is not clear or explained why it is necessary to have such classifications in the first place. Moreover, it would be very difficult for the OECD survey participants to apply such classifications with any accuracy in an international survey (a problem partly acknowledged by OECD). Finally, the classification schema would not be practical for screening firms to be included as biotech firms in any dataset seeking to represent a biotech industry.

3.4. Conclusions

Built on the potential of recombinant DNA, the first dedicated biotech firms (DBFs) emerged in the US around San Francisco, Boston and San Diego. Founded in 1976, Genentech is recognised as the first true DBF. When Genentech licensed recombinant human insulin to Lilly in 1978, it demonstrated that the DBF represented a new business model, one in which firms could use R&D to create value for investors without necessarily taking a product to market. While there have been multiple names for such firms, the dominant name used in the literature is ‘DBF’.

Like the definition of ‘biotechnology’, the definition of DBF has not been stable and has been used inconsistently. Variations in the definition have sought to capture regional differences, distinguish or limit the fields of application, distinguish independent firms from established firms and other

variables or dimensions. Various studies have applied different definitions in determining what firms were included in their database.

In addition, some authors have not adopted the DBF as the primary descriptor or definition for a biotech firm. The main alternatives offered and applied in some research have been new biotechnology firm (NBF) and new biotechnology enterprise (NBE). The definitions in each case have considerable overlap with the range of DBF definitions and like the DBF definitions, have been subject to variability and inconsistent use. Finally, a colour-coding system has been used (mainly in European studies), in an attempt to differentiate biotech firms by field of application. The human health variant, 'red biotech', has considerable overlap with the DBF conception, but again, has been subject to definitional variability and inconsistent application.

I identify two central challenges in trying to define a biotech firm, notably that biotechnology itself is not well-defined and that even if it were definable, the criteria for inclusion of firms as biotech firms would remain unclear based on the degree of their usage of biotechnology techniques and whether or not subsidiaries of established firms would qualify for inclusion. An attempt by OECD to resolve these questions fails to do so adequately or practically.

Given the promiscuity of the definition of biotechnology outlined in the previous chapter, it is not surprising that arriving at an unambiguous and robust definition for a biotech firm has been impossible. It is tempting to conclude that because of the PAB phenomenon, the definitional problems and the weak and often poorly-elaborated conceptual foundations were largely overlooked. Instead, the problems carried forward from the definition of biotechnology to the definition of the biotech firm and then further to the definition of the biotech industry, which is the ultimate manifestation of biotechnology's industrialisation. The biotech industry is discussed in the next chapter.

Chapter 4. The biotech industry

The notion that there is a biotech 'industry' is well-established and use of the term is widespread in the literature and industry circles (Greenwood, 2014; Jarvinen, 2007; Kolympiris et al., 2014), although there is no consensus about how the industry is defined or what its constituent firms are. Given the lack of consensus about what a biotech firm is, this is not surprising. This chapter reviews how the biotech industry has been defined in research studies and by various groups seeking to report on and measure the performance of the industry.

4.1. Industry definition

Intuitively, one might assume that the biotech industry is simply the aggregate of those firms that use biotechnology (Liebeskind et al., 1996; Oliver, 2001). However, as described in the previous chapter, defining what constitutes both biotechnology and a biotech firm is challenging. Jarvinen (2007) acknowledges that despite the widespread usage of the term, any definition is confounded by the breadth of utility of biotechnology..

Echoing this, some have argued the industry is effectively un-definable, being so diverse and ever-expanding that it is impossible to define as any single industrial space. According to Shimasaki (2014a, p. 113), it is better thought of as a group of 'sectors':

> When we speak about the 'biotechnology industry' it is in broad reference to a diverse group of treatments, biologics, diagnostics, medical devices, clinical laboratory tests, instruments, agricultural, industrial, and biofuel applications. The biotechnology industry encompasses many diverse sectors which are ever-expanding as new scientific and technical discoveries are uncovered and new applications are found…On the surface, the biotechnology industry may appear to be complex because of the seemingly endless and diverse array of products that biotechnology is capable of producing. However, it is surprising how each sector utilizes many similar tools and methods to create these diverse products.

In sociology, there is an extensive literature on field theory (Barman, 2016). Some have applied this approach in an attempt to understand and characterise the biotech industry. Powell et al. (1996) saw the industry as a field defined by a pattern of inter-organisational agreements between various actors. In the same vein, Liebeskind et al. (1996) saw the industry as a network of alliances governing the exchange of complementary assets between actors, including DBFs, scientists and established firms. Jarvinen (2007, p. 10) also echoed this view:

> Biotechnology industry can be defined as a group of actors applying different biotechnological methods and applications in their operations. With this definition, the industry consists of a large group of actors. They range from public research organizations, including universities,

> hospitals, research labs, foundations, and institutes, to large pharmaceutical, agro-chemicals, food, and chemical companies that are typically highly diversified multinationals with several divisions and intricate proprietary and control links.

While the field perspective may provide a useful framework for understanding the dynamics of the biotech industry based on the relationships between various actors, it does little to circumscribe the industry's boundaries in a way that is meaningful to performance measurement. Moreover, it does not provide any clear view of how performance should be measured.

As early as 1996, in elucidating the concept of the DBF, Powell et al. (1996) observed that the biotech industry is not really an industry, but a set of technologies with applicability in a range of fields (Powell et al., 1996). Oliver (2001, p. 471) concurred: "Biotechnology is not an industry, but rather a set of applications of processes including rDNA, monoclonal antibodies, protoplast fusion, cell and tissue culture, bio-processing and others." In the same vein, Smith (2009, p. 4) described it as "technology in search of applications."

Another commentator (McCormick, 1996), was more emphatic (p. 224):

> I used to start my public talks on the industry like this: 'There is no such thing as biotechnology, there are biotechnologies. There is no biotechnology industry; there are industries that depend on biotechnologies for new products and competitive advantage.' By that standard the biotechnology revolution is unstoppable.

As heralded by the last sentence of that quote, this technology-based view of the biotech industry, unbounded by consideration of industrial application, is undoubtedly a product of the PAB phenomenon. It is also the foundation for the OECD approach to measuring and collecting data on biotechnology industrialisation. For simplicity therefore, I will refer to the 'set of technologies' view of biotechnology and the industry as the 'OECD paradigm'.

As previously noted, a problem with the OECD paradigm is that there is no consensus about what biotechnology is, although in their reporting, OECD attempts to address this – ineffectively according to Miller (2007) – by stipulating a list of qualifying technologies. This fundamental problem presents a barrier to any conceptually sound translation to a definition of a biotech firm, which in turn, makes defining an aggregate of such firms extremely difficult.

In order to take the first step and define a biotech firm in a manner that is consistent with the OECD paradigm, OECD offers a definition of firms that embraces all possible users of biotechnology (according to their list definition). The conceptual contortions required to achieve this, results in a definition that is ambiguous and unworkable as a classification schema for firms. Beyond that, OECD avoids the translation to 'industry' by defining the industrialisation of biotechnology as the

extent to which biotechnology is applied, rather than the number of firms or other metrics related to participating firms.

In a similar vein, Pisano (2006b) describes the biotech industry as a 'meta-industry'. However, he successfully makes the leap to a workable industry definition as described below.

Pisano (2006b) states that technological innovation spans multiple businesses, creating blurred boundaries between traditional industries. Indeed, he asserts that traditional conceptions of industries and markets are no longer relevant because of technology and need to be replaced by technology platform conceptions. This necessitates a shift in focus from industry to the company itself. Under this meta-industry conception, no longer is the company's fate driven by the industry in which it operates or the existing business models; the company chooses which industries in which to operates and what its business model will be. Biotechnology is a meta-industry and biotechnologies supply new knowledge to various industries.

Pisano's view of biotech as a meta-industry spanning a range of industries and applications is consistent with the OECD paradigm. It represents a de-industrialised view of the aggregate of biotech firms and theoretically allows all firms using biotechnology, regardless of application, to be considered (and be counted as) part of the 'industry'. However, for the purpose of his analysis of the industry's performance (the primary focus of his book), Pisano defines biotechnology and a biotech firm exclusively in the context of a single application and a traditional industry – drug development in the pharmaceutical industry. Specifically, he defines biotechnology as any technology that contributes to drug R&D, including advances in biology, medicine, chemistry and computer science. This 'Pisano definition' of biotechnology is contrary to the OECD paradigm, which seeks to limit biotechnologies to a specific (albeit fluid) list. Pisano (2006b, p. 16) goes on to define a biotech firm as follows: "From an industry perspective, I define a biotechnology firm as any firm founded after 1976 for the purposes of advancing, developing, or commercializing the above new technologies for drug discovery."

Pisano has endeavoured to acknowledge the OECD paradigm with the meta-industry concept, but realises that practical performance analysis necessitates a more specific industry or application view. Powell et al. (1996) did the same – defining DBFs as focused on therapeutics and diagnostics, while simultaneously acknowledging that biotechnology is a set of technologies with potential also in chemicals, agriculture, veterinary science, medicine and waste disposal.

This shift to an industry focus for the purpose of defining the analytical pool recognises that for any performance analysis at a firm or aggregate level to be meaningful and useful, one needs to compare firms with similar business models and operating in similar markets. This recognition will become a key driver for my re-definition of the biotech firm, which is elaborated later.

Possibly in an attempt to compromise between the technology and industry views (or to avoid the issue), some have referred to the industry as a 'sector', in several cases using the terms interchangeably (Nicol et al., 2013; Vieira and Hine, 2005).

For the purposes of the current research and for general clarity, I intend to use the term 'sector' to describe all biotech firms in a country, region or worldwide. Those firms operating in specific industries, such as pharmaceuticals, will be distinguished on different bases and using specific nomenclature, as elaborated later.

4.2. Reporting on the biotech industry

Given the uncertain definition of both biotechnology and the biotech firm, one might conclude that reporting on the performance of a biotech 'industry' is a problematic endeavour. OECD reports (2005, 2009) tend to avoid an industry focus in their analyses, for reasons already discussed. However, there are other organisations, consultants and journals that regularly report on the biotech industry, its performance and the relative performance of countries with respect to their biotech industries.

I found three major reporting platforms for annual reports on the biotech industry: The consulting firm, Ernst & Young, produces annual global and regional reports on the biotechnology industry (Ernst & Young, 2016). *Scientific American* publishes an annual *Worldview Scorecard* on the biotechnology industry, comparing the biotechnology performance of 54 countries and providing a global ranking for each (Scientific American, 2016). Finally, *Nature Biotechnology*, a high-impact peer-reviewed journal, has for two decades published an annual feature report on the performance of the global biotech industry, based on public company data (Morrison and Lähteenmäki, 2016, 2017).

I will focus on the *Nature Biotechnology* (NBT) reports, as these are peer-reviewed, have been published annually for more than 20 years and the datasets are mostly available for analysis. Moreover, the NBT datasets are the same as used by Ernst & Young for their reports and are also used by *Scientific American* in providing key performance metrics for their *Worldview Scorecard*.

4.3. NBT annual industry reports

Examining the NBT datasets reveals that the biotech industry as reported by NBT includes a wide range of businesses, with differing business models and operating in different industries. Many of the firms appear to have little in common, other than their designation as *biotech*, which given the foregoing discussion, is destined to be problematic. According to their 2016 report, the authors of the NBT report explain the inclusion criteria in the dataset as follows: "We generally include innovative companies built upon applications of biological organisms, systems or processes, or the provision of specialist services to facilitate the understanding thereof. We exclude pharmaceutical companies,

medical device firms and contract research organizations to better focus on the unique attributes and situations that make up the biotech sector" (Morrison & Lahteenmaki 2016, p. 710).

However, like most of the definitions of biotechnology, the NBT definition would appear to be open to wide interpretation and subjective application. Also, it seems that the specific exclusions may not have been rigorously enforced. For example, in the dataset for the 2016 report, I found several companies that appeared to be either medical device firms or commercial pharmaceutical businesses. However, I found more telling examples of definitional dysfunction in the dataset, as described below.

The Australian company CSL is one example. In the 2016 NBT report, CSL was reported as one of the top 10 biotech firms worldwide, based on revenue growth (Morrison and Lähteenmäki, 2016). With $5.5 billion in revenues, CSL was fifth on the global biotech 'leader board', up from 10th the previous year (Morrison and Lähteenmäki, 2015, 2016). It also accounted for a prodigious 94% of reported biotech revenues from Australia and 22% of all biotech revenues outside the US, greatly inflating Australia's standing as a biotech revenue generator. However, CSL did not evolve from a biotech firm and its qualifications for inclusion in a representative biotech industry dataset are highly questionable.

Founded in 1916 and for nearly eight decades thereafter, the Commonwealth Serum Laboratories, as it was previously known, was a government-owned and government-funded pharmaceutical manufacturer, charged with maintaining Australia's supply of vaccines, antivenin and penicillin. After its privatisation in 1994 and its subsequent acquisitions in the early 2000s of blood products businesses, ZLB and Aventis Behring, it changed its name to CSL and focused its manufacturing on blood fractionation, generating most revenues from the sale of blood fraction products. Overall, it is a business with relatively low R&D intensity and two-thirds of its revenues coming from sales of immunoglobulin, albumin and other blood products.

CSL is undoubtedly a large-scale pharmaceutical manufacturer that engages in a modest level of drug discovery and development activity, some of which may involve biotechnology techniques. Also, it may meet the overall definition of a 'biopharmaceutical' manufacturer, since its products are biological in nature and involve bioprocessing (Rader, 2008). However, it is clearly a very different business to all the small biotech firms in Australia (and elsewhere), which mostly have no marketed products or revenues. Moreover, unlike CSL, they were all born as private start-ups since the advent of modern biotechnology (1976, as per the Pisano definition), not as a government-run manufacturing operation that morphed into a multinational blood-fraction products manufacturer and marketer.

CSL is not the only example of a company that contributes substantially to the reported biotech industry revenues each year, but was not born as a biotech firm and otherwise has doubtful biotech credentials. In the 2016 NBT report, the UK firm Shire accounted for $6.4 billion in revenues or 26% of ex-US biotech revenues, and was 10th on the revenue growth leader board. However, Shire started as a calcium supplement marketing business in 1986, which after its public listing 10 years later, grew as a specialty pharmaceutical firm by acquiring other pharmaceutical businesses. Its more recent acquisitions included various drug development biotech firms (Moran, 2014). In acquiring pipeline to expand its portfolio, Shire is unsurprisingly behaving like other major pharmaceutical firms, but should it be considered a biotech firm? It certainly did not evolve from one.

As a further example, the US firm Monsanto contributed biotech revenues of $15 billion in the 2016 report, making it the third largest biotech revenue generator in the world. However, Monsanto is a 115-year old chemical company that expanded into pharmaceuticals and agricultural products and then in the last 30 years, applied genetic modification to impart favourable attributes to some of its seed products. It merged with the Big Pharma business, Pharmacia & Upjohn, in 2000 and was then spun out again as a dedicated agricultural products business with a focus on GM products, but with half of its sales coming from its blockbuster herbicide, Roundup (not a product of biotechnology).

Clearly, Monsanto did not evolve from a small biotech firm. Further, to the extent that some of its products – notably GMO seeds – are the result of modern biotechnology techniques and could be considered 'biotech revenues', they only account for part of the firm's global revenues, although the amount is difficult to ascertain. However, the company's entire $15 billion in sales were counted as biotech revenues in the 2016 report, representing nearly 10% of reported global biotech revenues.

Not far down the revenue list in the dataset are others with questionable biotech heredity and credentials, such as Perkin Elmer and Bio-Rad, both of which are long-standing equipment manufacturers that now focus on research tools and diagnostics, and which together contributed more than $4 billion in biotech revenues to the 2016 NBT report (Morrison and Lähteenmäki, 2016). Should the entire revenues of large firms such as CSL, Shire, Monsanto, Perkin Elmer and Bio-Rad, which did not evolve from biotech firms, yet now engage in some degree of biotechnology, be counted as *biotech* revenues and their market value and other metrics reported as biotech for performance purposes?

These observations point to several challenges when reporting on the biotech industry. First, what constitutes a biotech firm needs careful consideration in the context of the purpose of the data reporting. If that purpose is to track the industrialisation of modern biotechnology, then it would seem to be important to report only the biotechnology portion of the activity and output metrics of firms. For example, to count the revenues of the herbicide Roundup as biotech is nonsensical and counterproductive. However, and setting aside the problem of defining biotechnology, the available

public company data mostly do not lend themselves to any accurate apportionment between biotech and non-biotech activity or outputs. Therefore, the reasonable solution would be to exclude those firms where the focus and activity output is clearly commercial in nature and not focused on or derived from biotech R&D. In my view, this would include CSL, Shire, Monsanto, Perkin Elmer and Bio-Rad.

Alternatively, if the purpose is to track the emergence of start-up biotech firms as DBFs and their maturation into successful commercial-stage firms, then it would seem important that all constituent firms be born biotech and not *bolt-on* biotech. For that purpose, the same five firms would equally be excluded from the numbers.

I should note that I submitted a paper[2] to NBT in 2016 that highlighted these problems in their 2016 report. The paper was rejected and their written rejection stated:

> We appreciate the issue that you raise and we congratulate you for your thoughtful analysis and dissection of our feature. However, we feel that we do include a variety of metrics in our analysis, and that we try to capture the varied nature of the industry, and not treat companies as if they were apples to apples.
>
> With this in mind, I regret that I am unable to offer to publish your feature in Nature Biotechnology. I have not been persuaded that the opinions presented will likely be of sufficient interest to Nature Biotechnology's broad readership.
>
> (Email received 12 November 2016 from Laura DeFrancesco, Feature Editor of Nature Biotechnology).

Despite this, their subsequent 2017 annual report (Morrison and Lähteenmäki, 2017) and associated dataset excluded several of the firms I highlighted as problematic to any dataset seeking to represent a biotech industry. They excluded CSL, Bio-Rad and Perkin Elmer, but retained Monsanto and Shire. In the 2017 report (Morrison and Lahteenmaki, 2017, p. 623), they also added the following addendum to their definition: "This year, we removed several companies that are not, strictly speaking, developing innovative biologics and services". The statement did little to explain why Monsanto's revenues would still be counted as biotech or how Shire is a qualifying biotech firm.

Also, the removal of these firms did not address the core conceptual concerns I expressed in the submitted paper, which first of all, was that attempting to aggregate firms based on an ambiguous and unknowable technology definition is a fundamentally-flawed exercise. Second, applied technology, even if it could be well-defined and consistently applied, may not be a meaningful way to aggregate firms when seeking to represent an industry and to report on its productive output. The term

[2] The working paper was entitled 'There is no biotech 'industry': The challenge of performance measurement for small biotech firms' by Peter Molloy, Michael Gilding and Lester Johnson.

'industry' implies some commonality in markets, customers, suppliers and competitors, not just an assemblage of companies based on the fact that they use a certain technology for some or most of their business activities, regardless of the commercial marketplace.

Third, and as a result, when one tries to measure the performance of such an aggregate, there are real challenges, because the relevant productive outputs vary widely. Sales and profitability are relevant to commercial firms like Monsanto and Shire, but are largely irrelevant to the vast majority of loss-making biotech firms that have no revenues and may never generate them.

4.4. Conclusions

The problems in defining what biotechnology is, and what a biotech firm is, translate into problems in defining the biotech industry. Some say the industry is undefinable, perhaps indicating that the attempted translation of poor definitions to an industrial level only amplifies the weaknesses of the definitions.

Technologies have generally been cross-industrial and biotechnologies are probably no different. Like microelectronics for example, biotechnologies span multiples industries – pharmaceuticals, diagnostics, research tools, agriculture, industrial processes, waste management and others. However, apparently driven by the PAB phenomenon, it seems that some have sought to view biotechnology differently. An attempt has been made to treat biotechnology as a supra-industry or meta-industry, which is sufficiently important – due to PAB – to be elevated about existing conceptions of industry and perhaps even too important to be subordinated by industry considerations at all. This is exemplified by what I have called the OECD paradigm.

The attempt to translate this OECD paradigm into a biotech firm definition has led to a confusing set of definitions of firms that have little practicability. It also necessarily fails to translate into a practical biotech industry definition.

Leaping over this translation problem (although not explicitly recognising it), Pisano (2006b) has defined biotech firms as firms born after 1976 (the birth of Genentech) that employ any modern technology to develop drugs. Powell et al. (1996) have offered a similar industry-specific firm definition in developing their database for industry analysis, although it embraced diagnostics as well as drugs (therapeutics).

Despite the uncertainty over the definition of the biotech firm and the industry, there have been major reporting platforms for annual performance reports on the biotech industry. The core source has been the annual *Nature Biotechnology* (NBT) reports, which have been produced every year since 1996. An analysis of the composition of the NBT dataset revealed that it included a wide variety of firms and that the inclusion criteria have perpetuated rather than resolved the definitional dysfunction. I

concluded that the PAB phenomenon is so entrenched that even clear elaboration of the definitional dysfunction will not be countenanced, as evidenced by the NBT response to the arguments made in this chapter. It is for this reason that a primary goal of this part of the thesis has been to find a way out of the definitional morass introduced and sustained by PAB, and to completely redefine the biotech firm so that meaningful performance analysis can occur. This is presented in the next chapter.

Chapter 5. Redefining the biotech firm

5.1. Pharmaceutical value chain

I propose that a pathway out of the definitional morass can be navigated by focusing on the most important industrial application of biotechnology (however defined), which is drug development. To substantiate this, I used the NBT 2017 dataset (Morrison and Lähteenmäki, 2017), which reported market values, revenues and other metrics for 586 public biotech firms across 27 countries. While I have concerns about the inclusion criteria for firms in the NBT dataset, for the purposes of assessing the extent to which biotechnology is applied across various industries, it represented a useful overall guide.

In that dataset, the US accounted for 325 firms or 55% of all biotech firms globally, for 82% of the global market value of all firms and for 84% of global revenues. Within the US, the 250 largest firms (based on market value) represented 99.8% of reported US biotech market value. I analysed these 250 firms and sought to classify them based on their principal field of industrial application. The results are shown in Table 6 and reveal the dominance of drug development as the industrial or application focus for the firms reported as 'biotech' in the dataset. Overall, pharmaceuticals represented 80% of firms and 86% of market value.

Table 6. Classification of 250 largest US public biotech firms

Principal industrial application	Number of firms	% of total	Market capitalisation ($ millions)	% of total
Pharmaceuticals	199	80%	621,529	86%
Diagnostics	20	8%	28,492	4%
Research tools	14	6%	22,797	3%
Medical devices	8	3%	3,020	-
Veterinary	2	1%	351	-
Food & Beverage	2	1%	150	-
Agriculture	1	-	46,133	6%
Other	4	2%	4,351	-
Grand Total	**250**	100%	**726,822**	100%

Biotech firms engaged in drug development operate within the pharmaceutical industry ecosystem (Pisano, 2011) and it is impossible to understand the nature of their business without reference to

their role in what has been called the 'pharmaceutical value chain' (Biswas, 2014; Champion, 2001; King, 2006). Value chain analysis is an approach introduced by Porter to examine the way in which the functional components within a firm create value for customers and ultimately contribute to the firm's competitive advantage in the market (Porter, 1985). Essentially, value chain analysis is a tool to disaggregate a business into strategically relevant activities (Brown, 1977).

However, outside academia and in the context of business strategy, the term 'value chain' has also been adopted and applied as an industry-level supply chain concept, in which intermediaries contribute value to the product that ultimately reaches the market. This value chain concept is particularly pertinent to the pharmaceutical industry, where the time to market for a new drug can be up to 15 years and there is a temporally long chain of parties involved in its ultimate delivery (Biswas, 2014; Champion, 2001; Gurau, 2004; King, 2006). The pharmaceutical R&D value chain starts with early research into a disease and ends with the launch and marketing of a drug, as depicted in Figure 2.

Figure 2. Pharmaceutical R&D value chain

Adapted from: *Unleashing Pharma from the R&D Value Chain*, 2013 report by A.T. Kearney, Inc. www.atkearney.com/documents/10192/1641099/Unleashing+Pharma.pdf)

Prior to the explosion of new technologies after the 1970s, including biotechnologies, Big Pharma undertook all steps in the R&D value chain. However, over the last three decades and faced with shrinking internal R&D productivity and increasing regulatory and commercial complexity, Big Pharma has turned to technology-focused drug-development firms to provide the candidate drugs to replenish their drug pipelines (Pisano, 2006b, 2015). Effectively, Big Pharma has outsourced its early stage drug R&D to small firms that specialise in drug discovery and development (Davies, 2013; Farag, 2009; Greiner and Ang, 2012; Higgins and Rodriguez, 2006; Kruse et al., 2014; Nicol et al., 2013).

In most cases, these small firms are referred to by pharmaceutical companies as 'biotech' companies, even though many employ drug discovery and development technologies that may not fit in the OECD list definition of biotechnology or qualify as biotechnology according to restricted definitions insisted on by others (Miller, 2007; Rader, 2008). Rather, consistent with the Pisano definition, these are firms that apply a range or mix of technologies – chemistry, biology, medicine and computer sciences – all aimed at drug discovery and development (Pisano, 2006b).

5.2. Biotech firms as intermediaries

What unites these firms is not their applied technology at all, but their business model and value chain. They in-license advances in basic science from universities, usually as patents or lead compounds, optimise and develop them into candidate drugs, take these candidate drugs through early clinical development, and then push them towards the market, usually via a pharmaceutical partnership. As described by Pisano (2006b, p. 143):

> Biotechnology firms are like middlemen in a R&D supply chain: they take on projects at early stages, develop them to some point, and then license (resell) them to pharmaceutical companies for further development.

For now, I will refer to these drug development intermediaries as 'drug development biotech' firms and by the abbreviation 'DDB' firms (or DDBs). This terminology has not been used previously in the literature[3]. I will offer a more refined and comprehensive definition of DDB, later in this chapter.

In a few cases, DDB firms have been able to migrate from their R&D intermediary role to commercial-stage businesses that market their own drugs, make sales and profits, and for the most part, resemble large pharmaceutical companies. Drawing parallels with big pharma, the largest of these firms are referred to as 'big biotech' (Katsnelson, 2005). According to Ernst & Young, the 'big biotech' title is reserved for those commercial-stage firms generating greater than $1 billion in revenues per year (Ernst & Young, 2013), although in some cases, $500 million in annual revenues has been used as the threshold (Aggarwal et al., 2006).

With Genentech acquired by Roche, Gilead and Amgen became the two largest big biotech companies, each with annual revenues greater than $20 billion a year, market capitalisations around US$100 billion and ranking in the top 20 pharmaceutical companies in the US. Despite their genesis as DDBs, such big biotech firms are essentially pharmaceutical companies, competing with Big Pharma in the marketplace for drugs, and competing with Big Pharma for licensing deals with DDB firms. Essentially, a drug big biotech firm is a DDB firm that has moved down the value chain to become a 'fully-integrated pharmaceutical company' or FIPCO (Shimasaki, 2014b). They still engage in R&D, as do their Big Pharma competitors, but no longer rely on it exclusively, pursuing in-licensing deals with DDB firms, just like big pharma.

The metamorphosis from DDB to big biotech is primarily a US phenomenon. In the 2016 NBT dataset, we identified 11 biotech firms that had started life as DDBs (Morrison and Lähteenmäki, 2017) and had 2016 revenues greater than $1 billion. These are shown in Table 7. Of the 11 big

[3] I first presented the DDB concept in October 2017 at a plenary presentation at the 2017 Ausbiotech National Conference in Adelaide. It is also the subject of a paper currently being prepared for journal submission entitled 'Redefining the Biotech Firm.'

biotech firms focused on drug development and commercialisation, only one was outside the US, Actelion in Switzerland. However, Actelion was sold in 2017 to Johnson & Johnson, leaving no drug-focused big biotech firms outside the US.

Table 7. Big biotech firms that started as DDBs

Firm	Country	2016 Revenue ($ Billions)	Year Founded
Gilead Sciences	United States	30.4	1987
Amgen	United States	23.0	1983
Biogen Idec	United States	11.4	1978
Celgene	United States	11.2	1986
Regeneron	United States	4.9	1988
Alexion	United States	3.1	1992
Actelion	Switzerland	2.4	1997
Vertex	United States	1.7	1989
United Therapeutics	United States	1.6	1996
BioMarin	United States	1.1	1997
Incyte	United States	1.1	1991

According to Owen (2016), the reasons attributed to the success of the US in breeding big biotech firms include: high quality universities where biomedical research is massively funded by the US Federal Government; efficient mechanisms for licensing or spinning out companies from these universities; a deep-pocketed venture capital community funded by a large population of high net worth individuals looking for high returns; and the US being the world's single largest domestic pharmaceutical market without centralised drug price controls (Owen, 2016). I would add that the widespread availability of grant funding under the Small Business Innovation Research (SBIR) program and access to National Institutes of Health (NIH) grants, gives many startup US biotech firms valuable early funding to support development programs. In addition to all this, the success of flagship companies like Genentech, Amgen and Gilead feeds the ambitions of others and whets the appetite of US investors, by signalling the high investor returns achievable from the biotech business model.

Whatever the reasons, big biotech is overwhelmingly a US phenomenon and outside the US, DDB firms tend to remain as drug development intermediaries, rather than mature and grow into commercial-stage businesses. However, and even in the US, it is important to appreciate that such a transformation requires capital, pipeline, infrastructure, competencies and culture that may be beyond the reach of small firms that are in the drug development intermediary role. It also requires time.

Gilead, the largest big biotech, took 15 years to become profitable and another 10 years to reach big biotech status (Owen, 2016).

While becoming a commercial-stage business and even achieving big biotech status may be the stated ambition for some DDB firms, few achieve it. If they do – like Gilead – they are usually successful in the R&D intermediary role first, which provides the springboard for their growth, migration and ultimate survival as true pharmaceutical businesses. For most, aspiring to become a FIPCO or big biotech is unrealistic (Marx and Hsu, 2015; Shimasaki, 2014b), because of the enormous cost of drug development, recently estimated to be US$2.6 billion for each approved drug (Pisano, 2015), and the high risk of failure in the market, which together necessitate large capital resources, well-developed marketing competencies and infrastructure, and a diversified portfolio of marketed drugs to make that infrastructure cost-effective and mitigate commercial risk. The gap between pre-commercial intermediary and big biotech is a bridge too far for all, but a few DDBs.

However, *success* for a DDB firm does not require that it grow into a full-scale commercial-stage business. In the 2016 NBT dataset, there were 32 DDBs firms that had market valuations in excess of US$1 billion, with the largest, Seattle Genetics, worth $7.5 billion. These DDB firms have created substantial value without ever directly commercialising a product or generating significant revenues. Indeed, most DDBs will never launch a product. Some may garner revenues from pharmaceutical licenses in their role as intermediaries in the R&D value chain and thereby create significant value for investors. They may even become profitable from these licensing revenues.

Some DDBs will secure a marketing approval for a drug in a limited indication (disease) and engage in small-scale marketing, especially in the case of rare diseases, where the target market may be very limited and can be managed by a pre-commercial business. DDBs may also make unapproved drugs available through special access and named patient programs (NPP), which allow doctors to obtain supply of unapproved medicines for treating nominated patients with life-threatening diseases who have exhausted all other treatments; in certain circumstances these NPP activities can generate sales. In my view, these limited marketing activities do not constitute the DDB becoming a commercial-stage firm or disqualify it from classification as a DDB. Rather than a signal of the firm's migration to commercial stage, such limited marketing may be simply adding value to the firm, by affirming the commercial opportunity, prior to its sale to a Big Pharma (or big biotech).

Importantly, many DDBs will be acquired by established pharmaceutical businesses and then disappear, yet they still will have been considered *successful* from the perspective of their investors. Survival is not necessarily a requirement or measure of success for DDB firms, at least from an investor perspective.

5.3. **Market for DDBs**

Markets are pools of demand where businesses sell products (or services) to meet that demand and receive revenues in exchange. When DDB firms are conceptualised as pre-commercial intermediaries in the pharmaceutical R&D value chain, it becomes apparent that their market is the demand from pharmaceutical firms for acquisition of their drug pipeline, usually via licensing deals.

DDBs develop candidate drugs that they sell or license to pharmaceutical partners at the perceived optimum time. The licensing transaction typically involves the payment to the DDB of an upfront license fee, the provision of R&D funding to support further development, the promise of milestone payments as the candidate drug progresses towards marketing approval and finally, royalties on sales of the product, if it is launched. These various revenue streams are vitally important to DDBs, because they are typically non-dilutive to existing investors. As previously mentioned, the licensing revenues may even allow the DDB to become profitable, although one would expect that most, if not all, licensing revenues would be reinvested in value-creating R&D.

A licensing deal adds further value in that it provides important third-party endorsement of the commercial value of the firm's candidate drugs (Campart and Pfister, 2007) and can signal to investors a reduced risk of failure for the drug development program, because of the additional capabilities, funding and commitment that the Big Pharma partner brings to bear. The other value embedded in the licensing transaction is the increased anticipation that the DDB firm ultimately will be acquired by its pharmaceutical partner, thereby delivering a valuable exit for its investors. An acquisition is often the preferred outcome for the pharmaceutical partner, because it puts control of the asset in the hands of the partner and avoids the potentially complex, joint decision-making and control involved with licensing partnerships.

Viewed in this way, the market for a DDB firm is not the pool of people affected by the disease that is targeted by its candidate drug or the prescription demand from doctors associated with that disease, but the pool of demand from pharmaceutical companies for the licensing or acquisition of new drugs to treat that disease. Even if the drug never reaches the market to treat the target disease, the DDB firm profits from the licensing transaction. In practice, therefore, large pharmaceutical firms (including big biotech) are the *customers* of drug development biotech firms. In contrast, for pharmaceutical and big biotech firms that are actively marketing drugs, the market is the prescriber demand for a product to treat a disease and generally their primary customers are the doctors who might prescribe their drug.

5.4. **DDB firms defined**

Based on the foregoing analysis, I now offer a more comprehensive definition of DDB firms as follows: DDB firms are independent, R&D-intensive, drug-development-focused, pre-commercial enterprises born after 1976 that primarily create value as intermediaries in the pharmaceutical value chain.

In line with the Powell DBF definition (Table 5), they are independent firms, not subsidiaries of commercial enterprises. In line with the Pisano definition and the year of birth of Genentech, they are firms born after 1976. Importantly, DDBs are pre-commercial firms. Where DDB firms report revenues, they are typically from licensing arrangements, rather than commercial marketing operations. They may engage in limited sales of their product to certain niche markets, but are not engaged in broader commercialisation activities and their focus remains on drug development R&D.

They are further distinguished by their market, which is the demand from pharmaceutical (or big biotech) firms for in-licensing or acquisition of new drugs. DDB firms are focused on drug development and generally seek to commercialise their candidate drug pipeline through partnerships with pharmaceutical companies.

Under my DDB definition, the term 'drug' refers to all therapeutic agents for treating or preventing human disease and that are treated as drugs from a regulatory perspective. The drugs in development may be biologics, vaccines or small molecules[4], because from a market perspective, they all compete for the same ultimate medical needs and the associated licensing demand. They can be new molecular entities (NMEs) or enhancements or repurposing of existing drugs. Moreover, they can leverage any technology that contributes to the development of drug pipelines that create value in the pharmaceutical value chain. The drugs could be the product of modern biotechnology (however defined) or any other drug discovery technology, including chemistry, biology, high-throughput screening, computer modelling or other approach that yields a candidate drug that can compete in the market for pharmaceutical licensing deals.

Further, under my definition, if a DDB firm becomes a commercial-stage business that shifts its operational focus from R&D intermediary to commercialisation activities, it is no longer a DDB firm, but a drug-focused, commercial-stage business. To assist with classification, I intend to refer to commercial firms that have emerged from DDBs as 'drug development and commercialisation' firms, or 'DDC' firms, reflecting their genesis as DDB firms and their change in business model from

[4] Biologics are defined by the FDA as drugs that are derived from biological sources and are comprised of at least 42 peptides (protein subunits). Vaccines are also of biological origin and generally classified as biologics; the reason I distinguish them here is that their role is generally (although not universally) disease-prevention rather than disease-treatment. Small-molecule drugs are drugs that are the product of synthetic chemistry or natural sources (e.g., plants) and generally not comprised of any peptides.

pre-commercial R&D intermediary to a drug development and commercialisation business. The largest of these DDCs would be classified as big biotech, if their revenues exceed $1 billion annually.

As previously stated, in addition to licensing revenues, DDBs may be able to generate modest revenues from limited marketing of an approved or unapproved drug, while continuing to focus on R&D as the core business activity. Under the current definition, this would not indicate that they have become DDCs, are no longer 'pre-commercial' or are otherwise disqualified from being classified as DDBs. Similarly, a DDB may generate sufficient licensing revenues to generate a profit; this does not constitute migration to a DDC.

5.5. Other biotech firms

Given that, as indicated in Table 6, drug development is the dominant industry focus for those firms classified as 'biotech' in the NBT dataset, one would predict that DDBs would be the dominant form of pre-commercial biotech firm. While the focus of this thesis is on DDB firms, it is helpful as context and to broaden the conceptual foundation for DDBs to distinguish other biotech (pre-commercial) firms operating outside the pharmaceutical value chain. As defined by one prominent industry authority, apart from drug development, these may include those engaged in the development of diagnostics, medical devices, digital health applications, research instrumentation and tools, biocrops, biofuels and industrial applications (Shimasaki, 2014a). Like DDB firms, the biotech firms operating in these other fields may be intermediaries in specific industry value chains and may seek to create and monetise value through licensing arrangements with large commercial firms in those value chains. Also, they may be able to evolve into commercial-stage businesses themselves in those same value chains.

For the purpose of broad classification in this study and without any substantive evidence or characterisation beyond DDB firms, I propose the descriptors and abbreviations in Table 8 for the most clearly discernible and prevalent types of pre-commercial biotech firms and further suggest abbreviations for the type of commercial firm into which each could grow.

Table 8. Types of pre-commercial biotech firms

Value chain	Name of pre-commercial firm	Proposed abbreviation	Commercial stage firm abbreviation
Pharmaceuticals	Drug development biotech	DDB	DDC
Diagnostics	Diagnostics biotech	DXB	DXC
Medical devices	Medical devices biotech	MDB	MDC
Research Tools	Research tools biotech	RTB	RTC

These represent the four main types of pre-commercial biotech firms, as per Table 6. Also, they tend to be reasonably well-defined with respect to their individual value chains. As indicated in the table, however, there are other types of biotech firms that can be identified, including those engaged in developing industrial applications, environmental products (biofuels, for example), animal health products and agricultural products (GMO seeds for example). However, as indicated in Table 6, these are relatively rare and can cover such a wide breadth of industrial applications that I am disinclined to associate a specific classification with each and so have designated them as 'Other'.

As discussed in Chapter 3, the Powell definition of DBFs allowed both therapeutics (drug) and diagnostic firms to be counted as DBFs. Intuitively, it might seem that because diagnostics and drugs are both aimed at human health, then biotech firms in these fields operate in the same value chain. However, I believe that these represent two distinct types of biotech firms operating in different value chains and therefore, they need to be distinguished in any comprehensive definition of the biotech firm.

In vitro diagnostics (IVD) are used mainly to diagnose diseases at point-of-care or to target treatment to certain patient sub-populations. As such, they may assist in drug treatment. Despite this crossover, biotech firms developing IVDs operate in a very different market and value chain to DDB firms. In the US, IVDs are regulated as medical devices and have lower regulatory hurdles, less burdensome clinical trials, and a shorter time to market than drugs. The estimated overall time and cost of development for IVDs are 3-7 years and $5-100 million respectively, compared with 12-15 years and $250-1,500 million for drugs (Shimasaki, 2014a). They also have different payer and reimbursement structures, and for the most part, different customers as commercial licensing or acquisition partners (Shimasaki, 2014a). For these reasons, DXBs are different to DDB firms and should not be aggregated with DDBs, except under a broader heading of a biotech firm to be presented below.

One confounding exception may be 'companion' diagnostics, which are diagnostic tests co-developed with a drug to target its usage to a specific sub-population of patients to improve the therapeutic effect or reduce side effects. The sales of companion diagnostics are relatively small (Akhmetov et al., 2015) and while they may be the product of the same technologies as IVDs, from a value chain perspective, I view them primarily as an augmentation of the drug, rather than a separate diagnostic product market. Parallels could be drawn with controlled-release drug delivery technologies that are licensed to pharmaceutical firms to enhance the efficacy or reduce the side effects of drugs. Like companion diagnostics, such technologies contribute to the pharmaceutical value chain rather than the diagnostics value chain.

5.6. **Redefining the biotech firm**

Based on the foregoing definitions and analysis, it is possible to present a comprehensive new definition for a 'biotech firm' as follows:

A biotech firm is defined as an independent, R&D-intensive, pre-commercial firm born after 1976 that utilises a range or mix of technologies to create value as an intermediary in an industry value chain.

The key defining features of this definition are:

- the fact that the firm must be pre-commercial and its business model must be that of intermediary in a value chain associated with a specific industry;
- despite the name 'biotech', it is technology agnostic, employing any and all technologies that can contribute to its ability to generate value in its value chain; and
- as an intermediary, its market is the demand for licensing or acquisition deals from commercial stage firms that are downstream in the same value chain.

I refer to this conception of the biotech firm as the 'Pre-commercial Intermediary' or PCI view of the biotech firm. Note that when referring to a biotech firm in the remainder of this thesis, I am referring to a PCI biotech firm according to this definition.

The PCI view of the biotech firm approximates the definition of the DBF, as discussed in Chapter 3. While the original DBF concept was restricted to biotech firms engaged in drug development and diagnostics (Powell et al., 1996; Powell and Sandholtz, 2012), many DBF studies included (or failed to exclude) firms engaged in other fields, such as medical devices, digital health, agricultural, veterinary and environmental biotechnology (Hoenen et al., 2014; Kolympiris et al., 2011; Moodysson and Jonsson, 2007; Moustakbal, 2014; Niosi, 2003; Oliver, 2001; Quintana-García and Benavides-Velasco, 2005).

If this broader DBF conception is applied, then it is essentially the same as my proposed biotech firm definition, provided that the DBF definition specifically excludes commercial stage firms. With this caveat, I will use the terms DBF and (PCI) biotech firm interchangeably.

The PCI view of the biotech firm has some important overlap with the Pisano view of the biotech firm (Pisano, 2006b). One of these is the technology agnosticism, which is a critical leap needed to resolve the definitional dysfunction around biotechnology. The Pisano definition also stipulates that the firm be born after 1976, a practical requirement that I would endorse to avoid misclassifying long-established commercial firms (like Monsanto or CSL, for example) as biotech firms, simply because they have added biotechnology to their R&D capabilities.

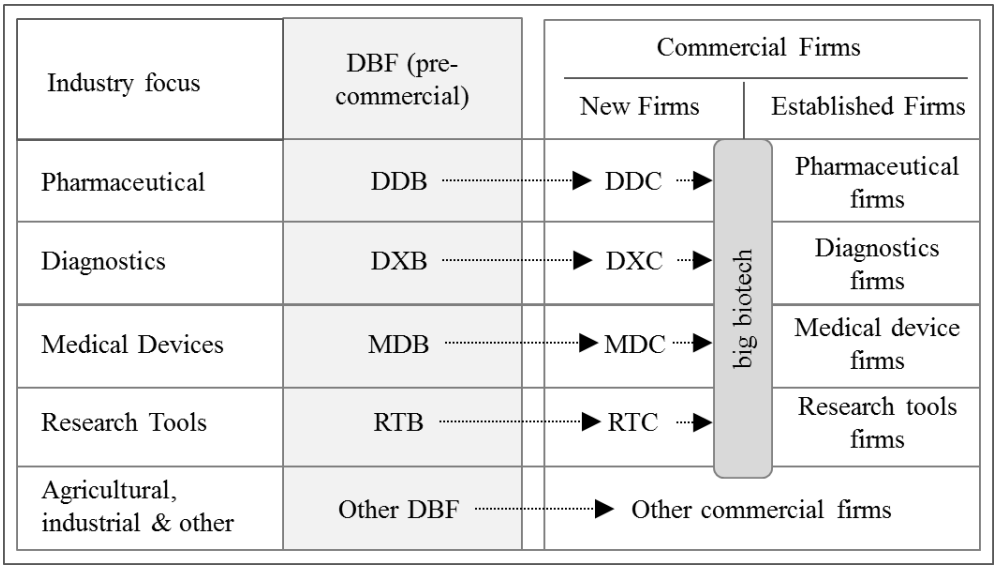
However, there are also important differences. First, the Pisano definition is limited to drug development. Second, it does not distinguish between commercial and pre-commercial firms, and this is a critical difference between the Pisano view and the PCI view. Table 9 seeks to compare and contrast the Pisano definition with the PCI view and more specifically, the DDB definition:

Table 9. DDB versus Pisano definition

<table>
<tr><td>Pisano definition of biotech firm</td><td>DDB</td><td>PCI view of biotech firm</td></tr>
<tr><td colspan="3">Born after 1976</td></tr>
<tr><td colspan="3">Technology agnostic – all modern technologies can be applicable</td></tr>
<tr><td colspan="2">Exclusively pharma</td><td>Includes non-pharma firms</td></tr>
<tr><td>Not exclusively pre-commercial intermediaries. Includes big biotech and other commercial firms</td><td colspan="2">Exclusively pre-commercial intermediaries. Excludes big biotech and other commercial firms</td></tr>
</table>

In contrast to PCI biotech firms, which are all pre-commercial by my definition, I define big biotech firms as those for which the business model is not that of an intermediary pursuing licensing demand, but a commercially-focused business competing in the broader pharmaceutical (or other) marketplace. While the term ‘big biotech’ is unlikely to be displaced, such firms are no longer *biotech* firms according to the PCI view, and I believe should not be aggregated with DBFs for analytical, research or policy purposes. Based on the foregoing, I offer the overall classification schema in Figure 3 to describe and differentiate firms in the biotech ecosystem.

Figure 3. Proposed classification of firms in the biotech ecosystem



As previously indicated, 'Other DBF' could include agricultural, animal health, environmental or industrial applications. For each of the four major industry classifications in Figure 3, there are numerous examples of established commercial firms as shown in Table 10.

Table 10. Largest commercial firms by industry focus

Pharmaceuticals	Diagnostics (IVD)	Medical Devices	Research Tools
Abbvie	Abbott Labs	Baxter	Agilent
Amgen	Becton Dickinson	Becton Dickinson	Bio-Rad
Gilead	BioMerieux	Cardinal Health	Bio-Techne
GlaxoSmithKline	Danaher	DePuy Synthes	Bruker
Johnson & Johnson	Exact Sciences	Fresenius	Danaher
Merck & Co	Ortho	GE Healthcare	GE Healthcare
Novartis	Roche	Medtronic	Merck KGA
Pfizer	Siemens	Philips Healthcare	Perkin Elmer
Roche	Sysmex	Siemens	Thermo Fisher
Sanofi	Thermo Fisher	Stryker	Waters

Table 10 shows the largest commercial firms in each industry category relevant to DBFs, based on various online sources[5] and shown in alphabetical order in each category. As is evident from the table, firms tend to specialise in one industry area, although there are some exceptions. For example, Roche has both pharmaceuticals and diagnostics businesses, Thermo Fisher is considered both a diagnostic and research tools company, and Becton Dickinson develops and markets both diagnostics and medical devices. Interestingly, Amgen and Gilead, both considered 'big biotech' firms, are classified as pharmaceutical businesses, which is in keeping with the conceptions that form the basis for the DDB and other DBF classifications.

Using the 2016 NBT dataset (Morrison and Lähteenmäki, 2017), I classified the 250 largest biotech firms in the US according to my proposed schema above. The results are shown in Table 11.

Based on my classification schema, there were 44 commercial-stage businesses reported in the dataset as 'biotech', of which 20 emerged from DDBs and qualified as DDCs and 11 qualified as big biotech firms, using the $1 billion revenue threshold. There were 11 DXCs, of which only two qualified as big biotechs. One of the five RTCs qualified as a big biotech and there was one MDC (not qualifying as big biotech).

There were seven commercial-stage firms in the dataset that were designated as 'biotech', but which I classified as 'other', because they did not evolve from DBFs. These included a nutraceutical manufacturer, a hospital products supplier, a contract chemical manufacturer, a company selling edible algae, an agricultural chemicals and seeds maker (Monsanto) and two pharmaceutical businesses that did not start as DDBs.

Among the 206 PCI biotech firms (DBFs), I was able to classify 177 firms as DDBs. I also classified nine DBFs as DXB, nine as RTB and seven as MDB. In addition, I found four other DBFs, two of which were involved in veterinary applications and one each in industrial and environmental applications.

[5] Sources:
Pharmaceutical top 10: http://www.pharmexec.com/pharm-execs-top-50-companies-2018
Diagnostics top 10: https://www.statista.com/statistics/331718/top-global-companies-by-in-vitro-diagnostics-revenue/
Medical devices: https://www.proclinical.com/blogs/2018-5/the-top-10-medical-device-companies-2018
Research tools: https://globenewswire.com/news-release/2016/08/19/865500/0/en/58-Billion-Life-Science-Tools-and-Reagents-Market-2016-Global-Report-2015-2020.html

Table 11. Classification of 250 largest US firms designated as 'biotech' by NBT

Type of firm	Number of firms	Market capitalisation $ millions	Revenues $ millions
Commercial firms			
DDC	20	500,828	96,445
DXC	11	25,340	5,491
RTC	5	20,524	2,718
MDC	1	450	37
Other	7	48,691	14,559
Total Commercial	44	595,834	119,250
DBF (pre-commercial)			
DDB	177	119,715	5,352
DXB	9	3,152	305
RTB	9	2,273	432
MDB	7	2,569	384
Other	4	3,278	229
Total DBF	206	130,988	6,702
Grand Total	250	726,822	125,952

5.7. Implications of the new definitions and analysis

Representing 86% of DBFs by number and 91% by value, it is clear that DDBs are the dominant form of biotech firm and therefore, a strong case exists for future DBF research to focus on DDBs as the primary unit of analysis.

Another implication is that DBF researchers should carefully scrutinise so-called 'biotech industry' datasets to identify and focus on pre-commercial firms (DBFs) and importantly, to discriminate DDBs from other DBFs. The NBT dataset demonstrates that the available aggregates may contain a mixture of pre-commercial and commercial firms operating across various industries.

The NBT dataset also contains commercial businesses that did not evolve from DBFs and do not seem to qualify as 'biotech' by any definition. I would recommend that the authors of the NBT

reports consider using the definitions proposed here, and replace their dataset with one dedicated to DBFs as defined here, with a focus on DDBs as a primary unit of analysis.

In regard to the NBT reports, along with those generated by *Scientific American* and Ernst & Young, I contend that aggregates of DBFs should not be referred to as *industries*, because an 'industry' embraces all participants in a particular value chain. For example, the pharmaceutical industry includes Big Pharma (and drug-focused big biotech), DDBs, bulk drug suppliers, contract manufacturers, clinical research organisations (CROs) and a vast array of legal, regulatory and other industry-focused service providers, all of which share in the pharmaceutical value chain. DDBs represent only one type of business operating in that industry.

To some extent and adopting a field perspective, universities and PROs also participate in the pharmaceutical industry value chain, as suppliers of technology, and as suppliers of scientific employees to DDBs and pharmaceutical firms. They also act as sites for the conduct of clinical trials and as a source of opinion-leaders to advocate for specific drugs. However, this participation by PROs is peripheral to their core activities and missions.

As already described in Chapter 4, the term 'sector' has been used to refer to aggregates of biotech firms, sometimes interchangeably with 'industry'. I believe there is a case for referring to biotech firm aggregates (at least at the DBF level) as a 'sector'. In a government policy framework, the term 'sector' generally implies a commonality in value chain, business model and market that would allow for cohesive policy-framing (Moustakbal, 2014). From an investor perspective, 'sector' implies a commonality in risk and return, which may be best described by value chain, business model and market considerations. From either framework, 'sector' may be a better way to described biotech firm aggregates than 'industry.' Therefore, I propose that it is appropriate to refer to an aggregate of DDB firms, at a country or global level, as a DDB 'sector'.

5.8. The emergence of 'biopharma'

Finally, and with respect to terminology, I need to comment on the growing use, especially in industry circles, of the term 'biopharmaceutical' or 'biopharma' to describe biotech firms focused on drug development (Ahn et al., 2018; Downs and Velamuri, 2016; Lazonick and Tulum, 2011; Morrison and Lähteenmäki, 2016; Rossi et al., 2015). It has also been used to embrace large pharmaceutical firms as well as DDBs, as in the 'biopharma industry' (Ahn et al., 2018; Banerjee and Siebert, 2017; Boni, 2016; Morrison, 2017; Walsh, 2014).

Because the term 'biopharmaceutical' technically refers to biologic drugs that are the product of bioprocessing (such as fermentation), the use of the term and its foreshortened variant 'biopharma' to refer to all companies in the drug development value chain has caused confusion and consternation (Rader, 2008). With the apparent growing use of 'biopharma', the confusion can only increase.

Given the importance of the drug development value chain to investors and participants, and the general failure to resolve the long-standing definitional problems around biotechnology in a way that is relevant to businesses operating in that value chain, it is not surprising that a term has emerged in an attempt to extract the pharmaceutical value chain from the morass. While 'biopharma' may adequately describe the ecosystem in which DDBs and pharmaceutical firms operate and create value, I recommend against the use of the term for two reasons: First, it does not discriminate the important business model and market differences between DDBs and commercial firms in the value chain. Second, it will lead to ongoing confusion between its meaning and the 'biopharmaceutical industry', which generally refers to firms engaged in the manufacturing and commercialisation of biologics.

5.9. Conclusions

Regardless of how biotechnology or biotech may be defined, the dominant industrial application is pharmaceutical drug development. I have examined the roles of players in the pharmaceutical R&D value chain and identified the unique business model, value chain and market for drug development biotech firms. I have referred to these businesses as DDB firms and provided a clear definition that distinguishes them from other biotech firms and all commercial firms, including big biotech.

I have noted that DDBs represent the most prevalent and important type of biotech firm in the US. Likely, this dominance of DDBs will apply outside the US also, although that analysis has not been done here. I have concluded that DDBs should be disaggregated from all other firms historically designated as biotech and the DDB sector should become a focus for policy formation and performance analysis.

I have demonstrated that historical analyses of what has been deemed to be the biotech industry have been underpinned by the notion that technology can define an industry, possibly out of a creditable desire to demonstrate the industrialisation of modern biotechnology. However, as a result, the industry reports over the last two decades have comingled DDBs with a mélange of other businesses, based on an ill-defined and problematic technological commonality, which largely ignores business models, value chains and markets. Understandably, such aggregates have resisted effective analysis and may have resulted in wasted years of reporting on an illusory industry, using metrics that are irrelevant to the most important and prevalent type of biotech firm – the DDB. I hope that this research may lead to a re-conceptualisation of biotech firms and a consequent revision of the aggregates used to represent such firms.

I contend that DDBs should become the focus for biotech performance analysis, planning and policy development. I hope that this thesis might lead to a redefinition of the biotech sector and that this

might contribute to more productive and realistic performance analysis, reporting and policy planning, with a focus on the DDB sector.

An important part of that planning must be the realisation that the US is a special case and not necessarily a model for the rest of the world. The challenge for countries outside the US is (and has been for three decades) to develop a successful DDB sector, potentially without the realistic prospect of a pathway to creating big biotech firms that can act as the anchor tenants.

I have proposed a comprehensive new definition for a biotech firm and for the first time in the literature, disentangle the business model of biotech firms from big biotech and other commercial businesses previously classified as 'biotech'. I have referred to this as the Pre-commercial Intermediary or PCI view of the biotech firm, and noted that, with certain specificities, the PCI biotech firm definition may be used interchangeably with the literature-prevalent term, DBF.

In addition to DDBs, I propose that other types of biotech firms can be defined based on the PCI conception of DBFs. I have suggested an initial classification schema, but cautiously note that apart from DDBs, the specific definitions and nomenclature for each of the other DBF types need further research and refinement. Despite this limitation, I believe that the new definitions may lead to more productive future thinking and research on DBFs. Using these classifications, analyses may reveal more meaningful data on the development and growth of each type of DBF in individual countries and potentially provide more granular input to policy formation and performance analysis.

Chapter 6. Measuring performance of biotech firms

The quotation below summarises the core challenge addressed in this chapter (Loffler, 2002, p. 346):

> How do we assess performance in the biotechnology industry? In the pharmaceutical industry, sales, profits, customer-base, or the richness of the pipeline, are common indicators of performance. None of these indicators are relevant to the biotechnology sector however, since most of the companies do not yet have products in the marketplace.

As stated in the introduction to Chapter 2, having a conceptually sound and clear definition for a biotech firm is essential to productive research into the performance of such firms, not only because it is needed to unambiguously define the pool of firms for which performance is to be assessed, but because without it, it is impossible to determine the appropriate performance criteria. Potentially, a conceptually sound definition of a biotech firm should enable deduction of the appropriate performance criteria. I explore this notion in this chapter, against an overview of the literature on biotech firm/industry performance, which to date has been hindered by the pervasive failure to resolve the underlying definitional problems that have plagued industry analysis.

6.1. Why measure performance of biotech firms?

As stated above, a primary driver for the proposed redefinition of the biotech firm is the quest for improved performance metrics. Therefore, the purpose and value of measuring biotech firm and sector performance warrants consideration.

One relevant perspective to that of the consumers of current biotech industry reports. Since 1996, NBT has published an annual report on the performance of the global biotech industry. In the last two years, the focus of these reports has shifted towards trends in mergers and acquisitions, licensing deals and investor sentiment (Morrison and Lähteenmäki, 2017, 2018). However, the underlying theme for previous years was about reporting on – and mostly celebrating – the performance of the biotech industry, based on financial metrics, especially revenues. The 2016 report referred to the "incredible performance" of the biotech sector in public markets (Morrison and Lähteenmäki, 2016). The 2015 report reported on the "rousing success" of the biotech sector, while the 2014 report hailed the "limitless" potential of biotech, in both cases highlighting a leader board based on revenue growth (Lawrence and Lähteenmäki, 2014; Morrison and Lähteenmäki, 2015). One way or another, the NBT reports for many years have attempted to highlight the performance of the biotech sector.

Presumably, the readers of *Nature Biotechnology* have an interest in understanding the development of the biotech sector and in seeing the successful industrialisation of biotechnology. Some of these readers may be scientists working on drug discovery technologies that they hope to see deployed by

biotech firms. Perhaps, some might contemplate starting their own biotech firm and riding the wave of success that the NBT reports convey. For these readers, the validity of the unit of the analysis and the performance metrics are important.

It is also useful to appreciate that the data used as the basis for the NBT reports is provided by Ernst & Young and that Ernst & Young uses the same data to produce their own annual reports on the biotech industry, which they promote to their consulting clients in the pharmaceutical industry and the biotech sector. Presumably, these clients would benefit from improved unit-of-analysis definition and performance metric validity.

The NBT data also has been used as a key input for the *Scientific American Worldview: A global biotechnology perspective*, which has been published annually since 2009. Australian governments and the local industry body, Ausbiotech, have repeatedly cited this report as evidence of Australia's biotechnology performance and international biotechnology leadership (Ausbiotech, 2015; Dalidakis, 2015). The purpose appears to be to promote more attractive government policies towards the biotech sector and to attract biotech firms and employment to Australia. Presumably, the policy-makers, firms and prospective employees would benefit from effective unit-of-analysis definition and performance metric validity.

Nature Biotechnology and the *Scientific American Worldview* are of sufficient prominence in the biotech sphere that a joint 'Super Session' has been devoted to them at the international BIO (Biotechnology Innovation Organisation) annual conference, to be held in June 2019. The 90-minute session is titled: "Nature Biotechnology and Scientific American WORLDVIEW: Biotech Innovation in a Faster Future" (https://convention.bio.org/program/, accessed April 25, 2019). To the extent that country or firm biotech performance is discussed in that session, the investors and biotech and pharmaceutical executives attending would surely benefit from effective unit-of-analysis definition and performance metric validity.

A related perspective is that of governments that have been seeking to build biotech as a strategically important sector. The fact that governments provide subsidies, tax rebates and grants to biotech firms demands a clear performance metric to assess the efficacy of these policies.

Boards of biotech firms need to understand firm performance because it affects executive compensation and the firm's market value (Chen et al., 2013; Guo et al., 2012). Naturally, investors have a keen interest in understanding biotech firm performance and how it is measured (Nesta and Saviotti, 2006). Entrepreneurs who seek to start new biotech firms need to understand the variables that affect performance (Cooper, 1993).

In summary, it is important to measure biotech firm performance from a number of perspectives. Boards and management need to know how their biotech business is performing, because it affects

executive compensation, portfolio strategy, funding strategy, employment and other crucial aspects of the biotech's operations. Entrepreneurs and investors need to be able to recognise a high-performing biotech business. Public research organisations (PROs) need to be able to recognise a high-performing biotech business, before they trust that business with a technology license. Governments need to be able to recognise a high-performing biotech business, to justify the provision of investments in the form of subsidies, tax credits, rebates and grants.

6.2. Other performance measures

Given the intangible nature of DDB assets, concepts such as intellectual capital (IC) and knowledge assets (KA) arising from the 'knowledge-based view' of the firm, are relevant to any discussion on DDB performance (Aino et al., 2014; Marr et al., 2004). IC and KA recognise the intangible nature of the value created by DDBs and that value creation can occur without a drug ever reaching the market (Cooper, 2000). Despite the recognition and popularity of the IC concept in the management literature, there is a lack of consensus on a precise definition (Carlucci and Schiuma, 2007).

Some have sought to design various measures by which IC performance can be assessed, such as the 'Balanced Scorecard', 'Performance Prism' and 'IC-index', to name a few (Marr et al., 2004). Some of these may have utility for measuring the value of intangible assets from an accounting perspective and others may be aimed at optimising internal knowledge management processes. However, these scales tend to be general in nature, akin to the R&D effectiveness and innovation performance scales. Like the R&D effectiveness and innovation performance scales, none of them is designed for DDBs or offers practical utility as a measure of the productive output of DDBs, DDB value or potential investor returns.

Some studies have used organisation survival as a measure of performance (Mayer-Haug et al., 2013). Intuitively this seems sound, because if an organisation fails to survive, then surely it has not been successful. However, this is not necessarily the case for DDBs. As noted in the previous chapter, a primary goal for a DDB firm may be to be acquired and deliver a valuable investor exit. As observed by Moustakbal (2014), merger and acquisition (M&A) transactions are the main 'exit' pathway for biotech firm investors and therefore represent a strategic choice, which may be prescribed by the DDB's investors (Moustakbal, 2014; Pajunen and Järvinen, 2018). Selling the firm before the development of a final product may be the preferred option, because it is less uncertain and hence more lucrative for investors (Andersson et al., 2010). Biotech firms are intermediaries and unlike virtually all other firms, are naturally ephemeral. This inevitably means the disappearance of the firm, yet the firm might be considered successful from the perspective of its investors. Survival is not necessarily a requirement for, or measure of, success for DDB firms, at least from an investor perspective. Indeed, from an investor perspective, *non-survival* may be preferred.

6.3. Biotech performance literature

The literature on performance measurement for biotech firms is extensive and has been reviewed by several researchers (De Luca et al., 2010; Kim, 2012; Mayer-Haug et al., 2013; Wu, 2013). These reviews indicate that a large variety of performance measures have been used and there is no unanimity about the best performance measurement; however, there is recognition that biotech firm performance is complex and difficult to measure (Mayer-Haug et al., 2013; Smith et al., 2014; Wu, 2013).

Most researchers agree that financial performance metrics, such as sales and profits, are not useful measures for the vast majority of biotech firms, which do not make profits and often have no products on the market (Coombs and Deeds, 1998; Loffler, 2002). Further, balance sheets do not capture or measure the intangible asset value of biotech firm output, because research and development (R&D) costs are generally expensed (Cumby and Conrod, 2001).

Despite this, the annual NBT reports and some DBF research studies have used financial performance metrics – notably sales – in their analyses, where their datasets have included a sufficient number of commercial-stage firms to make reporting of sales relevant, at least at an industry level (Hall and Bagchi-Sen, 2007). However, at an individual firm level, such measures have little value when the firm is pre-commercial, as are the vast majority of the more than 600 public and 8,000 private biotech firms worldwide (Wei et al., 2015). Further, when biotech firms are conceptualised as exclusively pre-commercial intermediaries, as in the PCI definition of the DDB, then it is self-evident that sales and profits are inappropriate as performance measures at any level.

Some have argued that revenues *are* a useful measure of overall industry performance, because they indicate the maturation of the industry from early-stage, pre-commercial firms to commercial-stage businesses (Lähteenmäki et al., 1999; Vieira and Hine, 2005). While I would argue that migration to a commercial-stage firm is not a necessary or realistic goal for a DDB, there may be some validity in this, especially in the US, where a number of firms have migrated from DBF to commercial-stage firms and a precious few to big biotech status. However, based on the NBT datasets, the annual revenue growth for 'biotech' in the US is almost entirely due to big biotechs, not newly minted DDCs. Therefore, measuring revenue growth is essentially just measuring the performance of a handful of US big biotechs and not the migration of new firms into the DDC ranks.

The extent that this revenue growth for big biotechs is greater than the growth of established pharmaceutical firms, could indicate a growing share of the total pharmaceutical industry by DDCs. This is potentially an interesting observation about the evolution of the pharmaceutical industry and the roles of various players in that industry. However, the validity of this rests on the dataset including only those commercial firms that have evolved from pre-commercial biotech firms. At least

for the NBT dataset, that is clearly not the case. In any case, regardless of their utility as a measure of the changing structure of the pharmaceutical industry, revenues have little utility as a performance metric for pre-commercial firms, such as DDBs.

Given the problems with financial performance measures for biotech firms, many studies have used surrogate performance measures. One of the most comprehensive reviews of this literature is by Wu (2013). As noted by Wu (2013), early studies of biotech performance used a simple patent count as a performance measure. According to Hoenen et al. (2014, p. 956), the rationale was that performance can be largely attributed to "monopolistic market rights and future technology options, protection from competitors, and improvements in the negotiating position of patent holders with partners, investors and remaining stakeholders."

However, there are several limitations with using patent count as a performance measure (Alegre et al., 2009; Quintana-García and Benavides-Velasco, 2005; Wu, 2013). One obvious one is that the commercial value of patents can vary widely. To address this, some research has used citation-weighted patent counts, because citations provide a measure of the patent's impact (Bontis, 2001; Liu et al., 2012). However, others have argued that even citation-weighted patents may not be a suitable performance proxy, because they typically reflect knowledge output in the discovery and development stage of a product, rather than products that actually reach the market (Rzakhanov, 2004). Other scales have incorporated the age of patents as a moderator to reflect value (Wu, 2013).

Recent studies have used more complex constructs such as 'R&D effectiveness' or 'innovation performance' (De Luca et al., 2010; Kim, 2012; Wilson et al., 2014; Wu, 2013). These scales are typically multi-dimensional constructs incorporating a range of innovation measures and/or R&D input or output scales. For example, the De Luca et al. (2010) R&D effectiveness scale employs items such as quality of scientific output, ability to attract key scientists and new patents generated (De Luca et al., 2010; Wilson et al., 2014) as key performance measures. Other studies have used scales that incorporate items such as the age of patents, degree of product differentiation and whether the company is first to market with a new product (Wu, 2013), scales with items related to product portfolio extension and opening of new markets (Alegre et al., 2009) or scales based on the number of products on the market and under development (Quintana-García and Benavides-Velasco, 2005).

In summary, there has been a proliferation of performance constructs and scales for biotech firms and the biotech industry, with little consistency between the various studies and no unanimity about the most effective scale. Moreover, all the scales measure 'generic' R&D outputs that may have some value as surrogates of performance in a research setting, but have little practical utility or validity as performance measures for DDBs, their management and investors. No board or investor has ever asked me for my firm's 'innovation performance' score!

Possibly one of the reasons why there has been a proliferation of these performance surrogates is that the biotech datasets available to researchers have not discriminated pre-commercial DBFs from commercial-stage biotech firms. In many cases, they have also included large, established, commercial firms that are very different in nature and genesis to DBFs. In this biotech *soup*, only the most generalised performance surrogates could be extracted. Once again, the problem boils down to the failure to resolve the definitional dysfunction around biotechnology and biotech firms.

6.4. **Investor captaincy**

I have repeatedly referred to the investor perspective and asserted that it is crucial in arriving at an understanding of the mission, purpose and performance of DDBs. While governments may fund the original scientific research via public research organisations (PROs) that allows a DDB to be born, in almost all cases, the DDB will generally only survive infancy and effectively advance its candidate drug pipeline if it has funding from private investors.

Consider the example of a new DDB that is created by in-licensing technology from a PRO. In return for the license to that technology, the PRO receives the promise of a share of the value subsequently generated by the DDB from the candidate drugs derived from the technology. This promise typically includes a royalty on future sales, milestone payments by the DDB, and a share of any non-royalty license fees received by the DDB from pharmaceutical partners. Also, it may include commitments by the DDB to a certain level of expenditure on R&D and the timely achievement of project milestones in order to retain the license. In essence, there is an arms-length commercial transaction, by which the PRO outsources the clinical development of a technology platform to a DDB, in the hope that the DDB will give the technology the best chance of commercialisation. This makes sense, because the DDB provides the entrepreneurial, clinical development and licensing skills that are outside the capabilities and the mandate of the PRO.

However, the PRO expects to receive a fair financial return from the licensing transaction. Over time, this return helps fund the operations of the PRO and defray the original research cost – and potentially reduce the need for additional government funding. Of course, the PRO also has reputational capital at stake in the transaction and wants to see its technology moved forward (and value created) by the best possible DDB. It is in this dynamic licensing setting that the PRO and DDB negotiate the terms of the license agreement. In order to secure the license, the DDB may need to convince the PRO that it already has investor seed funds available or has the ability to raise an agreed level of funding. Thereafter, in order to maintain the license, the DDB may need to demonstrate the availability of ongoing investor funding to ensure the timely achievement of R&D milestones. Indeed, the license may only be an option to license the PRO's technology, with the license not executable between the parties until the funds are raised. One way or another, investor funds are crucial to the birth, life and ultimate success of a DDB.

Why do investors invest in firms that are almost always cash-consuming and likely will never launch a product or make a profit? To answer this, let's examine the mechanisms and motivations around the interactions between DDBs and investors.

In the case of a private (unlisted) DDB, seed funding generally come from the founders and their circle of friends and family, sometimes referred to as 'friends, families and fools' (Vitale, 2004; Yagüe-Perales et al., 2013). However, the nature of drug development is such that the funding requirements escalate quickly as a candidate drug moves towards and into early human clinical trials. This means that professional investors are needed at an early stage, in order to make any real progress. These investors can take the form of angel investors and venture capital (VC) firms. In Australia – the subject of the current performance analysis – there are local angel investor groups (e.g., Melbourne Angels, Brisbane Angels) that may provide early-stage funding for DDBs. Alternatively, a DDB may be able to attract VC funding from one of the national venture capital groups (e.g., Brandon Capital, MRCF, Uniseed). Whether VCs or angel investors, the funds are scarce, especially in Australia (Vitale, 2004), and DDBs need to have a compelling story to attract funding and advance past the seed stage of funding.

After the seed or startup stage (some investors consider these separate stages), those DDBs that are able to attract ongoing funding will progress through a series of investment rounds, often referred to as Series A, Series B, Series C and so on. Ultimately, the most successful firms will graduate to an initial public offering (IPO) on a stock exchange. According to Vitale (2004), the average time from founding to listing of a biotech firm in Australia on the Australian Securities Exchange (ASX) is six years. However, it is well-known that Australian biotech firms tend to list earlier and faster than their US counterparts, due to a lack of venture funding and the lower listing thresholds in Australia, compared with NASDAQ (Jens, 2007; Vitale, 2004; Vitale and Sparling, 2004).

During its private company phase, the firm and its investors hope that the valuation of the firm implied by the pricing of each round will increase at each new round of funding, such that the firm has value growth momentum going into its IPO. After an escrow period, the IPO allows pre-IPO investors to sell their shareholdings onto new public investors who are hoping to see post-IPO growth in the share price. In this way, the IPO provides the earlier investors in the private firm with an 'exit' (Lazonick and Tulum, 2011).

The IPO is not the only exit option for investors in private firms. The alternative is a 'trade sale' where the DDB firm is acquired by a pharmaceutical partner. This may involve an outright acquisition, or more commonly, an initial (upfront) payment followed by downstream payments contingent on development outcomes. Regardless, the total value attracted by such a trade sale can represent a substantial return to the investors in the DDB.

The pre-IPO funding process as described is suggestive of a constant winnowing of the DDB firms towards the listing of only the best firms – those with the best prospects of success from an investor perspective. However, this image of positive curation of firms and stepwise value accretion is not necessarily the case. For private firms, investors in earlier rounds of funding may find themselves trapped in an underperforming firm with no prospect of escape via an exit, such as a trade sale or IPO. For these firms, a new round of funding may be a 'down round', where the implied valuation of the firm declines, sometimes drastically, due to a development setback. Investors from the previous round have the choice of participating in the down round and 'doubling down' on their investment commitment and hoping for a turnaround in the firm's fortunes, or not participating and seeing their share of the firm (and the implied value of that share) decline significantly due to the dilutionary effects of the lower pricing of the current round. In summary, progression between rounds of funding is not always value accretive and the process does not always imply a curation towards the best firms. This represents a significant risk for investors in any private DDB.

Understandably, during the private phase of the life of a DDB firm, the CEO spends considerable time promoting ('pitching') the company to new investors and managing the sentiments and aspirations of existing investors. Indeed, this focus does not diminish appreciably after the firm becomes public. In both phases, it is the 'aspirations' of the investors that need to be managed and that are crucial to the valuation of the firm. The nature of this aspirational value and how it translates into valuation is discussed in more detail in the next chapter. What is important to understand here is that investors invest in DDBs in pursuit of the growth in the capital value of their investment that accrues as the firm moves from one investment round to another at a higher valuation, or in the case of public firms, as there is growth in the share price.

What drives this valuation growth? It is the investors' hope that the intangible value of the DDB's candidate drug pipeline will increase over time and ultimately be converted into tangible value or 'monetised' via a trade sale or IPO that provides the investor with an exit.

As already outlined, the market for a candidate drug is the demand from commercial pharmaceutical partners for a license to the drug. Therefore, the 'commercial' value of a candidate drug is the value it can attract in such a licensing deal, which may include an outright acquisition. This is what many investors aspire to see and is how the value of a DDB's pipeline is ultimately determined and monetised.

Investor relay

For every exit, there is an entry by another investor; in the case of a trade sale, the investor is the pharmaceutical partner, and in an IPO, it is the retail and institutional investors who buy the stock in the public market. Different investors participate at various stages, both pre- and post-IPO, depending on their technical knowledge, investment capacity, risk appetite, transactional flexibility and other

factors. As observed by Andersson et al. (2010, p. 632): "…the investor is not participating in a marathon but instead, competing in a relay where handing the baton on to the next investor secures a (possible) realised gain on invested equity funds."

VCs participate early in the relay, where they can bring to bear substantial technical expertise to reduce risk and deploy significant funds from captive venture capital funds supported by a small number of wealthy investors. This gives them high negotiating leverage with biotech firm founders and potentially delivers management control of the firm to the VC fund. Later investors could include institutional investors, especially when technical risk is reduced, and eventually small retail investors, after the firm has finally gone public via an IPO.

Andersson et al. (2010) distinguish between 'productionist' and 'financialised' business models for biotech firms. In the productionist model, the emphasis is on the transformation of R&D spending and acquired knowledge into intangible assets that generate an above-average financial return. This model sees successful drug development as something that happens over decades and demands patient investors. According to Andersson et al. (2010, p. 639): "This productionist stereotype is used by policy makers and deployed by academics to describe innovation-led business models and how they might transform firm, industry and national competitiveness."

Andersson et al. (2010) contrast this with the financialised biotech model, in which investors move in and out of a biotech firm based on shorter-term financial returns. In this financialised 'relay' model of biotech funding, critical features include selecting the right type of investors, delivering persuasive narratives to those investors about pipeline progress and being tuned to the financial market. At least for public DDB firms in Australia, I suggest the financialised model is more applicable, where retail capital tends to be impatient and investors move in and out of stocks rapidly, often based on announcements about milestone performance.

In conceptualising the productive output (i.e., performance) of DDBs, is the investor perspective the dominant perspective that should be applied? I contend that the answer is 'yes'. Investors are the customers for the narrative of the CEO about the future prospects of the drug pipeline. If a CEO fails to deliver the narrative persuasively, then investors will not support the DDB with funding. If the CEO fails to deliver on the promised outcomes, then investors will disinvest, leaving the firm without ongoing funds to support further drug development and achieve any productive output. Unlike commercial firms, the performance potential of biotech firms is acutely affected by their ability to attract investor funds and retain the support of investors.

MSV

This is not to suggest that the investor imperative that applies to pre-commercial firms, like DDBs, is a virtuous or productive one for the other stakeholders, or the firm itself in the long-term. With

respect to established (commercial-stage) firms, the theory of maximising shareholder value (MSV) as an overriding imperative for firms, leads to value 'extraction' that serves the short-term interests of investors, rather than value 'creation' that serves a broader pool of stakeholders and leads to sustainable innovation growth (Lazonick, 2014). MSV leads to a 'downsize and distribute' regime, where corporate cash is extracted by shareholders in the forms of share buybacks and dividends (Lazonick, 2014; Lazonick and O'Sullivan, 2000).

This contrasts with a 'retain and reinvest' regime, where the cash is used to grow innovative value and generate better long-term outcomes for all stakeholders, including government, taxpayers and employees. This contributes to "sustainable prosperity," which is manifest as equitable and stable economic growth. Value extraction, on the other hand, undermines innovation and sustainable prosperity (Lazonick, 2018).

There is no doubt that the 'investor captaincy' paradigm that underpins key concepts in this thesis is an example of the MSV regime applied to pre-commercial firms. I have argued that because of the nature and mission of DDBs and the absence of any adequate alternative funding sources, investors have captaincy in driving the performance outcomes of DDBs; DDBs have no real choice as to which stakeholders' perspectives are paramount. Arguably, commercial firms do have the opportunity to incorporate other stakeholders' perspectives.

In the US pharmaceutical industry, MSV continues to be a force that allegedly damages sustainable innovation, with the investment in the industry propped up by NIH funding and government subsidies of various forms (Lazonick and Tulum, 2011). For DDBs, investor captaincy leads to a drive towards early value extraction in a pharmaceutical partnership that may see the DDB disappear, rather than continue to grow and develop towards a DDC or big biotech, which could become a powerhouse of future innovation.

This drive towards early value extraction, imposed by investors, makes DDBs ephemeral, especially outside the US, where NIH funding and government subsidies are unavailable or comparatively small. Self-evidently, this is not consistent with building a sustainable bioeconomy. From this perspective, the DDB business model could be viewed as an egregious example of 'predatory value extraction' by investors (Lazonick, 2018).

6.5. The Pisano Puzzle

The foregoing section proposes that investors invest in DDBs in pursuit of abnormally-high capital growth, which occurs as the DDB's candidate drugs advance towards pharmaceutical partnerships. However, some research does not support this view and suggests that the investor returns from biotech firms are not abnormally high at all.

Pisano (2006b) conducted a study of the profitability, R&D productivity and investor returns of public US biotech firms from 1975 to 2004. Between 1978 and 2004, venture capital firms invested $38 billion in US biotech firms, yet the profitability of the industry was poor. Lazonick and Tulum (2011) coined the term, the 'Pisano Puzzle', to refer to the seemingly paradoxical propensity of VC investors and Big Pharma to pour money into biotech firms that were perpetually loss-making.

Applying the PCI view, I would argue that the profitability criticism can be dismissed. The R&D productivity criticism may well be valid, but may also be irrelevant to DDBs, according to the following argument: The outsourcing of drug discovery and development by Big Pharma to DDB intermediaries may not have substantially improved overall pharmaceutical R&D output. However, there may be many reasons for this reduced output, including the increasing complexity of the regulatory requirements, the move from small-molecule drugs to more complex biologics, and the impact of personalised medicine. Regardless of the cause of the reduced productivity – or perhaps because of it – Big Pharma's appetite for acquisition of new pipeline has not diminished. For example, despite their longer and more costly development timelines, biologic drugs can attract much higher selling prices than those historically achieved for small-molecule drugs. From Big Pharma's perspective, this pricing and profit potential can offset the productivity decline and may be the reason that the appetite for in-licensing is growing in the face of poor productivity. In summary, from the perspective of DDBs and their investors, the productivity problem may actually be a positive force.

However, and of more concern to the PCI view, is the fact that Pisano (2006b) reported that investor returns from biotech were not high: US VC fund IRRs (internal rates of return) on biotech from 1986 through 2002 only averaged 16.6%. He also cited an analysis by the merchant bank, Burrill, which found that all biotech IPOs from 1979 through 2000 had only realised an average IRR of 15%.

However, this may be an artefact of timing. The terminus for Pisano's VC returns analysis was 2002, at the depth of a biotech 'recession'. From 2001 through the first half of 2003, there was a significant downturn in the biotech sector in the US, which followed the bursting of the 'genomics bubble' on the heels of the 'dotcom bubble' (McNamee and Ledley, 2015; Van Yoder, 2003; Vieira and Hine, 2005; Vitale and Sparling, 2004). This downturn was followed by a recovery in the second half of 2003 (Fazeli, 2004; Hodgson, 2006), led by the success of Genentech's new cancer drug, Avastin.

Any analysis terminating in 2002 would be expected to produce a modest IRR, at best. Perhaps a similar analysis terminating immediately after the global financial crisis (GFC) in 2008 would have revealed another set of modest IRRs. Indeed, one study found that VC returns on biotech investments between 2000 and 2010 were similar to the Pisano numbers, with an IRR of only 15.9% (Booth and Salehizadeh, 2011). Notably though, these were higher than the IRRs for medical devices, electronics and all other sectors over the same period, except for pharmaceuticals.

Regardless, since 2010, the VC returns from biotech in the US have been spectacular. US venture capital firms reported annual portfolio IRRs ranging from 32% to 101% for 2010 through 2016, on firms classified as 'Biotechnology/Biopharm/R&D' (Cambridge Associates, 2017). These are summarised in Table 12 for the five leading investment categories, based on internal rate of return (IRR). These were pooled IRRs (PIRR), in that they captured all the cash flows in and out of the portfolio of firms and were 'gross', in that they were assessed prior to VC fund charges, such as management fees and carried interest. The 'average' IRR was calculated as a simple average.

Given that the 'Biopharma' category excluded pharmaceutical and medical device firms, one can assume that the bulk of the investments were in DDBs. Moreover, the IRRs were consistently higher than all other categories, including pharmaceuticals.

Table 12. US venture capital statistics for 2009 to 2016.

Subgroup	Pooled Gross IRR (%) of Companies Receiving Initial Investment In:								Average IRR %
	2009	2010	2011	2012	2013	2014	2015	2016	
Biopharma	27.8	32.1	39.0	61.5	100.9	50.1	44.9	42.5	50
Telecom Network/Systems	17.5	3.5	5.0	8.5	33.3	223.4	-1.3	7.9	37
Pharmaceuticals	28.7	32.1	16.1	64.4	22.3	26.8	28.0	21.9	30
Health Care Services	25.4	6.8	26.1	27.2	44.0	21.7	34.6	37.5	28
Internet-eBusiness	34.1	27.1	21.3	24.0	22.9	29.1	19.3	44.2	28

Source: Adapted from "US Venture Capital Index and Selected Benchmark Statistics, December 31, 2017", Cambridge and Associates < https://www.cambridgeassociates.com/wp-content/uploads/2018/05/WEB-2017-Q4-USVC-Benchmark-Book.pdf> accessed February 26, 2019.

From a VC perspective, it is likely the promise of such abnormally high returns that drives investment in DDBs. While there may be other factors that drive investment in US biotech and pharmaceuticals, including various forms of government support (Lazonick and Tulum, 2011), in relation to DDBs, the Pisano Puzzle might be readily soluble.

6.6. **Pipeline performance**

Given the foregoing and subscribing to the investor captaincy paradigm, the most appropriate performance measure for a DDB should relate to pipeline progress. As noted in the last chapter, DDBs in-license patents or lead compounds, then develop them into candidate drugs that they push through stages of clinical development towards a pharmaceutical partnership (Pisano, 2006b). Further, as previously noted, the transaction may involve the sale of the firm or a licensing agreement involving payment to the DDB of license fees, R&D funding, milestone payments and the promise of future royalties on sales of the product. However, some of the perceived promissory or aspirational value of the drug development pipeline accrues to the DDB prior to any such transaction.

With each stage of clinical development, the risk of development failure for a candidate drug is reduced and its potential value increases with respect to a future licensing transaction (Shimasaki, 2014a). The notion that progress of a biotech firm's drug development pipeline adds intangible value is not new (McConomy and Xu, 2004; Shimasaki, 2014a), nor is the notion that such progress is reflected in the market value of the firm (Guo et al., 2005; Houston et al., 2013; Xu, 2006; Xu et al., 2007) and can help the firm raise investor capital (Shimasaki, 2014a). In this sense, pipeline progress represents 'value creation' for a DDB (McConomy and Xu, 2004; Shimasaki, 2014a).

Despite the extensive biotech performance literature and establishment of the idea that pipeline progress adds value, the research on measuring DDB pipeline progress as a performance construct is very limited. In the accounting literature, Guo et al. (2005) sought to capture the growing value of products at each stage of development by applying a weighting to the number of drugs at each stage based on the number of years of development needed to reach that stage, assuming that the final step of drug approval required 12 years on average, as shown in Table 13 (Guo et al., 2005):

Table 13. Weightings for each stage of development

Stage of development	Weighting applied
Screening	1
Development (lead identification/optimisation)	2
Preclinical testing	3
IND application	4
Phase I clinical trials	5
Phase II clinical trials	7
Phase III clinical trials	10
NDA (approval) application	12

Subsequently, Xu et al. (2007) created a measure based on the probability of approval at each stage, which is arguably more value-relevant than the years to reach each stage. Their construct (EQUD) measured the equivalent number of drugs under development by counting the number of candidate drugs at each stage of clinical development weighted by their probability of ultimate success (measured as drug approval), based on established 'DiMasi' approval probabilities for each stage (DiMasi et al., 2010). In that study (Xu et al., 2007), six development stages were used: (1) pre-clinical trial, (2) IND filing, (3) Phase I, (4) Phase II, (5) Phase III and (6) registration (approval) filing.

Houston et al. (2013) used a similar construct, E[Approved Drugs], based around five stages of clinical development (excluding the IND stage) and applying the DiMasi success probabilities to the number of drugs in each stage (Houston et al., 2013).

Xu (2009a) subsequently extended the EQUD model to measure pipeline progress. To create the 'progress' construct, the numbers of success-weighted candidate drugs were further multiplied by the number of movements from an earlier to a later stage of development, as summarised by the following equation:

$$AR\&DPG = \sum_{i=1}^{m} pi * ni$$

where AR&DPG was the firm's pipeline progress measure; pi was the probability of a drug at stage i to pass FDA final approval; n was the number of drug movements from stage i=1 to m, where m is the number of stages in the drug development process (Xu, 2009a).

One of the challenges with these approaches is that different diseases can have different value potential – in terms of the market for pharmaceutical deals – and it is a complex exercise to appropriately weight candidate drugs for their individual value in the context of a licensing transaction. A second challenge is that a single candidate drug could be developed for multiple diseases or conversely, a DDB could develop multiple drugs for the same disease, effectively competing with each other.

Xu et al. (2007) sought to partially address the first problem by applying a dummy variable to capture whether or not drugs were aimed at high-profile diseases. However, considering that the market for DDBs is the demand from pharmaceutical firms for deals, and that higher profile diseases may have more competition other DDBs vying for those deals, such an approach may not solve the problem.

Further, disease-weightings should accommodate the different development risk associated with different diseases. For example, drugs for treating acute infectious diseases, such as influenza, generally have lower development risks and costs than drugs for complex, chronic conditions, such as depression, diabetes or Alzheimer's disease. One reason for this is that there are well-elaborated disease pathways and clearer clinical endpoints for infectious disease drugs, compared with diseases where the disease pathology is not yet well-understood and endpoints may be less well-defined, more difficult to measure or where the clinical trials can take several years and be very costly. Against this, there is more demand from pharmaceutical partners for drugs for the chronic diseases, partly because of the ongoing revenue stream that chronic treatment provides.

Overall therefore, success-weighted pipeline measures are difficult to operationalise for DDBs. Moreover, while correlated to value creation in the pharmaceutical R&D value chain, the measures are not direct economic measures of pipeline value.

6.7. Introduction to value creation

As noted by Shimasaki (2014a, p. 117): "the goal of all start-up or early-stage biotechnology companies is to create value within the product being developed and within the company…Value is created incrementally every time a product development milestone is successfully reached."

While 'value creation' is a key goal for DDBs and potentially provides the most useful performance measure for DDBs, the value creation conception needs to be properly elaborated. Many have also used the term 'value creation' in the context of drug development firms and their goals, but it has not been adequately conceptualised or quantified (Coombs and Deeds, 1998; Lazonick, 2014; McConomy and Xu, 2004). If it is indeed the performance goal of DDBs, then a clear definition and approach to measurement of value creation is an important area of untapped research. This is explored in the next chapter, where I develop the idea of value creation as a DDB performance measure.

Chapter 7. Value creation and investor returns

This chapter seeks to define and quantify how DDBs generate value from the perspective of investors. A first step towards identifying changes in value is to understand the approaches to valuation of biotech firms.

7.1. Valuation of DDBs

For DDB firms listed on a stock exchange and thereby publicly-traded, valuation is a continuous, dynamic process based on the extant pricing of the firm's shares by the public investor market. The instantaneous share price multiplied by the number of shares on issue represents the equilibrium market value of the firm (MV).

In contrast, for private DDB firms, the MV is based on the price that investors, such as VCs, are prepared to pay for the shares in the firms. VCs and other professional investors refer to the 'pre-money' and 'post-money' valuations, with the pre-money being the value of the firm prior to any injection of new capital and the post-money being the value that incorporates the new cash injection from the investment. For determining the pre-money valuation of a private DDB, professional investors will typically undertake a valuation of the DDB's pipeline and prospects. From the perspective of these investors, the value of a private DDB firm should grow in a positive, step-wise process of value accretion with each round of funding, culminating in a monetisation event, such as an IPO or trade sale. That monetisation event provides the VCs or other professional investors with an 'exit' opportunity to liquidate their investment and crystallise a financial return.

There are several techniques for valuation of DDB investments, but by far the most widely-used approach is the risk-adjusted net present value method or 'rNPV' (also called eNPV, rDCF and eDCF), which is based on discounted cash flow (DCF) analysis (Jens, 2007; Shimasaki, 2014c; Villiger and Bogdan, 2006). The rNPV valuation for a single candidate drug involves projection of the cash flows from the approved drug over its commercial life, typically from launch to the end of its patent life. This is discounted by a cost of capital interest rate, the development costs to reach approval and the risks associated with success at each stage of development. As previously discussed, the DiMasi stage success probabilities are often used for this latter purpose (Villiger and Bogdan, 2006). 'Real options' methods can enhance the valuation methodology by incorporating investment options at each stage (Farag, 2009; Jens, 2007; Villiger and Bogdan, 2006).

For private DDBs seeking to attract investors in a funding round, it is commonplace for the firm to undertake an rNPV valuation of its candidate drug pipeline to give prospective investors a measure of the value of the firm's pipeline prior to making an investment (i.e., on a pre-money basis). For private DDBs intending to 'go public' and list on a stock exchange, such as the ASX, an expert report is required, which includes a valuation; various consulting or accounting firms specialise in such

valuations. Once the firm is listed, investment research houses may also conduct periodical rNPV valuations on a firm's pipeline in order to sell their research reports to interested investors, or in the case of company-sponsored investment research, to help the DDB promote the value of its pipeline to the public investor marketplace.

For both public and private firms, the rNPV approach is also generally used as a framework for negotiations with pharmaceutical partners for the purposes of licensing of a candidate drug asset (Bratic et al., 2014). Whatever its limitations, the rNPV approach provides a common language and negotiation platform that is generally understood and accepted as a valuation framework by both sides, thereby making the negotiation process more efficient. It also forces explication and modelling of assumptions about market size and growth, market share, marketing costs, pricing and competitive strategy, all of which are important variables for discussion and agreement during the negotiation process (Anthony and Haworth, 2014; Bratic et al., 2014).

The framework is so important for partnering success that there are businesses dedicated to preparing valuations to support partnering (e.g., Venture Valuation AG, www.venturevaluation.com). This indicates both the sophistication of the technique and the degree of technical knowledge needed to conduct a single valuation. In each case, it demands an intimate knowledge of the drug candidate's technical benefits, clinical development plan and costs, regulatory pathway and risks, competitive drugs on the market and in development, as well as pricing and manufacturing costs and risks.

As discussed, for private DDB firms, the market value of the firm is discontinuous and stepwise, with the MV at any time generally regarded as the post-money valuation achieved in the last round of funding. For public DDB firms, the MV is continuously adjusted by public investors' perceptions about the progress and potential progress of the firm's candidate drug pipeline. Theoretically, public investors are constantly adjusting their perception of the firm's rNPV in response to signals about R&D progress or failure. As observed by Xu (2009a, p. 527):

> Given that investment opportunities are priced due to their expected Net Present Value (NPV) effect, my intent is to show how their pricing varies with the dynamics of investment success as captured by R&D progress, assuming that the rate of R&D progress provides an investment success signal that alters the expected NPV of these opportunities…Results indicate that R&D progress provides risk relevant information that allows investors to alter their expected NPV of investment opportunities.

For public DDB firms, these prospects can be conveyed by presentations at investor and shareholder meetings, valuations conducted by independent research analysts, and most importantly, by public announcements by the DDB firm on R&D progress. For example, the announcement of a failed clinical trial by a public DDB could lead to an immediate reduction in market value. On the other

hand, the announcement of a commercial alliance with a major pharmaceutical firm could lead to an immediate positive revaluation of the firm's market value.

In other words, the market value of a public DDB can be thought of as the equilibrium weighted average of investors' perceptions about the rNPV of the DDB's future prospects to create value from its drug development pipeline, plus any other assets the firm may have, such as cash. Investors invest in the potential future capital gain of their investment and look for signals of 'value inflexion', such as a clinical trial outcome or a licensing deal with a pharmaceutical partner, potentially involving the sale of the firm to the partner, thereby generating an exit. As noted by McConomy and Xu (2004, p. 30):

> The market value of biotech firms is mainly driven by hope — the hope of realised earnings potential stemming from approved drugs. Managers of biotech firms often employ a disclosure strategy to communicate their drug development status, to either strengthen or clarify that hope.

For DDB firms, where the market is the demand for partnerships with pharmaceutical companies, value growth is driven by changes over time in investors' perceptions of the rNPV of future financial gains from the DDB's candidate drug pipeline, which are realised when a pharmaceutical license or acquisition occurs. Notionally, that rNPV calculation includes perceptions about the financial value of such a deal, its likelihood of occurring and its temporal proximity. Inflexion points, such as clinical trial outcomes, provide signals about likelihood and proximity.

For DDB firms, therefore, success is achieved by investing in R&D to create and advance a pipeline of candidate drugs, such that the increased value of the pipeline elevates the aspiration or *hope* of investors and translates into growth in the firm's overall perceived market value, and thereby, growth in its share price. This 'pipeline value' is the key asset of a DDB firm. It is also an intangible asset and in the case of public DDBs, is subject to significant and rapid revaluation by the market in response to milestone announcements by the firm and other events that affect an investor's estimation of the future value of the pipeline (Andersson et al., 2010; Farag, 2009; McConomy and Xu, 2004; Nicolau and Santa-María, 2015; Perez-Rodriguez and Valcarcel, 2012).

7.2. Pipeline value

As pre-commercial firms, DDB firms generally have minimal tangible assets, other than cash, and typically no liabilities. Apart from cash, the primary value-driver for a DDB is its pipeline of candidate drugs, which is an intangible asset. In summary, the value of a DDB firm is comprised of the value of its primary tangible asset – normally its cash reserves – plus the value of its primary intangible asset – its drug development pipeline. This intangible 'pipeline value' or 'PV' entraps the aspirations of investors for the realisation of future tangible value by the firm. This future value may take the form of a monetisation event, such as a pharmaceutical alliance that generates substantial

license fees and royalties, or an outright acquisition of the DDB at a premium to its current market value. In essence, investors are betting that the intangible PV will be converted into a tangible asset, such as cash, which will be returned to investors. Naturally, these aspirations must be tempered by the risk, cost and time of achieving the monetising deal. In this way, the PV can be thought of as the risk-adjusted net present value (rNPV) of the drug pipeline.

The most common way for a DDB to grow its PV is to advance a candidate drug from one phase of drug development to a more advanced phase. This signals to investors that development risk has been reduced and the drug is potentially one step closer to commercialisation. However, the PV concept is not restricted to clinical trial progress. The aspirational value of future monetary gain for investors could be increased by the firm's receiving licensing revenues or even revenues unrelated to its drug development technology.

In Australia for example, a public DDB called Arana maintained a market value of between $200 million and $250 million from 2005 through 2008. This value was based not primarily on the future prospects of its candidate drug pipeline, but on the net present value of a royalty stream that it received from two Big Pharma firms. Arana held patents relating to anti-inflammatory drugs and after Abbott Laboratories and Centacor (Johnson & Johnson) launched their blockbuster anti-inflammatory compounds, Humira and Remicade (respectively), Arana claimed patent infringement. The patents suits were settled in 2003 and 2004 (respectively), with Abbott and Centacor agreeing to pay Arana a royalty on sales. When Arana was acquired by Cephalon in 2008 for $320 million, it was likely that a majority of the acquisition value related to the ongoing royalty stream, not the potential of the drug pipeline.

In summary, the market value attributed to a DDB entraps the full spectrum of investors' aspirations for financial returns. With a few exceptions, the primary value driver is the potential of the firm's candidate drug pipeline and therefore I believe it is appropriate to refer to this intangible asset as the 'pipeline value' or PV. At any time, the market value (MV) is equivalent to the sum of PV and the cash reserves. That is, the pipeline value (PV) is equivalent to the market value (MV) minus the cash:

$$PV = MV - C$$

Cash holdings are traditionally thought of as zero net present value (NPV) investments, such that one dollar of cash should increase the market value of the firm by one dollar. This is true in the frictionless world of perfect capital markets, but in reality, the market value attributed to cash can vary depending on the prospects of the firm (Pinkowitz and Williamson, 2007; Xu, 2009b). Those with good growth or innovation opportunities have a higher premium placed on cash, relative to firms with poor growth opportunities. Firms facing financial distress have their cash valued at less than a dollar, presumably because of the squandering risks.

On average, however, the marginal value of one dollar in cash has been shown to be roughly equivalent to one dollar in market value (Faulkender and Rong, 2006; Pinkowitz and Williamson, 2004; Pinkowitz and Williamson, 2007). On that basis, for DDB firms, it is reasonable to assume that the difference between the total value ascribed by the market to the DDB firm (MV) approximates the value of its cash reserves plus the value attributed to its primary non-cash asset, PV.

A commonly used measure in investment circles is the enterprise value or 'EV' of a firm (https://corporatefinanceinstitute.com/resources/knowledge/valuation/what-is-enterprise-value-ev/). EV is essentially a measure of the net cost of acquiring a company, and it is calculated as the market value of common stock plus the market value of debt, minus cash and cash equivalents (Ahn et al., 2018). The idea is that cash can be used directly to offset acquisition costs, so net acquisition cost is the value of acquiring all outstanding shares and paying off debts.

DDBs rarely have any significant debt, because they are loss-making and risky, and therefore are unattractive to loan providers. For most public DDB firms, especially outside the US, debt is generally not a factor, so the EV equates to MV minus cash, and therefore, is arithmetically equivalent to the proposed PV measure.

This is not the case for DDCs and pharmaceutical firms, where MV and EV include not just the value of the candidate drug pipeline, but debts, fixed assets and non-pipeline intangible assets, such as infrastructure, brand value, customer base and market access. In addition, for commercial-stage firms, the EV includes the intangible value of the future cash flows associated with the firm's marketed products.

Generally, where growing the EV is a stated or implied goal for biotech firms, it is in the context of acquisition value (Danzon et al., 2007; Jacobs, 2006), rather than as a measure of the firm's performance in creating pipeline value, which is the context here. Therefore, in this research, the term 'pipeline value' (PV) will be used, rather than EV, as the context is not acquisition cost and it more clearly distinguishes the market value attributed to the DDB firm's primary non-cash asset, which is its candidate drug pipeline. Based on the above discussion, one might conclude that value is created when the PV of the DDB firm grows:

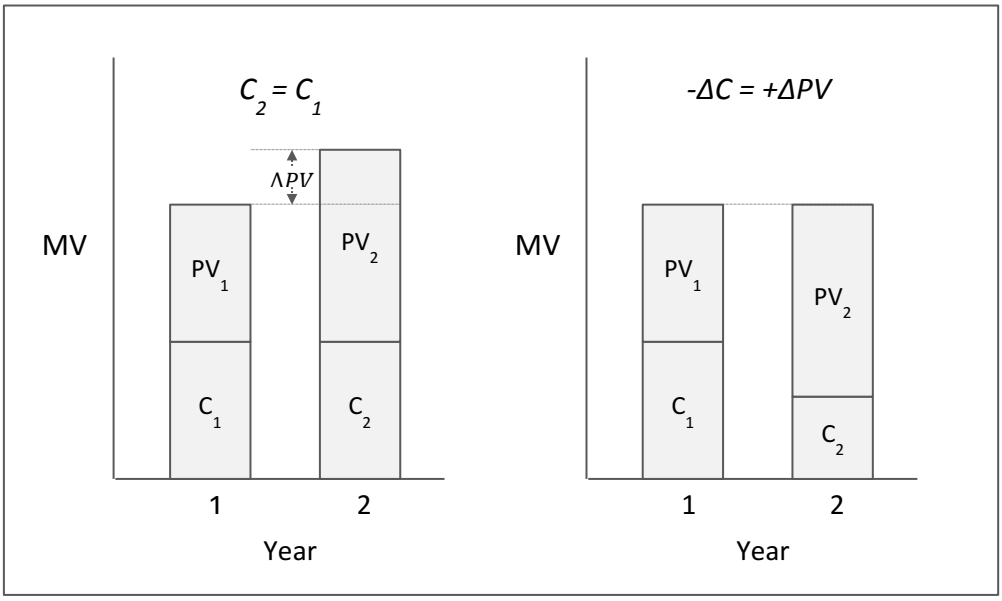
$$\Delta PV = \Delta(MV - C)$$

ΔPV is the change in PV between two time points, such as years. A positive ΔPV means that the DDB has succeeded in growing the market-perceived value of its candidate drug pipeline over time. Further, because PV = MV - C, if the cash between years 1 and 2 is constant, then:

$$\Delta MV_{2-1} = \Delta PV_{2-1}$$

For example, a 20% growth in PV would translate into a 20% increase in the MV. However, for DDBs, which are mostly loss-making, PV can only grow by the DDB's spending cash on R&D to move candidate drugs forward. This means that cash should decline from year 1 to year 2, with the result that ΔPV needs to be larger than the decline in cash for the MV to grow. If the PV growth is equal to the cash needed to generate it, then the MV will not change. This is depicted in Figure 4.

Figure 4. PV and the impact of cash



7.3. **Value creation**

The implications of the foregoing are important for measuring value creation by DDBs. Is value created when a DDB simply generates PV growth, regardless of the cash cost of generating the PV growth? I contend that the answer must be 'no'. If the cash cost of producing new PV is greater than (or equal to) the increase in PV, then it makes no economic sense to expend the cash in the first place, because there is no gain from the investment. Clearly, no fully-informed investor is going to fund an enterprise that converts $1 of cash into less than $1 in output. Therefore, PV growth *per se* does not constitute 'value creation'. I assert that value is only created if the growth in PV is greater than the cash consumed to generate it.

For publicly-traded DDB firms, the cash cost of producing PV growth – which I will also refer to as 'PVG' – is measured by the reported net operating cash outflow each year in the firms' annual reports. This is often referred to as the 'burn rate' for a biotech firm, which I will abbreviate to 'BR' and which represents the total amount of investor cash consumed in that year on the operations of the firm, which have the primary purpose of delivering PVG. The BR can be reduced by cash inflows, such as grant funding, R&D tax credits, license fees and other revenues that can accrue to DDBs. Indeed, these revenues could be sufficiently large in a given year to completely offset the operating

expenses of a DDB and thereby generate a net operating cash inflow (or negative BR). However, this is uncommon, because unlike DDCs, most DDBs have limited revenues and are generally cash-consuming, spending heavily on R&D to drive PVG.

It should be noted that for the purposes of measuring PVG, the BR is restricted to operating cash flows and excludes financing cash flows. This is because operating cash flow is the cash expensed directly in pursuit of PV growth, while the financing cash flows – notably cash inflow from equity fundraising (selling of shares to raise new funds) – are not directly related to current BR. There is no doubt that cash raised in one year through an equity fundraising might be used in the subsequent year to fund the BR in pursuit of PV growth. However, prior to that usage, the cash is not 'burned' (expensed), but rather sits on the firm's balance sheet as an asset and theoretically could be returned to shareholders in the event of liquidation. In summary, financing cash flows are different in nature to operating cash flows and to count financing cash flows as part of the BR for the purposes of determining PV growth would be double-counting the cash cost of that PV growth.

The other category of cash flow reported by firms and excluded from the BR calculation is 'investing' cash flows. These are cash flows associated with the acquisition of assets. These cash flows can be associated with PV changes and are discussed in section 7.5 below.

I now propose the following value creation construct, VCR:

$$VCR_n = \text{PVG}_n - BR_n$$

where VCR_n is the value creation in year n, PVG_n is the growth in PV in year n, and BR_n is the net operating cash outflow in year n. VCR measures the efficient use of funds by a DDB to generate PVG and I propose that it can be used as a performance measure for public DDB firms. This construct and conception have not been elaborated previously or used as a performance measure for biotech firms, or any other firms, based on literature searches.

For a DDB, the largest contributor to BR will be R&D expenditure, which I will abbreviate to 'RDE'. However, BR also includes corporate, business development and other costs that are unrelated to R&D, so:

$$VCR_n = \text{PVG}_n - (RDE_n + NRDE_n)$$

Where NRDE equals non-R&D expenses.

From an individual company performance perspective, VCR represents the extent to which RDE translates efficiently into PVG and to such an extent that the PVG exceeds the total cost base of the firm, including RDE.

If one thinks of a DDB's technology as an 'engine' for productive output in the form of PVG, then RDE represents its fuel and VCR its efficient output. The greater the RDE (and thereby, BR) consumed to deliver a given PVG output, the lower the efficiency of the engine.

Due to the variable capacity and efficiency of different firms' technology engines, one firm may be able to consistently generate VCR, while another may never be capable of producing VCR. From an investor perspective, a technology engine that is incapable of generating VCR should not be funded, because $1 in cash is not generating more than $1 in net output (PVG). From the investor perspective, VCR could be considered an important new measure of productive output for DDBs.

7.4. Technology asset quality

Clearly, one important question is: What determines the capacity of a firm's technology engine? I propose that it is the quality of the underlying 'technology asset' of the DDB. I will refer to the technology asset to as the 'TA' and its quality attribution as 'TAQ'. For a DDB, the TA is a DDB-specific type of knowledge asset.

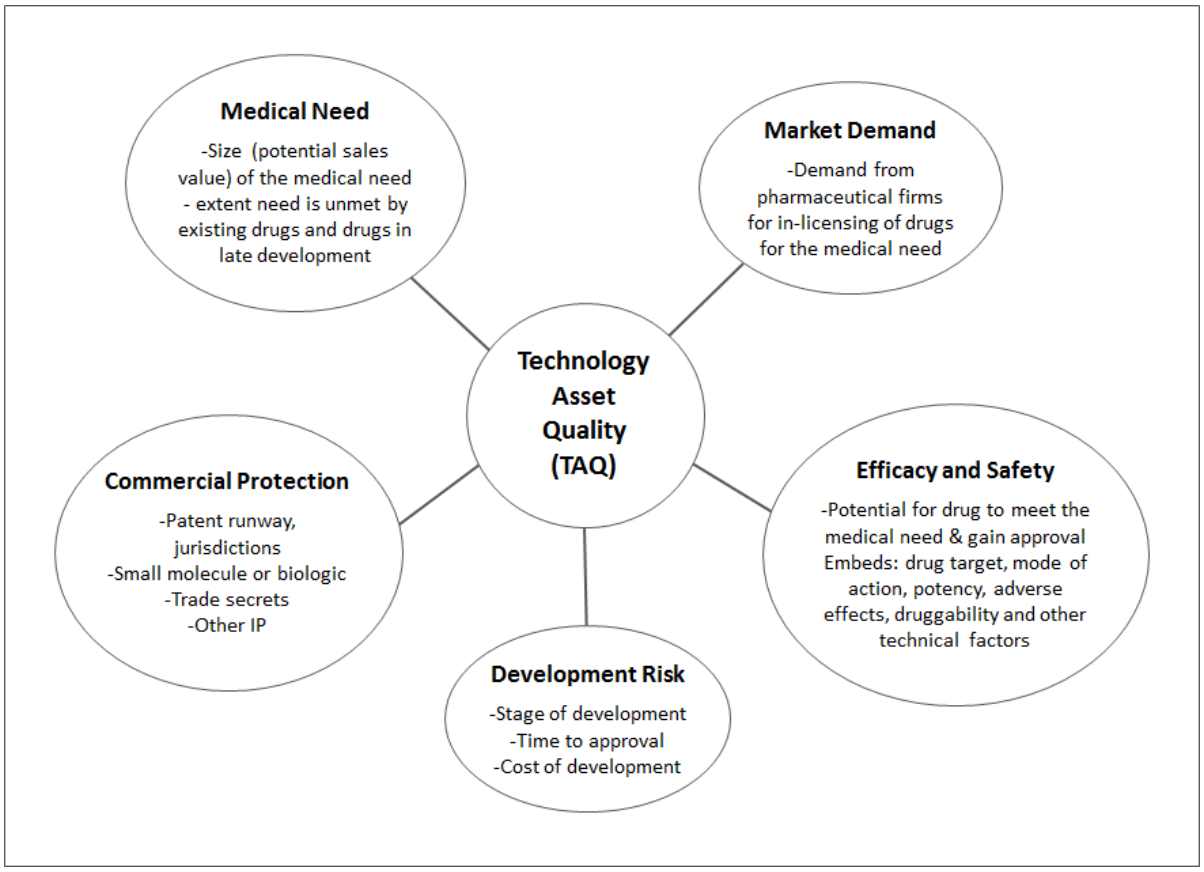
In line with the intermediary role of DDBs, the TA likely was acquired or in-licensed, typically from a PRO, and became the firm's primary platform for drug development and attendant value creation. Over time, the value of the TA – its TAQ – can change due to improvements in the TA made by the DDB or market changes, as discussed below.

For DDB firms, the market is the demand for partnerships with pharmaceutical companies and the rNPV calculation embeds perceptions about the financial value of such a deal, its likelihood of occurring and its temporal proximity. Therefore, the concept of TA *quality* must embed those attributes that will contribute to making the candidate drug pipeline attractive to a pharmaceutical partner and increase the value, likelihood and proximity of a deal.

I suggest that these attributes include (a) the strength of and time remaining on ('runway' in industry parlance) the patents and other intellectual property that provide commercial protection for the candidate drug; (b) the size of the medical need being targeted by the candidate drug (in terms of sales potential) and the extent to which it is unmet by existing marketed drugs and other drugs in development; (c) the extent to which pharmaceutical firms are actively pursuing the in-licensing of drugs for that medical need – a factor that will vary depending on each Big Pharma's therapeutic priorities; (d) the potential for the candidate drug to meet that medical need, based on its projected efficacy and safety profile, which further embeds concepts such as the drug target, mode of action, potency, adverse effects and its potential for formulation and delivery as a drug ('druggability'); and (e) the riskiness, time and cost of the development pathway.

TAQ is seen as a multidimensional construct comprising a range of attributes that affect its potential to create investor-relevant PV growth. A model of TAQ is shown in Figure 5.

Figure 5. Proposed TAQ Model



The specific nature and relative importance of each TAQ attribute will depend on the specific medical need and many other factors, so this makes TA an idiosyncratic and mercurial construct, which is not subject to ready quantification. TAQ can also vary over time as the appetite and priorities of pharmaceutical partners change, regulatory changes occur and medical needs change.

For example, the passing in the US in 2010 of The Biologics Price Competition and Innovation Act (BPCI Act) conferred a 12-year post-approval exclusivity period on biologic drugs – protein-based drugs, as distinct from synthetic, small-molecule drugs – dramatically improved the value proposition for biologics and increased the appetite of Big Pharma for biologic drugs. Because proximity to, likelihood and value of a deal drive the TA output in the form of PVG, the BPCI Act increased the potential PVG that a biologics TA would generate and for a DDB firm engaged in biologics drug development, increased the 'quality' of its TA and its capacity to generate VCR.

Conversely, in 2005, hepatitis C virus (HCV) infection represented a deadly liver disease for which the only recourse was a liver transplant and the waiting lists were years-long. Due to the successful drug development and partnering efforts by a handful of DDBs, by 2015, there were several effective

HCV drugs on the market and the disease was considered conquered. So, the unmet medical need changed significantly, Big Pharma mostly lost interest in new HCV partnerships and DDBs firms working in the field lost the potential to create VCR, because their TAQ decreased.

Because of all these factors, TAQ is difficult to operationalise and difficult to measure directly based upon a sum of its components. Despite this, I contend that it is an essential concept for understanding VCR, and indeed, the purpose of DDBs as custodians and drivers of TA engines.

Essentially, the higher the quality of the underlying TA and therefore (by definition), the greater its potential to be a springboard for candidate drug progression and valuable partnerships, the more efficiently the TA should convert R&D expense (RDE) into PVG and thereby, the greater likelihood of positive VCR. A high-quality TA will generate substantial PVG and VCR in response to RDE. However, a weak TA will limit a DDB's capacity to create any value, regardless of the amount of funding, because of the inherent insufficiency in the TA as a platform for value creation. Understanding the nature and importance of TAQ, in the context of Figure 5, is an important strategic frame for DDBs and their investors.

7.5. R&D productivity

TAQ determines and limits the potential for RDE to convert into PVG. Therefore, one possible measure of TAQ at any time is the PVG/RDE ratio. High quality TA will lead to a high PVG, while low quality TA will see the PVG/RDE ratio at less than 1.0. While TAQ is difficult to measure and generalise, the PVG/RDE ratio may provide a surrogate of TAQ. It may also provide a measure of 'R&D productivity' that is investor-relevant.

In contrast, VCR measures the total PVG minus the BR. While BR includes RDE, it also includes NRDE – all the firm's other operating costs, such as business development and corporate overheads. VCR seeks to measure whether the firm was able to create investor-relevant value (PVG) that is sufficient to exceed all operating costs (RDE + NRDE). R&D productivity (PVG/RDE) measures whether the investor-relevant R&D output (PVG) exceeded R&D expenses. In this way, PVG/RDE represents a primary measure of R&D output, the capacity for which is determined primarily by TAQ.

Finally, one should recognise that regardless of the TAQ, management plays a crucial role in driving the TA engine towards PVG output. Despite a high-quality TA, poor R&D management could lead to reduced or negative PVG/RDE. Therefore, in addition to technology-pipeline-market considerations embedded under the concept of TA, investors' assessments of the value of a DDB also integrate perceptions about management's ability to manage the TA engine effectively. Further, because PV includes perceptions about the value, proximity and likelihood of a pharmaceutical partnership, PV

incorporates investors' perceptions about management's ability – given the TAQ – to effectively secure and execute a pharmaceutical deal.

7.6. Impact of acquisitions

What happens when a DDB acquires new TA, such as an additional pipeline of candidate drugs? This could occur through the DDB's in-licensing of new technology from PROs or acquiring additional pipeline from other DDBs or DDCs. Effectively, the new pipeline adds new 'hope' for investors and the value of the firm (MV) increases by an amount equivalent to the perceived value of the newly-acquired pipeline.

To address the VCR impact, I will designate the TA associated with the original technology of the firm as TA_1 and the newly-acquired TA as TA_2. The PVs associated with the two TAs would then be PV_1 and PV_2 and the MV post-acquisition would be as follows:

$$MV = (PV_1 + PV_2) + C$$

If no cash was used in the acquisition – due to an acquisition for equity or an in-license with deferred license fee payments – then C does not change and the value of MV instantaneously increases by an amount equivalent to the value of PV_2. This means that in the acquisition year, there is an increase in total PV without significant (or perhaps any) offsetting additional RDE; as a result, there is a positive impact on VCR in that year.

This is not 'true' value creation, in that the existing TA was not leveraged to generate PVG and there is no real investor value created in the process. What has occurred is that the TA capacity of the firm has been increased by the additional capacity of the newly-acquired TA. Put another way, the engine size has increased, but so has its fuel consumption. Whether VCR occurs in subsequent years depends on the efficiency of the overall engine (combined TA) in the subsequent 12 months, as discussed below.

Because each drug development program typically comes with its own additional R&D costs (rarely would one expect substantial R&D expense synergies), one can assume that each TA would have its own dedicated RDE, which I will designate RDE_1 and RDE_2. Moreover, the two TAs could have different TAQs and therefore, different PVG/RDE ratios. Generally, one could also assume that corporate overheads and other NRDE costs would not change as a result of the acquisition. On this basis, the VCR in the year after the acquisition is calculated as follows:

$$VCR = (PVG_1 + PVG_2) - (RDE_1 + RDE_2) - NRDE$$

For simplicity, if the VCR in the year prior to the acquisition were zero (i.e., $PVG_1 - RDE_1 - NRDE_1 = 0$), then VCR in the year after the acquisition will only be positive for the firm if the PVG from the

new TA exceeds its additional RDE in that year (assuming NRDE is constant). In other words, if the PVG_2/RDE_2 ratio is greater than 1.0, then the VCR in the year after the acquisition will be positive.

In summary, acquisition of new pipeline will increase PV by the market-perceived value of the additional pipeline. This will lead to additional PVG and an artificially inflated VCR in the year in which the acquisition occurs. Whether VCR is generated in any subsequent year will depend on the firm's overall R&D productivity and its NRDE costs.

If VCR is to be used as a measure of performance, then adjustments need to be made for the PV impact of any such acquisitions. This is addressed in more detail in the methodology chapter (Chapter 8) in Part B.

7.7. Internal rate of return (IRR)

While VCR may be a useful short-term performance metric for DDB firms and the DDB sector, Investors in public DDB firms are primarily interested in share price growth. Excluding dividends, which are unusual for DDB firms, economic value for public DDB shareholders is generated by growth of the share price (SP).

The internal rate of return (IRR) for the investor is the compound average annual rate of growth between the time that an investor buys and then sells (exits) a DDB stock. IRR is the most common metric used by VC firms to evaluate the financial performance of their investment portfolios. The IRR needs to be at least equivalent to the investor's required rate of return, taking into account the risk associated with DDB investments, which is high. A common target IRR cited for VCs is 30% (http://www.jmyang.com/blog/2014/6/24/30-irr-a-primer-for-first-time-entrepreneurs). If the IRR is likely to be less than the required rate of return, then all things being equal, VCs are not likely to invest in the DDB, or may disinvest. The same applies to all DDB investors in both private and public firms, who are seeking an above-average IRR to maximise their capital return on their investments.

Given that a positive VCR represents a growth in MV, then VCR should translate into SP growth and a positive IRR, all things being equal. However, all things are not equal and the relationship between VCR and IRR is complex. Indeed, it is possible for a DDB to create value (have positive VCR) and yet have zero or negative SP growth (zero or negative IRR).

At any point in time, the SP of the DDB is the MV of the firm divided by the number of shares on issue (SI). For example, if SI does not change from year 1 to year 2, then the share price should grow proportionately to the MV:

$$\Delta SP_{2-1} = \frac{\Delta MV_{2-1}}{SI}$$

Further, if C remains unchanged, then ΔSP equals PVG/SI and PVG should be highly correlated with VCR, assuming the burn rate is constant (VCR = PVG – BR). However, none of BR, C or SI is constant, as described below. SI typically grows from year to year with public DDBs, because of their need to raise funds to pay for their BR. For example, most Australian public DDBs engage in fundraising each year in order to cover their anticipated forward operating cash burn.

For Australian public DDBs, these fundraisings commonly take the form of private placements that are managed by investment bankers or brokers. However, they may also include share purchase plans, rights offerings, share options and occasionally, convertible debt. In all cases, the ultimate result is the issue of additional shares in exchange for cash from investors. When new shares are issued, an existing investor's share of the total SI of the firm is reduced (assuming they do not participate in the new issue). So, growth in SI as a result of fundraisings is considered 'dilutionary' for current shareholders.

For example, if the MV grows 40% between year 1 and year 2, but 40% more shares have been issued by the end of year 2, then the SP at the end of the year should be unchanged. This example is shown in the following equation:

$$\Delta SP_{2-1} = SP_2 - SP_1 = \left(\frac{MV_2}{SI_2}\right) - \left(\frac{MV_1}{SI_1}\right) = \left(\frac{1.4}{1.4}\right) - \left(\frac{1.0}{1.0}\right) = 0$$

Further, assuming the 40% additional shares brought in exactly enough cash needed to cover the BR during that year, so that cash levels remained unchanged at the end of each year, then the PV will have increased by 40%, but the SP will not have grown. Moreover, if the growth in PV exceeded the BR for the year, then VCR will be positive – value will have been created – but the SP will not have grown and shareholders will not have seen a positive IRR.

In other words, VCR will not translate completely or faithfully into SP growth due to the dilution effect of SI. Simplifying the above equation and substituting, the impact of the dilution factor, SI_1/SI_2, becomes apparent:

$$\Delta SP_{2-1} = MV_2 * \left(\frac{SI_1}{SI_2}\right) - MV_1 = (PV_2 + C_2) * \left(\frac{SI_1}{SI_2}\right) - (PV_1 + C_1)$$

Providing a discount on the prevailing SP is common practice for DDBs seeking to raise funds, with the discount acting as an incentive for investors. However, the dilution problem is exacerbated if the cash raised is the result of selling shares at a SP that is less than the average SP of the previously-raised cash. This is because the BR is funded by previously-raised cash, which has a notional cost in terms of the number of shares it represents; when new cash comes in at a lower SP, the dilution factor is amplified by the discount rate in SP.

Indeed, when cash is raised at a large discount to the market price, the value leakage due to dilution can be so high, that it is possible for a DDB firm to create value (have a positive VCR), while also experiencing a declining SP and negative IRR. This occurs most profoundly when a financially-distressed DDB undergoes a re-capitalisation at a drastic discount, in order to bring in new funds to survive.

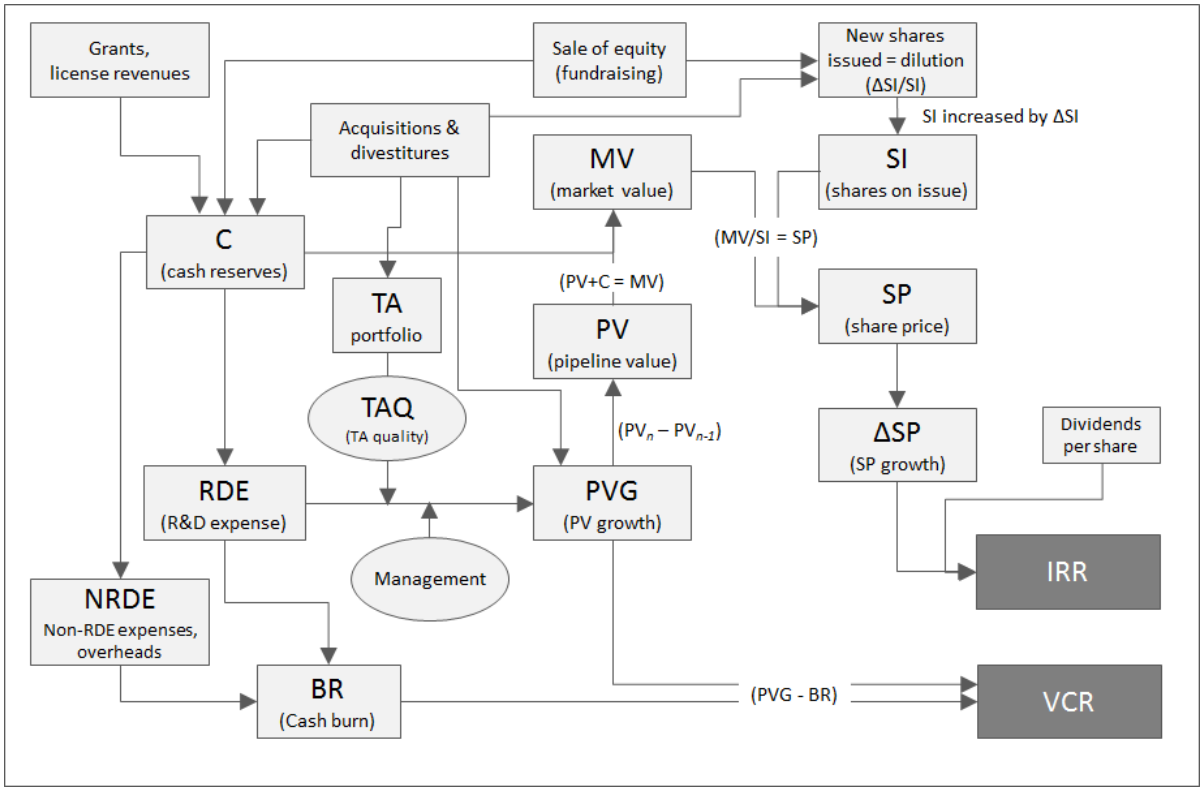
To complicate matters, DDBs can have cash inflows other than from financing. These include grant funding, R&D tax credits, license fees and other revenues. Occasionally, these revenues are large enough to offset the DDB's annual operating expenses and generate positive operating cash flow, or a negative BR. In that circumstance, it is possible for growth in SP to occur – due to the impact of accumulating cash on the market value – and thereby, a positive IRR, without (necessarily) any growth in PV or VCR.

As already noted, PVG can be achieved by simply acquiring or in-licensing new candidate drugs from PROs or acquiring other DDB firms. Whether the acquisition is paid for in cash or by issuing new shares to the third party, then all things being equal, the IRR impact for an existing shareholder is theoretically neutral, despite the PV and short-term VCR impact. If the acquisition is paid for in cash, then the reduced cash balance for the DDB would lead to a reduced MV (and SP), but this would be exactly offset by the increased PV of the new pipeline acquired, assuming it was acquired at market value. So theoretically, SP should remain unchanged. Alternatively, if new shares are issued to acquire the additional pipeline, then the growth in MV and PV that occurs is at the expense of existing shareholder dilution. Again, all things being equal, the SP again should remain unchanged.

7.8. Model of VCR and IRR

A general model that incorporates and integrates the variables discussed in this chapter is shown in Figure 6. In this model, RDE drives PVG (after adjustment for any acquisitions), which in turn generates VCR after deduction of BR (which includes RDE). PVG affects PV and thereby impacts MV, which in turn determines IRR, subject to SI dilution effects. TAQ is seen as an important moderating variable that determines the efficient translation of RDE into PVG. Therefore, it is a critical determinant of the value creation and investor return outcome. As previously discussed, management quality is seen as an additional moderator of the translation of RDE into PVG.

Figure 6. Proposed general model of VCR and IRR



Cash reserves tended to be relatively stable and small compared with MV, at least in this study. As a result, there was a very high correlation between MV and PV (correlation = 0.98, based on the data in this study). Therefore, MV can be used as a surrogate for PV and this allows the relationship between VCR and IRR to become somewhat clearer as follows: SP growth, which determines IRR, will only occur when the MV per share (MV/SI) grows. If the firm is issuing a large number of shares to top up C, in order to fund its BR, then positive SP growth (and IRR) will only occur if the growth in MV is more than the growth in SI (the 'dilution'). With most firms issuing new shares each year – leading to a substantial ΔSI – the MV (PV) growth and therefore, VCR, will need to be high in order to deliver SP growth (IRR). This means that the TAQ needs to be very high in order to deliver MV growth per share that is sufficiently high to generate above-average IRR.

A primary purpose of the empirical research is to determine how the Australian drug development biotech sector performs with respect to investor returns, which can be measured as IRR. A second and related purpose is to assess whether the sector 'creates value', with value creation measured by the VCR construct proposed here. The above model provides the opportunity to validate VCR as a value creation performance metric, by assessing its relationship with IRR. To conceptually align the two measures, VCR needs to be determined on annual basis, since IRR is a compound annual measure, while as reported in this research, VCR is a total cumulative measure.

As suggested above, dilution plays a significant role in the translation of VCR into IRR, and this needs to be taken into account in the validation. VCR is a measure of efficiency and quality of PV output based on the cash consumed (BR) to create that output. VCR is largely unaffected by dilution, while IRR is significantly affected by dilution. Therefore, any model seeking to establish the strength of the relationship between VCR and IRR should accommodate dilution as an explanatory variable. Again, this variable needs to be calculated on an annualised basis to align with IRR.

7.9. Conclusions

Enterprise value (EV) has long been used as a surrogate for net acquisition value of technology firms. The concept of pipeline value (PV) is arithmetically equivalent to EV for DDB firms, but is conceptually more appropriate for DDB firms. PV represents the total value, as perceived by investors, of the drug development programs under development by a firm at any time. For publicly traded DDBs, which have a clear current market value (MV), the PV is calculated as the MV minus the firm's primary tangible asset, which is cash (C).

PV represents the investor-perceived value of a firm's drug development pipeline. PV growth (PVG) occurs when a firm's TA engine is fuelled by RDE to generate improved investor perceptions of the PV premium over cash.

However, PV growth alone does not constitute value creation by DDBs. Value is only created by a DDB if the PVG is larger than the operating cash cost (BR) to produce it. On this basis, I have proposed a value creation construct, VCR, as a measure of the efficient growth in PV and as a performance metric for public DDB firms. This conception of value creation has not been elaborated previously or used as a performance measure for biotech firms. Others have used the term 'value creation' in the context of biotech, but without explicit definition or measurement methodology (Coombs and Deeds, 1998; Edwards et al., 2003; Ernst & Young, 2015; Farag, 2009; Lazonick and Tulum, 2011; McConomy and Xu, 2004; Mindruta, 2013).

PVG and thereby, VCR, can be artificially generated by acquisitions and in-licensing of new candidate drugs by the firm. In calculating VCR, the PVG needs to be adjusted for the impact of acquisitions on PV.

DDBs are cash-consuming, and applying the investor captaincy paradigm, can only exist and raise the funds to create value if they are able to generate adequate returns for shareholders, as measured by the internal rate of return (IRR). Therefore, IRR represents an important long-term measure of DDB performance.

While VCR measures the efficient growth of the pipeline value of firms, it may not fully or faithfully translate into IRR. A model of the relationships between a range of variables and VCR and IRR has

been presented. I propose that both VCR and IRR be used as important and interdependent performance metrics for DDB firms.

It would be useful to measure the VCR and IRR performance of DDB firms over a period of a decade or more. This would wash out short-term fluctuations in market sentiment and allow the full potential value of a firm's drug development pipeline to be manifest. Such an analysis also may allow the distillation of valuable insights into the characteristics of successful DDB firms.

In addition to examining the performance of individual firms, the same metrics could be usefully applied to the DDB sector as a whole, in specific countries. Without significant sector-wide VCR, the DDB sector in a particular country may not be viable. Moreover, without attractive returns for investors in the local sector, there will be little funding available to generate VCR and the local sector could stagnate despite high-quality TA. Finally, I propose that the utility and validity of VCR as an annual performance metric can be assessed by its predictive power of IRR, when the former is adjusted for annual SI growth.

This concludes Part A and the elaboration of the conceptual contribution of the thesis. It also sets the stage for Part B of the thesis, in which I seek to measure the performance of the Australian DDB sector using the definitions and performance constructs developed in this Part A.

Part B: Empirical Research

Chapter 8. Methodology

The current study used VCR and IRR to assess the performance of the Australian DDB sector over a 15-year period from 2003 to 2018. Australia is a unique setting in the biotech world (Gilding, 2008; Herpin et al., 2005; Rasmussen and Sweeny, 2002), claims a relatively high innovation performance (measured by patents and research papers), has a relatively large number of public biotech firms and boasts a top-five ranking by the *Scientific American* in their annual biotechnology performance rankings (Nogrady, 2018). However, the Australian DDB sector has failed to produce a big biotech firm or even a flagship DDB firm that could be considered a sustained success.

To date, no rigorous analysis has been conducted of the performance of Australian DDB firms, at least with respect to value creation and investor returns. This study fills that gap and asks the question: Do Australian public DDB firms create value and achieve attractive returns for their investors?

To answer this question, I conducted empirical research using data for Australian public (ASX-listed) DDBs, excluding private (unlisted) DDBs. Using public firm data was practical, because the data needed for VCR and IRR calculations were only available in an accurate, reliable and consistent form from public firms. However, it was important to assess the impact of excluding private firm data and restricting the dataset to public firms only.

8.1. Dataset

8.1.1. Mapping the Australian DBF sector

A recent study at Swinburne University of Technology sought to identify all DBFs – private and public – that had existed in Australia between 2003 and 2014 (Gilding et al., 2019). The purpose of the study was to map the Australian biotech (DBF) sector in a similar way to the landmark longitudinal research conducted by Powell and colleagues (Powell et al., 2002; Powell et al., 1996; Powell et al., 2005), who mapped the trajectory of US DBFs, clusters and networks between 1988 and 2002. In the Australian study (Gilding et al., 2019), the authors selected 2003 to 2014 as the review period, asserting that Australian DBFs in 2003 compared in age, size and scale to US DBFs in 1988, so the period was comparable to the US study.

Unlike the US experience, there was no central repository of data on the Australian biotech industry, so the authors had to assemble their dataset from a range of sources, including the 'Australian Biotechnology Directory' prepared by AusBiotech, State government biotechnology directories and other publicly available sources, such as media reports and publications. The goal was to capture all

biotech firms that existed in Australia during each year of the study and to report on a range of criteria: gross assets, revenues, whether listed or private, numbers and types of partnerships, numbers of employees (FTEs) and other variables. Assembly of this dataset was a major undertaking that took place over several years at Swinburne University. As I will refer to this dataset on several occasions, I will call it the 'Swinburne DBF Dataset'.

Like the US study, the Australian study defined DBFs as 'independently operated, profit-seeking entities involved in human therapeutic and diagnostic applications of biotechnology' (Powell et al, 2005, p. 1148). Importantly, the Swinburne DBF Dataset discriminated DBFs based on whether they were 'therapeutics' (TH) or 'diagnostics' (DX); in a few cases, firms were classified as 'DX&TH', where they appeared to be developing both types of products. The one listed DX&TH firm, Cellmid, I reclassified as TH, because its main focus was drug development. Similarly, I was able to reclassify two other private DX&TH firms as primarily TH. It is not uncommon that early stage biotech firms would be developing technology platforms that could be taken in either the direction of DX or TH, but it is the more lucrative TH opportunities that generally drive the future development of the platform and the orientation of the firm.

The firms were further classified by whether they were privately-held (private) or ASX-listed (public) in each year. I selected the data for the most recent year of the study, 2014, for further analysis and the breakdown between DX and TH in that year was as shown in Table 14.

Table 14. Classification of Australian listed and private DBFs in 2014

	DX	TH	Total
Private	14	49	63
Public	3	38	41
Total DBF	17	87	104

In 2014, there were 104 DBFs in Australia; of these, 40% were ASX-listed and 60% private. Overall, and in line with US NBT data, the overwhelming majority (84%) of Australian DBFs were focused on therapeutics – pharmaceutical drug development. However, it should be remembered that the DBF definition used in the Swinburne DBF Dataset, excluded all biotech firms outside diagnostics and therapeutics, whereas the US NBT data included many of these. As my interest was in DDBs only, I focused on the TH category of DBFs. While some of these DDBs reported revenues in 2014, all were pre-commercial firms and otherwise qualified as DDBs by the PCI definition. Of these, 44% were ASX-listed.

I further analysed this set of DDBs based on various descriptive statistics collected and reported in the Swinburne DBF Dataset, notably employees (FTEs), revenues, assets and the number of partnerships. 'Partnerships' included all types of partnerships – with pharmaceutical firms, PROs, government, other biotech firms, financial firms (including VCs) or other firms. Table 15 shows the summary breakdown between private and public firms on these four measures.

Table 15. Dimensions of Australian private and public DDBs in 2014

	Number of FTE	Number of partners	Gross assets $m	Revenues $m
Private	44	249	66	15
Public	484	322	1,582	175
Total	528	571	1,647	190

Based on Table 15, public DDBs accounted for 92% of all employees, the majority of partnerships, 96% of assets and 92% of revenues. However, unlike public firms, private firms in Australia are not required to report data and 50 of the 66 private firms did not report asset or revenue data, and 51 of the 66 did not report FTE data (partnership data was mostly obtained from other sources). This suggests that the data on these metrics in Table 15 are significantly under-stated for the private segment. On the other hand, if one assumes that the smaller private firms were the ones that failed to report the data – probably a reasonable assumption – then it could be that the numbers in the table are only slightly understated. As an alternative perspective, I calculated the averages of the four variables for private and public firms, excluding those that did not provide data. Results are shown in Table 16.

Table 16. Averages of Australian private and public DDBs in 2014

	Average number of FTE*	Average number of partners	Average gross assets $m	Average revenues $m
Private	3	4.0	4.4	1.1
Public	22	7.9	39.5	4.4

* Only 22 public firms and 15 private firms reported FTEs

Again, assuming that the smaller firms were the ones that did not provide data, then the averages may actually overstate the size and value of the private segment of the DDB sector. Regardless of the missing data for private firms, what is clear from the tables – and what one would expect – is that public DDBs are larger and more advanced than their private counterparts with respect to access to cash and revenues, and in the development of partnerships. Of course, one would intuit this, because it fits with the notion that public listing would be available to only the firms with better quality TA and prospects. Public firms have 'made the grade' and succeeded in listing, whereas private firms have yet to achieve much at all. This certainly seems to be view of one of the editors of *Nature*

Biotechnology (Hodgson, 2006) who conducted a landmark survey of private biotech in US and Europe, and noted (p. 635):

> The performance of publicly quoted companies is a rough proxy for the current status of a given country's biotech sector…The founding of new companies, on the other hand, is often taken as an indicator of the dynamism and reinvention that is going on in the sector, a proxy for the extent of productive technology transfer. In reality, the founding of companies is not remotely an indicator of anything even vaguely productive. It is simply an event in a private company's development that happens to be measurable and is therefore frequently measured. Starting a company is easy, it's what you do with it that counts.

The author further describes private biotech firms as 'black box' phenomena – they "start, something happens and then they reappear years later as public companies" (Hodgson, 2006, p. 636). Of course one should recognise that this dismissive view of private biotech firms endorses NBT's long-standing reporting of public biotech firm data as a proxy for the biotech industry. Regardless, based on the data collected, the author concludes (Hodgson, 2006, p. 638):

> It is a misconception, therefore, to think of the biotech sector as a uniformly vibrant, pulsating collection of thousands of firms worldwide, even though this is undoubtedly the way to get the attention of those politicians who are interested in innovation as a means to economic dynamism. Rather, the reality is that 75% of biotech's employees work for just 600–700 firms (the public companies and the largest private ones).

Assuming Australian public and private firms are similarly distributed, with the vast majority of the productive output and access to funds restricted to public firms and the largest private firms, then it can be concluded that Table 15 and Table 16 *are* indicative of the whole Australian DDB sector. Public DDBs represent a more mature, evolved and curated group of firms compared with their private counterparts. They are representative of the 'best' of Australian DDB firms and therefore should be expected to represent a higher level of DDB performance than private firms.

I believe there may be reasons to challenge this view and some of these reasons may be Australia-specific phenomena. However, I will leave discussion of that point to the chapter discussing the research results. In the meantime, I believe there is a strong case for using public firm data, if not as a proxy for the whole DDB private-plus-public sector, because of the discontinuities between private and public firms, then as a sector in itself, constituting a pool of firms that represent the best DDB firms that a country has to offer.

8.1.2. Australian public DDB sector

My research is restricted to ASX-listed DDB firms. At September 30, 2018, there were 84 firms listed under the ASX Global Industry Classification Standard (GICS) heading of 'Pharmaceuticals, Biotechnology & Life Sciences'. I reviewed the websites, annual reports and where necessary, ASX announcements to ascertain which ones qualified as DBFs and within that category, which were DDB firms, according to the PCI definition. Note that my DBF definition is not restricted to just diagnostics and therapeutics like the Swinburne DBF Dataset and therefore the number of DBFs identified is larger than identified in the Swinburne DBF Dataset. I determined that 60 firms qualified as DBFs according to my definition, of which 37 (62%) were DDBs, as shown in Table 17.

Table 17. ASX 'Pharmaceuticals, Biotechnology & Life Sciences' companies

Focus of biotech firm	DBF category	Number
Drug development	DDB	37
Medical devices	MDB	10
Diagnostics	DXB	8
Research tools	RTB	2
Agriculture, Animal health	Other	3
Total biotech firms (DBF)		60

While still the dominant form of public DBF, DDBs in Australia were less dominant than in the US (based on the NBT dataset), where 86% of all public DBFs were classified as DDBs (refer Table 11). 'Medical devices' was the second largest category of public DBF in Australia, with 10 firms (17%). This included one firm that was developing therapeutic products, but their main product was classified as a medical device from a regulatory standpoint and therefore did not meet the definition of DDB. 'Diagnostics' accounted for eight firms or 13% of Australian DBFs. This might suggest that, in Australia, medical device DBFs are more prominent than in the US (refer Table 11).

The other 24 non-DBFs in the ASX list comprised 12 commercial-stage pharmaceutical firms (including the large pharmaceutical manufacturer, CSL) and nine service businesses, such as contract manufacturers, pathology services, tissue banking services and other healthcare or service-focused businesses that were not DBFs. I also found three other firms that did not fit neatly into either the 'pharmaceutical' or 'services' categories, namely a hospital supplies business, a company making dietary supplements, and one developing cannabis-based edibles and energy drinks.

Table 17 represents a snapshot of the DBF sector in Australia in 2018. However, my performance analysis is longitudinal and therefore needs to extend beyond the current pool of listed DDBs to all DDBs that existed over a period of time. As a first step, I identified all public DDB firms that existed since Biota, the first Australian public DDB, which listed in 1985.

A complete graphical history of the DDB sector through the end of 2018 is shown in Figure 8. This shows new entrants and exits from the sector over the period, with dates where applicable, as well as name changes that occurred. In total, 56 DDB firms existed or came into existence at one time since the sector's inception in 1985.

Figure 7 depicts the flux of DDB entrants and exits by year and the number of ongoing firms, each year since 2002. The number of ongoing DDBs grew from 21 in 2002 to 38 by 2005. Despite some fluctuations since 2005, notably a reduction in DDB numbers after the 2008/2009 GFC, the overall number of DDBs has remained relatively stable.

Figure 7. Entrants and exits in the DDB sector

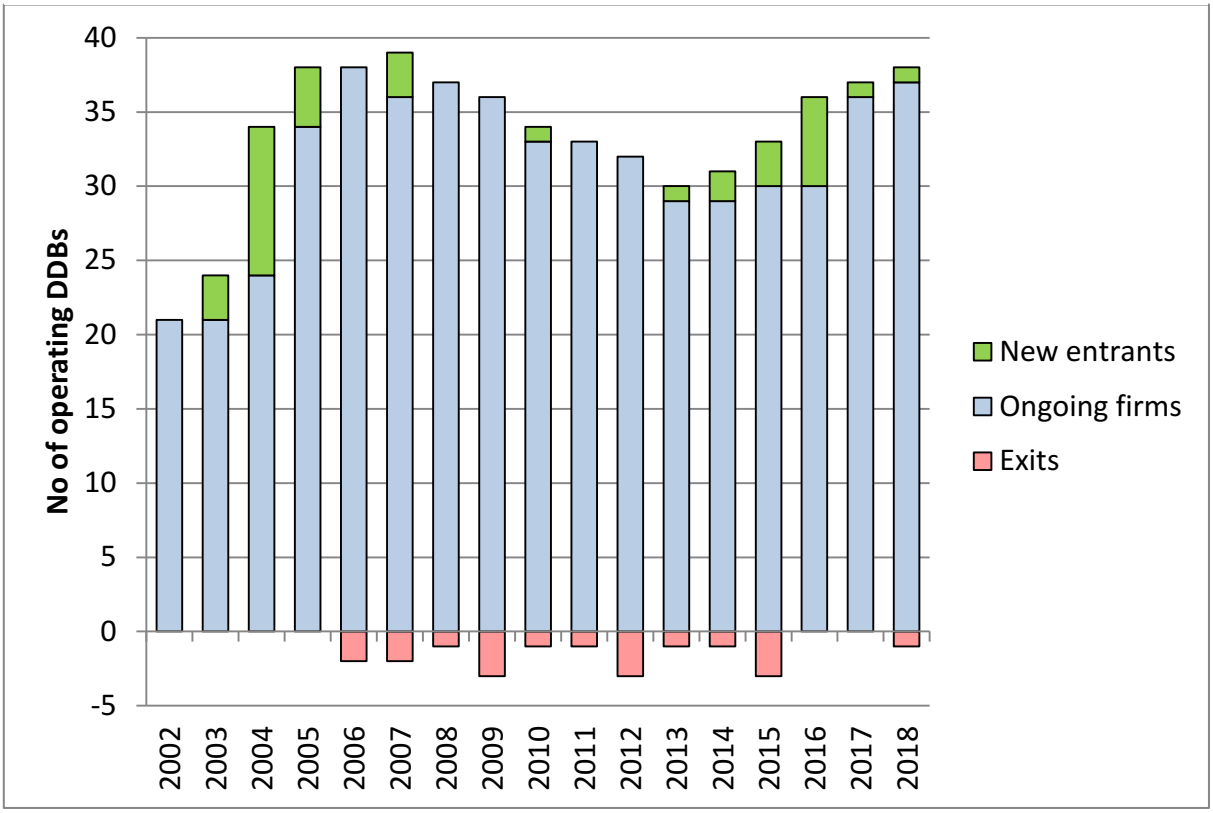


Figure 8. History of the Australian DDB sector

	History of the Australian DDB sector																			
	Latest DDB name (previous name)	ASX Code	Birth Pre-03	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
1	Biota	BTA	1985										11/12	Acq. by Nabi					
2	Zenyth (Amrad)	AMR	1986	Amrad	Zenyth		11/06	Acq. by CSL											
3	Meditech	MTR	1994				08/06	Acq. by Alchemia											
4	Progen	PGL	1995													11/15	Exited drug devt.		
5	Arana (Peptech)	AAH	1996	Peptech				Arana		08/09	Acq. by Cephalon								
6	Kazia (Novogen)	KZA	1997	Novogen														Kazia	
7	Virax	VHL	1997										08/12	VA (reborn later as PTX)					
8	Metabolic	MBP	1998							12/09	Exited drug devt.								
9	Bionomics	BNO	1999																
10	Immuron (Anadis)	IMC	1999	Anadis					Immuron										
11	Prana	PBT	2000																
12	Australian Vaccine	AVT	2000	AVT	AVT Bioplasma			08/07	Delisted, exited drug devt										
13	Starpharma	SPL	2000																
14	Peplin	PEP	2000							10/09	Acq. by Leo Pharm								
15	Biotron	BIT	2001																
16	Clinuvel (Epitan)	CUV	2001	Epitan			Clinuvel												
17	Solbec	SBP	2001						12/08	Exited drug devt.									
18	Immutep (Prima)	IMM	2001	Prima														Immutep	
19	Antisense	ANP	2001																
20	Benitec	BLT	2002																
21	Imugene	IMU	2002																
22	Select Vaccines	SLT		06/03								07/11	Exited drug devt.						
23	Pharmaxis	PXS		11/03															
24	Alchemia	ACL		12/03															
25	Biodiem	BDM			01/04									11/13	Delisted				
26	Phosphagenics	POH	Prev. Vital Cap		02/04														
27	Chemgenex	CXS	Prev. AGT		04/04							07/11	Acq. by Cephalon						
28	Acrux	ACR			09/04														
29	Cytopia	CYT			07/04						02/10	Acq. by YM							
30	Bone Medical	BNE			08/04									12/13	Shell, reborn as Botanix				
31	Avexa	AVX			09/04											12/15	Exited drug devt.		
32	Living Cell	LCT			09/04														
34	Mesoblast	MSB			12/04														
35	Neuren	NEU				02/05													
36	Phylogica	PYC				03/05													
37	Evogenix	EGX				08/05		08/07	Acq. by Peptech										
38	Cellmid (Med Ther)	CDY				12/05	Medical Therapies				Cellmid								
33	Viralytics	VLA			Prev. Psiron		12/06										Acq. By Merck		06/18
39	Qrxpharma	QRX						05/07								05/15	VA, delisted		
40	Patrys	PAB						07/07											
41	Actinogen	ACW						10/07											
42	Invion	IVX									02/10	Cbio	Invion						
43	Regeneus	RGS												09/13					
44	Amplia (Innate)	ATX													01/14	Innate			Amplia
45	Prescient	PTX											Prev. VHL		12/14				
46	Paradigm	PAR														08/15			
47	Dimerix	DXB														11/15			
48	Opthea	OPT												Prev. CIR		12/15			
49	Recce	RCE															01/16		
50	Vectus	VBS															02/16		
51	Botanix	BOT													Prev. BNE		07/16		
52	Noxopharm	NOX															08/16		
53	Adalta	1AD															08/16		
54	Zelda	ZLD															11/16		
55	Telix	TLX																11/17	
56	Neuroscientific	NSB																	07/18
	Number of DDBs at year end		21	24	34	38	36	37	36	33	33	32	29	29	30	30	36	37	37

Legend
Entry Date
Exit Date

New entrants comprised new IPOs, the re-classification of a previously listed firm into a DDB or a reverse takeover (RTO) of an ASX-listed shell. There were 36 new entrants over the period and 19 exits. The reasons for exits were: (a) acquisition of the firm, (b) re-classification after exiting the sector, (c) voluntary administration and/or dormancy as a shell, and (d) voluntary delisting. Of the original 21 listed DDBs in 2002, only 11 were still listed and active in 2018. Of the 19 exits, nearly half occurred between 2008 and 2012, in the wake of the global financial crisis. The nature and number of exits within the selected dataset for performance analysis are discussed in more detail in section 8.2.

Since 2001, there were two significant periods of DDB sector growth, 2003-2004 and 2013-2016. As previously noted, from 2001 through the first half of 2003, there was a recession in the biotech sector in the US and Australia. This was followed by a recovery in the second half of 2003 and with it came a re-opening of the biotech IPO 'window' in Australia and a surge of new entrants. Another surge of entrants occurred in 2013-2016 after a new wave of positive biotech sentiment in the US, driven in part by the exciting prospects for immunotherapy in cancer.

8.1.3. DDB dataset for performance analysis

For the purposes of assessing VCR and IRR by Australian ASX-listed DDB firms, I selected the 15-year period after 2003, with 2003 as the baseline year and 2018 as the terminus year. Because 2001/2002 was a recessionary period, I concluded that using either 2001 or 2002 as a baseline year for performance analysis potentially set an unduly low baseline. Further, most of the DDBs of relevance to the performance analysis emerged after 2002, with a surge in new listings from 2003 to 2005.

I limited the DDB firms to those that I could clearly identify as DDBs and that had active drug development operations and filed annual reports for at least five consecutive years during the period. Given the long development cycle for drug development, five years seemed to be a reasonable minimum time to expect a DDB to create any significant value.

This produced a final list of 40 DDB firms (of the 56 firms that existed in the period) for performance assessment as shown in Table 18. For analytical purposes, the firms were listed alphabetically and given an ID number. For ease of reference, I have used, and will continue to use, only their principal identifying firm name, rather than their full firm legal name; for example, 'Prana Biotechnology Limited' is shown and described simply as 'Prana'. Where the name included internal capitalisation, such as 'QRxPharma', I excluded the capitals, as in 'Qrxpharma'.

Although all 40 firms were listed on the ASX for the period of their performance assessment, not all firms had their operations or headquarters in Australia. This was not considered an exclusion criterion. Also, several firms were initially listed on the ASX and then obtained a second listing

elsewhere, typically on the US NASDAQ. Similarly, these dual-listed firms were not excluded from the dataset.

Table 18. List of DDB firms analysed

ID	Firm Name	ASX Code	ID	Firm Name	ASX Code
1	Acrux	ACR	21	Invion	IVX
2	Actinogen	ACW	22	Kazia (Novogen)	KZA
3	Alchemia	ACL	23	Living Cell	LCT
4	Amplia (Innate)	ATX	24	Mesoblast	MSB
5	Antisense	ANP	25	Metabolic	MBP
6	Arana	AAH	26	Neuren	NEU
7	Avexa	AVX	27	Patrys	PAB
8	Benitec	BLT	28	Peplin	PEP
9	Biodiem	BDM	29	Pharmaxis	PXS
10	Bionomics	BNO	30	Phosphagenics	POH
11	Biota	BTA	31	Phylogica	PYC
12	Biotron	BIT	32	Prana	PBT
13	Bone Medical	BNE	33	Progen	PGL
14	Cellmid	CDY	34	Qrxpharma	QRX
15	Chemgenex	CXS	35	Regeneus	RGS
16	Clinuvel	CUV	36	Select Vaccines	SLT
17	Cytopia	CYT	37	Solbec	SBP
18	Immuron	IMC	38	Starpharma	SPL
19	Immutep (Prima)	IMM	39	Viralytics	VLA
20	Imugene	IMU	40	Virax	VHL

Some specific inclusions and omissions are worthy of note:

a) I excluded Pharmaust (PAA). Despite the company's claim on its website to being a clinical-stage company developing targeted cancer therapeutics, its revenues and reported expenditure have been predominately associated with its legacy service business, Epichem; further, to the extent it has R&D, it appears to have been focused on animal health, not human drug development.

b) I excluded Cynata Therapeutics (CYP). Listed in 2013, Cynata is a manufacturer of stem cells for therapeutic use and has been seeking partnerships where its primary role appears to be that of a manufacturer rather than a DDB, although it may seek to develop a drug pipeline in the future.

c) I excluded Sirtex (SRX). Sirtex has had considerable success commercialising its SIR-Spheres for the treatment of liver cancer and in 2018 was acquired by a Chinese pharmaceutical firm for $1.9 billion. However, the firm has mostly been a commercial-stage business and SIR-Spheres were classified as medical devices, so the company did not qualify as a DDB.

d) I excluded Psivida. Psivida claims to be developing sustained-release drug-delivery products for treating eye diseases. Like Sirtex, its products are classified as medical devices.

e) I included Amplia (ATX), which until 2018 was known as Innate Therapeutics. This is a DDB that listed on the ASX in January 2014 and therefore operated for one month short of the requisite five years by the end of 2018. However, it did issue five annual reports during the period and therefore I considered it sufficiently qualified on that basis.

f) I excluded Circadian (CIR), which listed in 2005. Like a small number of other listed companies in the early 2000s, this company was established as a Pooled Development Fund (PDF) that held investments in several private biotech firms, including DDBs and other biotech firms. However, Circadian itself did not qualify as a DDB and therefore was excluded. In December 2015, Circadian changed its name to Opthea (OPT), which is a DDB focused on ophthalmic therapeutics; Opthea was excluded from the current analysis due to its lack of a five-year operating history.

g) I excluded Psiron (PSX), which was the precursor to Viralytics (VLA). Like Circadian, Psiron had investments in several private biotech firms until December 2006, when it changed its name to Viralytics and became a DDB.

h) I excluded Prescient (PTX). This company is a DDB that listed in December 2014, as a reverse merger into what was the shell company left behind by Virax (VHL). Prescient was vended (merged) into the Virax shell and is treated as a new firm for performance analysis. However, being born in December 2014 meant that Prescient had only four years of evaluable life during the 15-year period with only four annual reports filed; therefore, it was excluded. There were 11 other DDBs launched after Prescient, which were similarly excluded due to having less than five years of history: Paradigm (PAR), Dimerix (DXB), Opthea (OPT), Recce (RCE), Vectus (VBS), Botanix (BOT), Noxopharm (NOX), Adalta (1AD), Zelda (ZLD), Telix (TLX) and Neuroscientific (NSB).

8.2. Data handling and calculations

I obtained all share price and market value data from the *DatAnalysis Premium* database offered by Morningstar, Inc. through the Swinburne University of Technology library. I used the same database to obtain annual reports (and half-year or quarterly reports, where required) for each firm and for up to 16 years (inclusive) from 2003 to 2018. I also reviewed ASX announcements and firm presentations to identify any changes in the businesses relevant to the performance analysis, such as any share consolidation or split, acquisition, delisting or change of business focus.

For each firm, I established a baseline year, against which growth in outcomes such as pipeline value (PV) and share price (SP) could be assessed, as these outcome measures were essential for calculation of VCR and IRR. The earliest baseline year was set at 2003, while 2018 was the latest terminal year. Where a firm entered the sector after 2003, the baseline year was deemed to be the first year that the firm produced an annual report after 2003. Entry date was defined as the date of listing on the ASX or, in the event that the firm was already listed and became a DDB due to a change of business or reverse takeover, it was the date of that change.

8.2.1. Treatment of exits

There were 15 exits from the 40-firm dataset prior to December 31, 2018. These are summarised in Table 19 and their specific treatment discussed below.

There were six exits due to trade sales to (acquisitions by) international pharmaceutical firms. There were no exits that saw the DDB's technology or pipeline remain in Australia or in an ASX-listed entity. Where the acquisition was for cash and there was a specific price per share paid, I used the closing share price (adjusted for a reverse-split, in the case of Viralytics) on the last day of trading to calculate the MV, rather than a weighted average MV over several months. The rationale was that for ASX acquisitions, it takes several months for the acquirer to buy 90% of outstanding shares, after which all shareholders are obliged to sell. During that time, investors continue to trade, perhaps betting that the acquisition will not be consummated, that the offer price may be increased or that some naïve shareholders will be unaware of the acquisition price. Regardless, the last trades are made at the offer price (with no discount) and this is the price received by all the ASX shareholders who decided to sell to the acquirer and represents the true exit market value. This approach was used for the acquisitions of Viralytics, Chemgenex, Peplin and Arana.

Table 19. Summary of exits in the DDB dataset

DDB	Reason for exit*	Final Report
Trade sale (acquisition)		
Arana	Acquired by Cephalon; last ASX trade 2/7/2009	Mar 2009
Peplin	Acquired by Leo Pharmaceuticals in 2009; last ASX trade 5/11/2009.	Jun 2009
Cytopia	Acquired by YM Biosciences with last ASX trade 18/1/2010	Jun 2009
Chemgenex	Acquired by Cephalon with last ASX trade 21/6/2011	Dec 2010
Biota	Acquired by Nabi Pharmaceuticals; last ASX trade 30/10/2012	Jun 2012
Viralytics	Acquired by Merck in 2018; last ASX trade 5/6/2018	Mar 2018
Exit from drug development to another field		
Solbec	Exited drug development on 9/9/2008, announcing plans to acquire laser eye care business in Malaysia; changed name to 'Freedom Eye Limited'	Jun 2008
Metabolic	Exited drug development on 30/11/2009 to refocus on biodegradable polymers; changed name to 'Calzada Limited'	Jun 2009
Select Vaccines	Exited drug development in 19/12/2011 with announcement of its becoming a mining business	Jun 2013
Bone Medical	Following a recapitalisation in 2013, BNE effectively ceased all drug development activity (last trade prior to recap was 23/1/2014);	Jun 2013
Progen	Exited drug development on 1/5/2015, when it announced acquisition of TBG, refocusing on diagnostics	Jun 2015
Avexa	Exited drug development 12/10/2015 with announced acquisition of TALI Health	Jun 2015
Other exits		
Virax	Voluntary administration; last ASX trade on 29/2/2012	Jun 2011
Biodiem	Voluntarily delisted 18/11/2013 to continue as a private DDB	Jun 2013
Qrxpharma	Administration; ceased trading shares on 22/5/2015	Jun 2014

* All dates shown are in dd/mm/yyyy format

There were two acquisitions where shareholders received shares in the acquiring firm, rather than cash. This applied to Biota and Cytopia. In these cases, I assumed that Australian investors decided to cash out their shares on the ASX prior to cessation of trading, rather than receive shares in a foreign entity on a foreign exchange, given the trading complexities, exchange rate risks, distance perceptions and unknown risks. In both cases, there was considerable notice to shareholders about the acquisition and plenty of time for them to make a value judgment about the MV (and PV) prior to the final trading day. Therefore, I have assumed that any shareholder who was minded to do so, would have sold out of the stock over the period prior to the final trading day to ensure they could exit. To reflect this, I used the volume-weighted average MV over the months prior to the last month of trading.

Throughout, I have proposed that trade sale exits to a pharmaceutical partner may be a key mechanism for DDBs to deliver value to investors, which in turn drives further investor interest in the DDB sector. Therefore, some detailed description of the treatment of each trade sale is warranted.

Arana ceased trading on the ASX on July 2 2009, subsequent to its all-cash acquisition by US-based Cephalon and before an annual report could be lodged in 2009. I used the MV on July 2 as the MV for 2009, as it captured the acquisition price of $1.40 per share. Because Arana reported on a September 30 financial year, I used the half-year report at March 31, 2009, to determine C and BR.

Peplin ceased trading on the ASX on November 5 2009, subsequent to its all-cash acquisition by Danish pharmaceutical company, Leo Pharma. I used the June 30 2009 annual report (a US 10-K filing) for C and BR, and calculated the MV based on the closing price on November 5, as it captured the final acquisition price ($0.91 per share). It should be noted that Peplin Limited (PEP) delisted from ASX on October 8, 2007 and then relisted the same day on ASX as Peplin Inc. (PLI), a US domiciled company. Given the continuity of the business and shareholding, PEP and PLI were treated as the same firm for performance analysis.

Cytopia ceased trading on January 18, 2010, subsequent to its acquisition by YM Biosciences, a Canadian company; instead of cash, Cytopia shareholders received shares in YM Biosciences. I used the June 30 2009 annual report for C and BR, and calculated the MV based on the six month period from July to December 2009.

Chemgenex ceased trading on June 21, 2011, subsequent to its all-cash acquisition by Cephalon and before an annual report could be lodged in that year. In that case, I used the June 21, 2011 MV as the MV for 2011, as it captured the acquisition price ($0.70 per share) paid by Cephalon. As there was no quarterly report filed for March 2011, I used the half year report (December 31, 2010) to estimate the cash balance for C and BR. It seemed reasonable to use the December 31 cash and BR, since the

firm was deeply engaged in the acquisition process and unlikely to have incurred any significant new operational expenditure in the last six months leading up to the consummation of the acquisition.

Biota ceased trading on October 30, 2012, after it migrated to a NASDAQ listing via a reverse merger into NASDAQ-listed Nabi Pharmaceuticals, which was a dormant shell. Like Cytopia, Biota shareholders received Nabi shares in lieu of their Biota shares. Like Cytopia, I assumed that they sold during the period prior to consummation of the Nabi acquisition. The final ASX trades were on October 30, 2012, so I used the volume-weighted MV for the four months from July through October to calculate the exit MV. The 2012 annual report was used for C and BR determination.

Viralytics ceased trading on the ASX on June 5, 2018, subsequent to its all-cash acquisition by US-based, Merck, and before an annual report could be lodged in 2008. Like Arana, I used the MV on June 5, 2018, as it captured the acquisition price ($1.75 per share, adjusted to $0.175 for its 10:1 reverse-split in 2011) and the quarterly report at March 31, 2018, to determine the C and BR.

In the cases of Biota and Cytopia, it is worth noting that, had shareholders decided to take the risk on shares in the foreign entity, then in the case of Biota, their shares in Nabi (name later changed to Aviragen) became virtually worthless. However, for Cytopia, YM Biosciences was itself acquired in 2012 by Gilead for US$510 million, which anecdotally translated to a positive return for those Australian shareholders who held their YM shares for the three-year period after Cytopia was acquired.

Apart from trade sales, there were six exits due to the DDB's ceasing drug development and moving into another field, as outlined in Table 19. In each case, the exit was deemed to have occurred when the DDB firm announced that it was exiting drug development to focus on the other field.

For example, on September 9, 2008, Solbec announced plans to exit drug development and acquire an eye-care business in Malaysia; I used the June 2008 annual report and calculated MV based on the two months of trading after June 30 (July and August 2008). Metabolic exited drug development on November 30, 2009, to focus on biodegradable polymers, changing its name to Calzada; I used the June 2009 annual report and calculated MV based on the five months of share trading thereafter. Select Vaccines announced on December 19, 2011, that it had acquired mining assets in Tanzania and was becoming a mining company; I used the June 2011 annual report and calculated MV based on the six months of trading thereafter.

Bone Medical substantively ceased all operations in mid-2013 and became a shell. After a failed attempt to vend in a geospatial technology company in 2015, Bone Medical finally succeeded in vending in Botanix Pharmaceuticals in 2016, changing its name to Botanix. While I classify Botanix as a DDB, from an investor perspective, the operating life of Bone Medical as a DDB ended on November 28, 2013, when it announced a massive recapitalisation that saw 7.5 billion shares issued

at 0.04 cents each, effectively washing out all pre-existing shareholders. Given the trajectory of events, I assumed that shareholders would have sold out over the six months prior to the consummation of the recapitalisation event (July – December 2013), so I used a volume-weighted MV over that period, and the June 2013 annual report for C and BR.

Progen exited drug development on May 1, 2015, when it announced it was acquiring a diagnostics business and in December 2015, changed its name to TBG Diagnostics; I used the June 2015 annual report and the volume-weighted MV over the five months from July to November 2015. Avexa exited drug development on October 12, 2015, when it announced that it was acquiring a diagnostics business (TALI Health); this was followed by a 20:1 reverse split and recapitalisation in November 2015. I assumed all DDB investors sold out prior to the recapitalisation, so I used the June 2015 annual report and calculated the volume-weighted MV over the four months from July to October 2015.

Finally, there were three exits for reasons other than acquisition or moving into a new field. Biodiem voluntarily delisted in November 2013 to continue as a public un-listed DDB firm. The stated rationale was that the ASX valuation was understating the company's real value. I used the June 2013 annual report and calculated MV based on the four months from July to October 2013.

Virax shut down its operations and went into voluntary administration in February 2012, but it was made clear to shareholders that the company was struggling during the second half of 2011. I assumed that informed DDB investors sold out prior to the final administration decision, based on the trajectory of events and share price. I used the June 2011 annual report and calculated MV based on the six months from July to December 2011.

Qrxpharma ceased trading on the ASX in May 2015, after failing to gain FDA approval for its lead program. During 2015, its US investors launched a class action suit (in the US) against the company's directors and CEO. This ultimately forced the Australian company into administration. I determined the firm to have exited in May 2015 and used the June 2014 annual report, calculating MV based on the six months from July to December 2014.

In the nine exits that were not due to acquisitions, these were firms that had failed in their mission to successfully develop candidate drugs and the failure process occurred over months or even years in some cases. As a result, the precise timing of the calculation of the terminal C, BR and MV had no material impact on the performance outcomes of the firms.

8.2.2. PV and VCR calculation

As previously described, PV was calculated as the MV minus the firm's cash balance (C). In order to calculate PV, the reported cash balance at June 30 was deducted from the firm's MV calculation (as described below). The cash balance used for the PV calculation was generally the figure reported on the firm's balance sheet as 'cash and cash equivalents' plus any short-term deposits or other liquid assets that were readily convertible to cash. Any receivables, prepayments, inventory or other current assets were ignored in the cash balance determination.

Thirty-five of the firms reported financial results at June 30, so the reported cash balance was at that specific date (June 30) and the BR was the operating cash outflow for the previous 12 months (July 1 – June 30) as reported in the annual report. Five of the 40 firms reported on annual financial years that ended on dates other than June 30. Three of these reported on a January-December year (Neuren, Phosphagenics and Select Vaccines). In these cases, I used half-year reports to provide the cash data at June 30 and BR over the previous 12 months, and thereby aligned the results with the other 35 firms. One firm reported financials at September 30 (Arana) and one at March 31 (Amplia). In the case of Arana, quarterly reports were unavailable, so I ignored the three-month misalignment and assumed the data were at June 30 of the applicable year. Arana exited the sector in 2009, which was early in the assessment period, so I determined that any misalignment had a minimal effect on the overall sector results. In the case of Amplia, I used quarterly reports to calculate the June 30 cash levels and 12-month BR. Three DDB firms reported in foreign currencies at some time during the 15-year period: Mesoblast, Neuren and Peplin. In most cases, I converted the numbers to Australian dollars at the prevailing average annual exchange rate. Mesoblast was dual-listed on ASX and NASDAQ from 2016; I used its 2018 US 20-F filing, which showed data for 2016, 2017 and 2018 in US dollars and indicated that all Australian dollar payments had been converted into US dollars at an exchange rate of 0.7391, so I used this rate to convert all the data for those three years into Australian dollars.

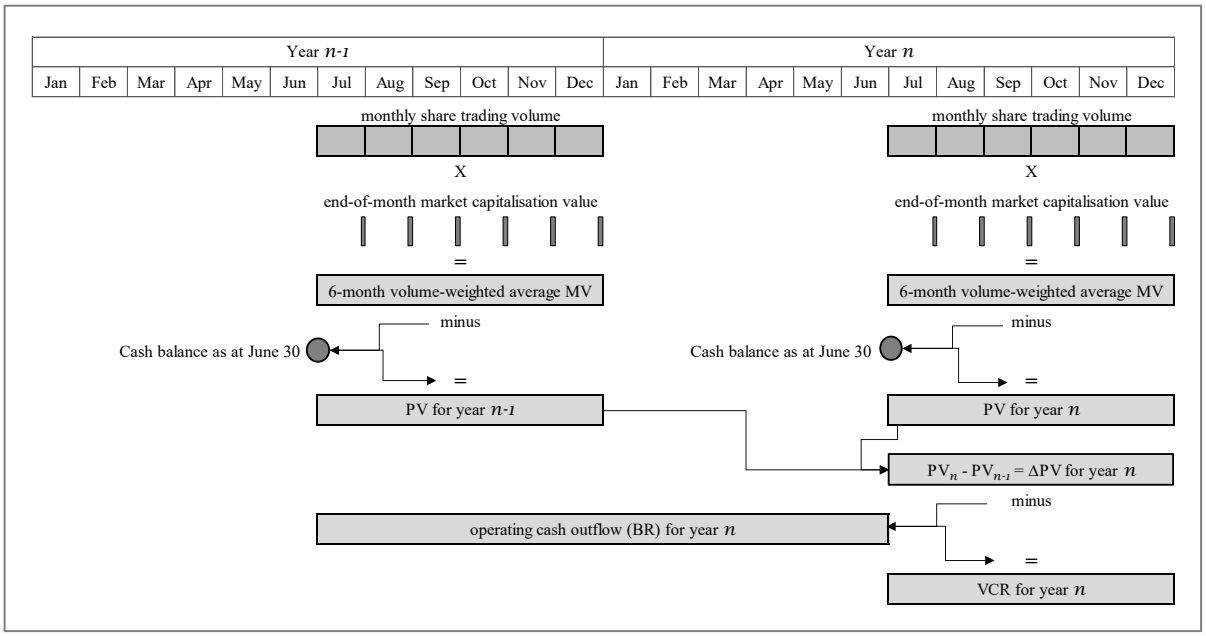
MV was determined as follows: Rather than use the MV on a single date, such as June 30, I used a volume-weighted average (VWA) of the MV over the six-month period after June 30. The rationale for this was several-fold: First, I considered that given the volatility in the share prices of DDB firms, it would be inappropriate to use a single day's pricing (e.g., June 30) as a measure of PV. Further, because PV is a measure of market perception of the pipeline value of a DDB, it is important to consider the timing of investors' awareness of and reaction to financial value-relevant data. For example, the value of the year-end cash is not released to the market until the release of the annual financials, usually in August. However, shareholders do not receive a physical copy of the annual report until sometime in September, which may be the first time that some become aware of the results. Finally, the annual shareholders' meeting, which could be as late as the end of November, is when some shareholders may form their view of the firm's value and prospects, based on

presentations by and discussions with the board and CEO. If investors make buy or sell decisions based on all this information, they may be executed as late as December of that year. On these bases, I determined that it was reasonable and valid to calculate MV based on a six-month VWA of the MV from July through December and that PV reasonably could be calculated based on that MV calculation minus the cash reported at June 30.

Specifically, to calculate the volume-weighted MV, I multiplied the volume of shares traded in each of the six months (Jul-Dec) by the reported market value on the last trading day of each month. Daily-weighted monthly MVs were not available through the *DatAnalysis* database, so I used the end-of-month MV and weighted it by the total monthly volume. Ideally, I would have used a monthly MV that was a VWA of all trading days in the month, but this was not available and given the six-month span of the data, using the end-of-month MV was unlikely to significantly distort the results. These weighted values were then aggregated and the total divided by the total volume for the six months to arrive a volume-weighted MV for the six months.

VCR was calculated as the change in PV for each year, compared with the previous year, minus the operating cash burn (burn rate, BR) for the year. The BR was the operating cash outflow in the annual report for the July-June financial year, which was reported as 'net cash inflow/(outflow) from operating activities'. Note that this is the cash flow, net of all revenues, grants, tax credits and other income, and it represents (is conceived here as) the net draw down on investors' funds to drive PV growth. The PV for each year was calculated for the same July to December period as MV (since PV = MV - C). These calculation methodologies are shown graphically in Figure 9.

Figure 9. VCR calculation methodology



The share trading volumes were adjusted for splits (or 'forward splits') and consolidations ('reverse splits'). Splits are used by rapidly growing firm to increase the shares on issue and reduce the share price, so that investors are not dissuaded from buying shares by the high price per share. Forward splits have occurred frequently in the US over the years, with the average pre-split price being US$50 per share; a 'reverse-split' or consolidation is where the firm reduces the number of shares on issue to increase the share price, usually in the face of share price weakness (Wei et al., 2015).

In the 40-firm Australian dataset, there were no forward-splits, perhaps indicating that none of them had been that successful, but there were nine reverse-splits (consolidations), aimed at reducing shares on issue and increasing the listed share price. These are shown in Table 20. While some of the consolidations led to MV growth, several had a significantly negative effect on MV.

Table 20. Share consolidations in ASX DDB sector 2003-2018

	Year	Consolidation ratio (x:1)	Gain/-Loss in MV post- consolidation*
CUV	2010	10	8%
VLA	2011	10	-44%
ANP	2013	10	0%
BLT	2013	25	18%
IMC	2014	40	-25%
NEU	2017	20	33%
CDY	2017	20	-14%
ATX	2018	10	-44%
KZA	2018	10	8%

* Based on volume-weighted MV three months prior, compared with three months post.

In addition, there was one significant share buy-back – by Progen in 2009. In early 2006, Progen's share price was around $6, but during 2007 and 2008, it dropped to below $1. With $77 million in cash reserves, the company engaged in a massive share buy-back (where the firm uses its cash reserves to buy shares on market) in an attempt to bolster its flagging share price; by mid-2009, it had reduced the number of shares on issue by around 60%, but the share price continued to decline. As the buy-back did not represent a recapitalisation of the share structure, but simply the transfer of shares from public shareholders to the company, I made no adjustment for it.

8.2.3. Acquisition adjustment

As previously described, acquisitions can lead to overstatement of the VCR calculation, because of their direct impact on PV in the acquisition year. PVG that arises through acquisitions does not

constitute value creation from a firm's extant TA, so the PV impact of these needs to be deducted from the PVG used for the VCR calculation for each DDB. Table 21 shows all the acquisitions and in-licensing deals in the sector, since 2003, which produced a MV increase of greater than 25%.

Table 21. Acquisitions and in-licenses in the Australian DDB sector 2004-2018

DDB	Acquired business	Description	Announced	Completed	PVG $m	PVG %
Actinogen	Corticrine	UK DDB	8/2014	12/2014	31	860%
Arana	Scancell	UK DDB	12/2006	12/2006	73	34%
Avexa	In-license	EU pharma (Shire)	1/2007	1/2007	121	191%
Bionomics	Iliad	AU private DDB	5/2005	7/2005	7	59%
Bionomics	Eclipse	US DDB	9/2012	9/2012	26	27%
AGT (CXS)	Chemgenex	US DDB	4/2004	6/2004	9	34%
Immuron	In-license	Israel PRO	4/2009	9/2009	14	220%
Imugene	Biolife	AU private DDB	10/2013	12/2013	11	346%
Imugene	In-license	AU PRO	12/2016	12/2016	14	66%
Invion	License/funding	China pharma (Cho Grp)	4/2017	12/2017	123	3853%
Kazia	Triaxial Pharm	AU private DDB	11/2012	12/2012	22	295%
Patrys	In-license	EU pharma (Debiopharm)	10/2009	10/2009	6	27%

In each case, the PV impact was calculated as the VWA of the MV for the three months after completion of the deal, compared with the VWA of the MV for the three months prior to the announcement of the deal. I chose three months for the VWA calculation, rather than six months, as used in other calculations, to minimise the time available for non-acquisition-related events to intervene. I also made the simplifying assumption that cash levels over the two periods and any intervening period did not change significantly and therefore that the difference in MV would be a reasonable estimate of the difference in PV. This assumption also pointed to the need to keep the assessment period short.

In some cases, an acquisition or license had a negative impact on PV. For example, Alchemia acquired Meditech, another ASX-listed DDB, in 2006; the merger was announced in March 2006, but not consummated until August. Because of the long consummation period, the MV had moved considerably – likely due to non-acquisition factors – and the calculated impact of the acquisition

proved to be negative. In this case and others where acquisitions led to negative calculated PV effects, or the PV effects were reasonably attributable to other factors, I ignored the acquisition.

Theoretically, divestitures of pipeline assets would have led to a reduction in PV and an adjustment for that loss in PV should have been made accordingly in calculating VCR. However, where DDBs engaged in divestitures, it was generally for underperforming technologies or candidate drugs, so the PV impact was negligible. Based on ASX announcements, I found only three cases of divestitures, none of which appeared to have any significant negative impact on MV. Therefore, I decided to ignore divestitures in the analysis and focus on the impact of acquisitions only.

There were some clear examples of DDBs' acquiring new technology, not to supplement existing TA, but as a substitute for failed TA and a means to give the firm a new lease of life. For example, in 2007, Avexa in-licensed the HIV drug, ATC, from UK-based Shire. In 2013, Imugene acquired the license to a new cancer drug from a PRO in Austria, through its acquisition of Biolife. In 2014, Actinogen acquired a UK spinout, Corticrine, and in the process acquired the Alzheimer's drug, Xanamem. In 2017, Invion consummated a value-accreting funding and licensing deal with Cho Group in China. In all cases, the deals rescued the DDBs from failed or underperforming programs and gave them a significant, immediate MV uplift.

In some cases, the PV impact of the newly-acquired TA was only realised over time, rather than in the three-month period used for calculating the PV impact in Table 12. For example, Patrys in-licensed PAT-DX1 from Yale University in June 2007, after its original TA failed. However, the immediate impact on MV was negligible and it was not until mid-2018 that the efficacy of the drug became apparent and the market realised that the asset represented valuable new PV.

In summary, the PV impact of acquisitions was estimated using a three-month pre- and post-assessment of the impact on the VWA MV. Where the impact was greater than +25%, the change was considered to be due to new TA and the estimated PVG impact was deducted from the PVG for the firm in calculating the cumulative VCR for that firm.

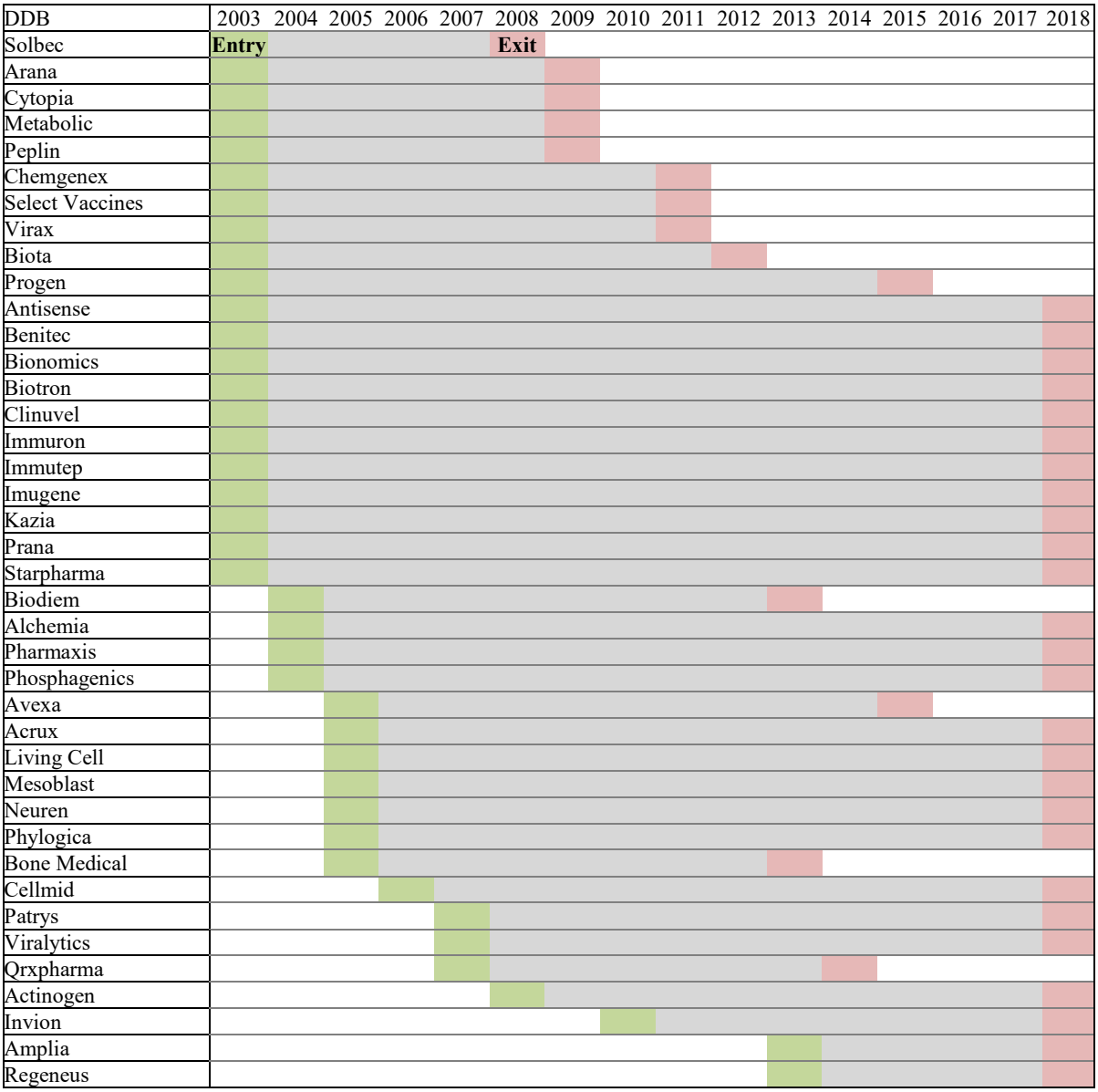
8.2.4. RDE

In order to assess the relationship between R&D expense (RDE) and VCR and IRR, and to calculate and assess R&D productivity, I collected RDE data for all firms. For each firm, the PVG/RDE ratios were used to represent R&D productivity and as a surrogate for TAQ. RDE data was obtained from annual reports and where necessary, from quarterly or half-yearly reports, in the same way as cash and BR, as described above.

8.2.5. Investor return calculation

The investor rate of return was determined using standard IRR methodology. In order to calculate the annual cash flow for each firm, I simply used entry (purchase) and exit (sale) share prices as the primary negative and positive cash flows. For the 21 firms operating in 2003, their base year for the IRR calculation was 2003. For firms that entered after 2003, their entry year became their base year. The terminus year was 2018, or an earlier year, if an exit occurred. A graphical summary of entries and exits (sorted by earliest entry and exit year) is shown in Figure 10.

Figure 10. Portfolio entries and exits for IRR calculation



I used the MV values from the VCR work and divided these by the total shares on issue (SI) at any time to determine the average share price (SP) for each year. SI was volume-weighted and adjusted for any reverse-splits. In this way, the average annual SP was generally based on the average of the six months from July to December in each year. This provided an entry SP and an exit SP for IRR calculation. The value of any dividends was added to the exit SP by calculating the dividend value per share and incorporating that into the cash flow in the year in which the dividend was received. The IRR formula in Excel was used for all IRR calculations based on the per-share value flows.

In addition to calculating the individual firm IRRs, I sought to calculate an overall sector IRR. To do this, I treated the portfolio of 40 firms as if it were a venture capital or private equity portfolio and calculated the gross pooled IRR (PIRR) for the portfolio as if it were a VC portfolio of investments. PIRR is a method for calculating the IRR from a number of concurrent projects by aggregating their cash flows as if a single project. The calculation is 'gross' in that it is before any VC management fees and carried interest and solely reports the cash flows in and out of the portfolio, as firms are added or they exit. The methodology used was similar to that described by Cambridge Associates (2017).

I assumed that 2003 was the 'vintage' (inception) year of the VC fund and the fund life was 15 years, expiring in 2018, at which time, any firms not exited, would be liquidated at market value. I assumed the fund invested an equal amount in dollar value in each firm in 2003 and in any new DDB firm that entered the sector after 2003, and prior to the end of 2013 (ensuring a minimum of five years' in the fund. To simplify the portfolio IRR calculation, I assumed the fund purchased $1,000 in share value in each firm. This was consistent with the idea that the fund believed in the value potential of the overall sector rather than trying to pick individual 'winners', which is in line with my performance assessment goal. On this basis, the fund spent a total of $40,000 on the 40 firms between 2003 and 2013.

It could be argued that an equal investment of $1,000 in each firm is not the best approach for an investment portfolio of DDB firms, and that there may be other appropriate bases for allocation of investment funds within the portfolio. For example, it might be suggested that the amount invested in each firm be based on the value of the investee firm, thereby equalising the percentage share ownership in each firm.

However, assuming the financialised, 'investor-relay' model of biotech investing, which is an important premise of this research, there is no basis for any other approach than an equal investment value in each firm. Biotech investors are seeking above-average returns; they want to turn one dollar into one dollar plus a percentage gain, which on an annualised basis, is significantly higher than they would achieve investing elsewhere. Each investee firm represents an opportunity to create a higher than normal return, but unless one adopts the view that the investor is able to 'pick winners', which

would presuppose the outcomes of this research, then the potential percentage return from each firm is unknown. Therefore, the value of the investee firm and the percentage ownership of each firm by the investor are largely irrelevant. Each firm has a potential to deliver an unknown percentage return (regardless of its value), so an equal value of investment in each firm seems justified.

As with the individual firm IRRs, I used the MV calculations to calculate the purchase share price and sale share price, adjusted for reverse-splits. Initial investments by the fund were treated as negative cash flows in the purchase year, while liquidation of remaining shares in 2018 was treated as positive cash flows in that year. In the event that the fund was forced to sell shares prior to the second half of 2018, due to an acquisition or other exit, then I used the MV calculations as previously described to calculate the effective share price and thereby determine the cash proceeds received by the investor in the exit year. Like the individual firm IRRs, I added dividend flows as positive cash flows in the year in which they were received.

For each year, the net cash flow from the portfolio was calculated based on the aggregated cash flows of all the firms. This took into account cash outflows on new entrants (each $1,000), cash received from exits, the liquidated value of the residual portfolio in 2018 and any dividends received. The total annual portfolio cash flows ($'000) on this basis are summarised in Table 22.

Table 22. Portfolio cash flows

$'000	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
New investments	-21.0	-4.0	-7.0	-1.0	-3.0	-1.0		-1.0			-2.0					
Dividends			0.1				0.2		0.9	0.0	0.1	0.4	0.1	0.1		0.0
Sale proceeds						0.1	2.2		1.2	1.1	0.1		0.2			12.9
Net cash flow	-21.0	-4.0	-6.9	-1.0	-3.0	-0.9	2.4	-1.0	2.2	1.1	-1.8	0.4	0.3	0.1	0.0	12.9

8.2.6. Data management

All data was collected into two Excel workbooks that were regularly saved locally as differently-dated versions to avoid any significant losses due to potential corruption. One workbook contained the monthly share prices, market capitalisations, shares on issue, and monthly trading volume data for each firm and for each year from June 2003 to December 2018. This data was downloaded from the DatAnalysis price history queries for each firm, using the end of month data for closing prices, market capitalisation and shares on issue, and the monthly volume of shares traded for weighting calculations. Separate worksheets were created for each firm's data (40 worksheets) and the data imported from the DatAnalysis directly into each firm's worksheet. The variables collected as raw data were: MV and SI. SP was calculated as MV/SI on a six-month, volume-weighted basis for each firm, adjusted for any reverse-splits. In total there were 11,356 raw data points (5,678 per variable). A further worksheet was created to record the nine consolidations (reverse-splits).

The second workbook contained the annual cash balance (C) and burn rate (BR) data in separate worksheets, which was obtained from annual reports or, where applicable, half-yearly or quarterly reports. Where any data (C or BR) for a specific year were re-stated in a subsequent report, then I used the later report as the basis for the data collected. Another worksheet collected annual dividend data (DIV) by firm, assembled from annual reports and ASX announcements. There were 10 annual dividends paid across five firms over the 15 years. In the same workbook, individual worksheets integrated this data with the SP, MV and volume data to import the annual volume-weighted share prices (SP), market values (MV) and pipeline values (PV) by firm and by year, which were then used to calculate value creation (VCR) by firm by year and in total over 15 years. The annual volume-weighted SPs were used to calculate the IRR by firm over the 15 years, or fewer years, where applicable. For the sector portfolio IRR calculation, worksheets calculated portfolio cash flows (PORT) based on dividends paid and the flows of share value (shares x SP) in and out of the portfolio for each year.

As per Table 21, I also collected data for relevant acquisitions in a separate worksheet (ACQ). For each firm, the value of any acquisitions was deducted from PVG in the year of the acquisition, before VCR was calculated.

I also collected the R&D expense (RDE) data for each firm per year, because of its role in the model presented in Figure 6 and the potential to measure R&D productivity. In total, there were five primary input worksheets: RDE, C, BR, DIV and ACQ across the 40 firms. This represented up to 2,410 data points (up to 482 per variable). All other variables (PV, PVG, VCR, IRR and SP) were imported from the first workbook or calculated from the composite data. A separate worksheet was used to report the acquisition impact on PVG for each firm (where applicable) and for each year. The annual PVG for each firm was then adjusted for the acquisition value and the adjusted PVG was used for the VCR calculation.

The individual worksheets from the second workbook are presented in the data tables in the Appendix. The second workbook also contained a worksheet that summarised the results for presentation in tables and figures. These were used for all the tables and figures in the results.

8.2.7. Analysis of firm results

Individual firm performances were summarised using charts of cumulative VCR and annual MV to show trends in value over time. Annual reports, ASX releases, newspaper reports and online reports were used to identify, elaborate and examine key events that may have occurred over the firm's life and that might have explained the trends in MV and VCR over time.

Chapter 9. Results

9.1. DDB sector and portfolio results

The overall DDB sector summary statistics and value creation results are presented in Table 23. The data are shown graphically in Figure 11 and Figure 12.

For the 40 firms and comparing 2018 with 2003, the MV of the sector grew from around $1.68 billion to $3.95 billion, which represents a growth of $2.27 billion or 135%. Because overall cash levels were relatively constant, the total PV of the sector grew by a similar amount, $2.03 billion. After adjustment for a total $0.46 billion in acquisition value, the PV growth (PVG) was $1.59 billion. However, the sector burned $2.85 billion in cash (BR) to deliver that PV growth. The resultant negative VCR of $1.27 billion represented value destruction by the DDB sector, not value creation. The total sector spend on RDE was $2.90 billion, essentially equivalent to the total BR and suggesting that the non-RDE expenses were offset by an equivalent level of revenues (although revenue data was not collected).

At the end of 2018, taking into account all exit values and dividends, the original $40,000 portfolio had a liquidated value of $17,695. However, adding total dividends paid of $2,029, the total portfolio liquidated value was $19,724, representing a portfolio value loss of 50.7% over the 15 years. Based on the annual cash flows for the portfolio over the 15 years, the portfolio IRR was -6.2%. In other words, the compounded average growth rate in the value of the portfolio was a loss of 6.2% each year, over 15 years. The DDB portfolio not only failed to generate an above-average return, it failed to generate *any* positive return on investment over 15 years.

9.2. Individual firm results

Individual DDB firm results are presented in Table 24, which shows the key data for the 40 DDB firms, listed in alphabetical order by name. Only 10 firms (25%) created value over the 15 years and only 9 (23%) delivered positive IRRs; conversely, 75% of DDBs destroyed value and 77% delivered negative investor returns.

Only 10 firms had PVG/RDE ratios greater than 1.0 and overall sector R&D productivity was 0.55. In other words, the $2.9 billion in R&D funds spent by the sector only generated $1.6 billion in new pipeline value.

Only five firms generated VCRs greater than $100 million each, but none delivered an attractive investor return, with IRRs for those five firms varying between 4.0% and 8.5%. Thirty-one DDBs (78% of DDBs) delivered negative IRRs and 26 (65% of DDBs) produced negative IRRs of -10% or lower. The distributions of IRR and VCR by individual DDB are shown in Figure 13 and Figure 14.

Table 23. DDB sector summary statistics and value creation over 15 years

Total Public DDB Sector (40 DDB firms) $m	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Market Value (MV)	1,676	2,235	2,582	3,120	3,815	1,977	3,283	3,242	4,929	4,193	4,282	3,259	2,550	2,352	2,705	3,946	
Cash on Hand (C)	136	320	393	471	805	796	673	481	619	598	600	515	509	490	410	403	
Pipeline Value (PV)	1,540	1,915	2,189	2,649	3,010	1,181	2,610	2,761	4,309	3,595	3,681	2,744	2,042	1,863	2,295	3,543	
PV Growth (adj.)*		218	105	381	128	-1,829	1,412	416	1,548	-545	42	-962	-708	-179	309	1,248	1,585
Cash Burn (BR)		54	126	203	213	256	245	116	66	262	214	214	215	229	229	210	2,851
Value Creation (VCR)		163	-21	177	-85	-2,085	1,167	301	1,482	-807	-172	-1,176	-922	-408	80	1,039	-1,266
Average per DDB $m	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Ave.
No. of Firms	21	25	32	33	36	37	36	33	33	30	31	29	28	26	26	26	
Market Value (MV)	80	89	81	95	106	53	91	98	149	140	138	112	91	90	104	152	
Cash on Hand (C)	6	13	12	14	22	22	19	15	19	20	19	18	18	19	16	15	
Pipeline Value (PV)	73	77	68	80	84	32	73	84	131	120	119	95	73	72	88	136	
PV Growth (adj.)*		9	3	12	4	-49	39	13	47	-18	1	-33	-25	-7	12	48	54
Cash Burn (BR)		2	4	6	6	7	7	4	2	9	7	7	8	9	9	8	94
Value Creation (VCR)		7	-1	5	-2	-56	32	9	45	-27	-6	-41	-33	-16	3	40	-40

* Adjusted for acquisition

Figure 11. DDB sector by year: MV and PV

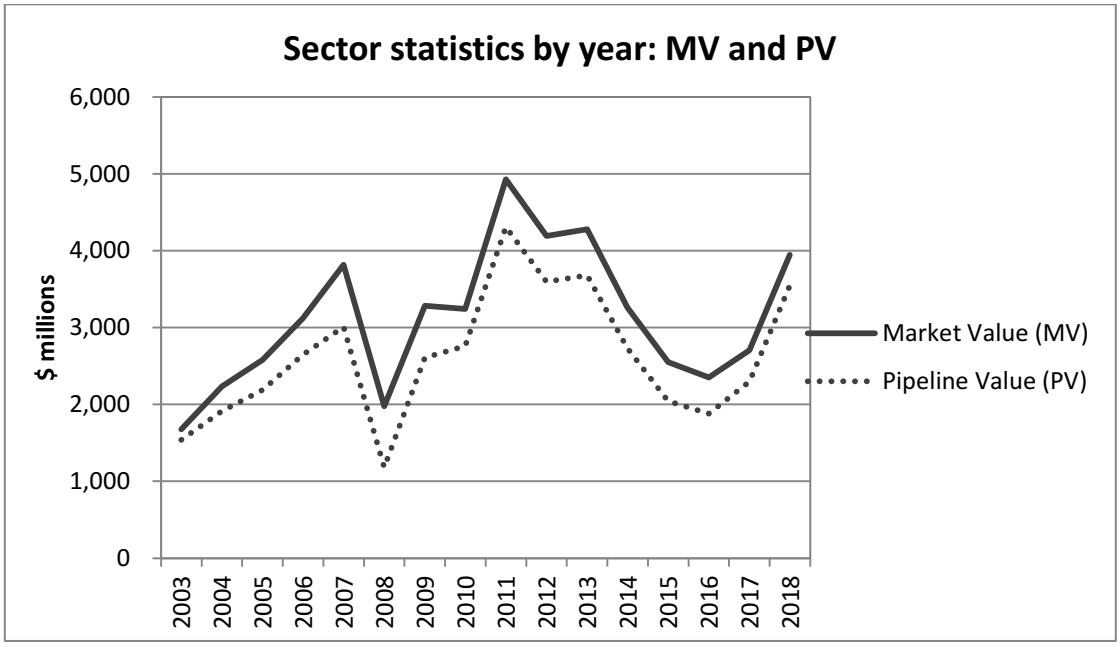


Figure 12. DDB sector by year: Cash and BR

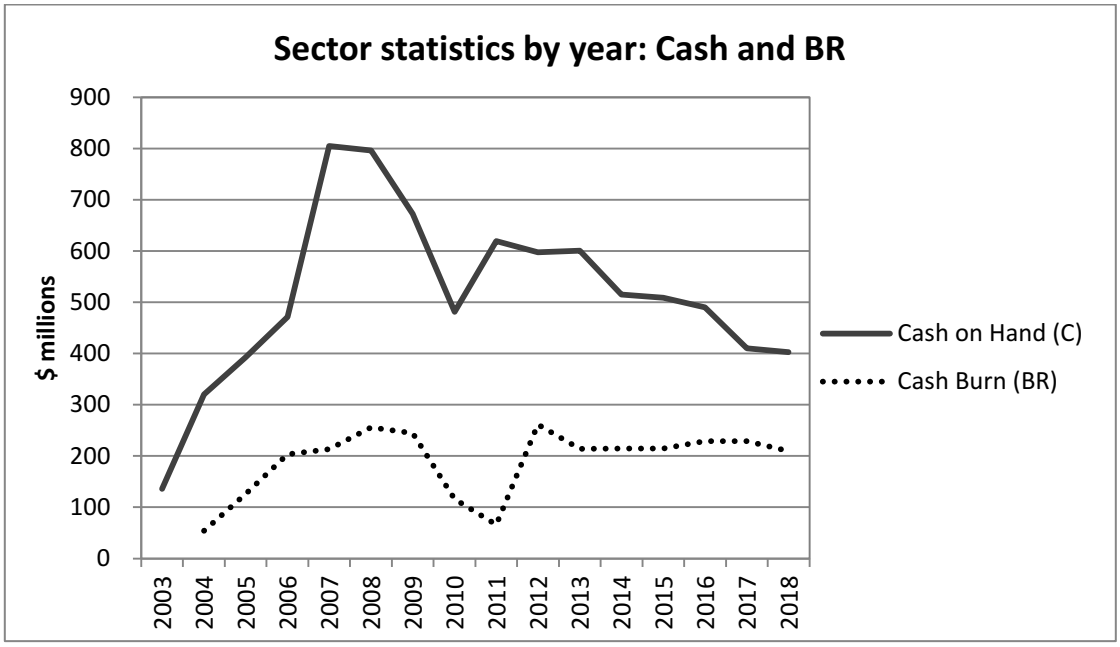


Table 24. Individual DDB firm results over 15 years

DDB	Ave Cash $m	Total PVG $m*	Total RDE $m	PVG/RDE	Total BR $m	VCR $m	IRR
Acrux	29	-38	33	-1.15	-157	119	8.5%
Actinogen	4	10	21	0.50	21	-11	-9.6%
Alchemia	11	-50	77	-0.65	97	-147	-17.1%
Amplia	4	-23	17	-1.32	20	-43	-32.1%
Antisense	5	-12	35	-0.33	39	-50	-22.0%
Arana	95	-157	38	-4.11	-80	-77	0.4%
Avexa	22	-131	81	-1.62	125	-256	-28.6%
Benitec	9	-40	44	-0.91	107	-147	-28.7%
Biodiem	4	-3	21	-0.14	25	-28	-25.2%
Bionomics	17	29	195	0.15	103	-74	-3.7%
Biota	55	35	114	0.31	-29	64	2.8%
Biotron	3	55	32	1.75	36	19	-6.1%
Bone Medical	0	-5	12	-0.36	13	-18	-50.5%
Cellmid	2	18	7	2.57	29	-11	-19.4%
Chemgenex	11	169	68	2.49	91	79	2.1%
Clinuvel	16	746	78	9.55	84	662	7.2%
Cytopia	10	-27	46	-0.57	38	-65	-28.8%
Immuron	2	0	23	0.00	43	-43	-21.3%
Immutep	12	78	97	0.80	126	-48	-13.7%
Imugene	2	21	19	1.09	23	-3	-15.3%
Invion	3	46	20	2.30	45	1	-20.1%
Kazia	26	-527	137	-3.85	175	-702	-27.7%
Living Cell	5	-0	29	-0.00	50	-50	-11.5%
Mesoblast	103	732	496	1.48	550	182	4.0%
Metabolic	16	-231	37	-6.20	52	-283	-44.9%
Neuren	7	92	108	0.85	92	-1	-14.8%
Patrys	6	-13	51	-0.26	47	-60	-21.7%
Peplin	17	89	109	0.82	101	-12	1.1%
Pharmaxis	62	40	278	0.14	260	-220	-6.4%
Phosphagenics	10	-34	51	-0.67	108	-142	-21.7%
Phylogica	4	63	38	1.65	45	18	-12.7%
Prana	16	-39	89	-0.44	122	-161	-17.1%
Progen	22	-29	56	-0.51	89	-117	-16.3%
Qrxpharma	19	-58	81	-0.71	114	-172	-43.0%
Regeneus	2	-23	23	-0.98	15	-38	-16.0%
Select Vaccines	1	-7	6	-1.28	12	-19	-45.7%
Solbec	2	-18	5	-3.93	8	-26	-36.9%
Starpharma	25	414	157	2.64	130	284	6.2%
Viralytics	18	417	58	7.18	61	356	7.2%
Virax	2	-8	9	-0.87	19	-27	-29.8%
DDB Portfolio	**17**	**1,585**	**2,895**	**0.55**	**2,851**	**-1,266**	**-6.2%**

* Adjusted for acquisitions

Figure 13. VCR by DDB firm over 15 years

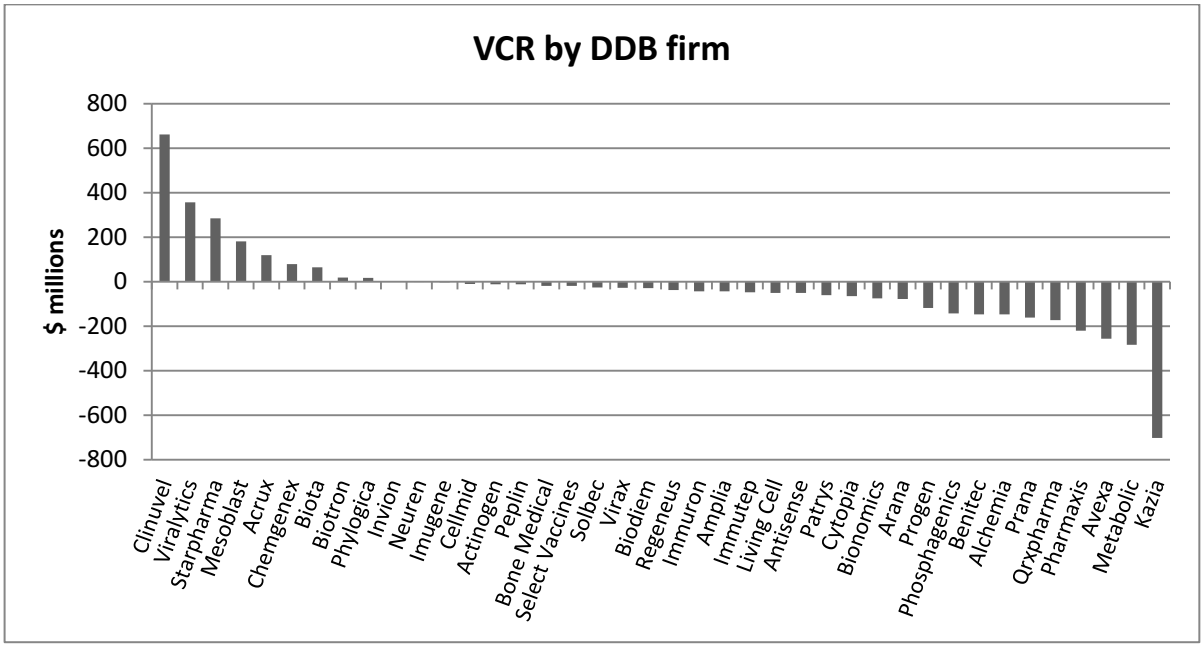
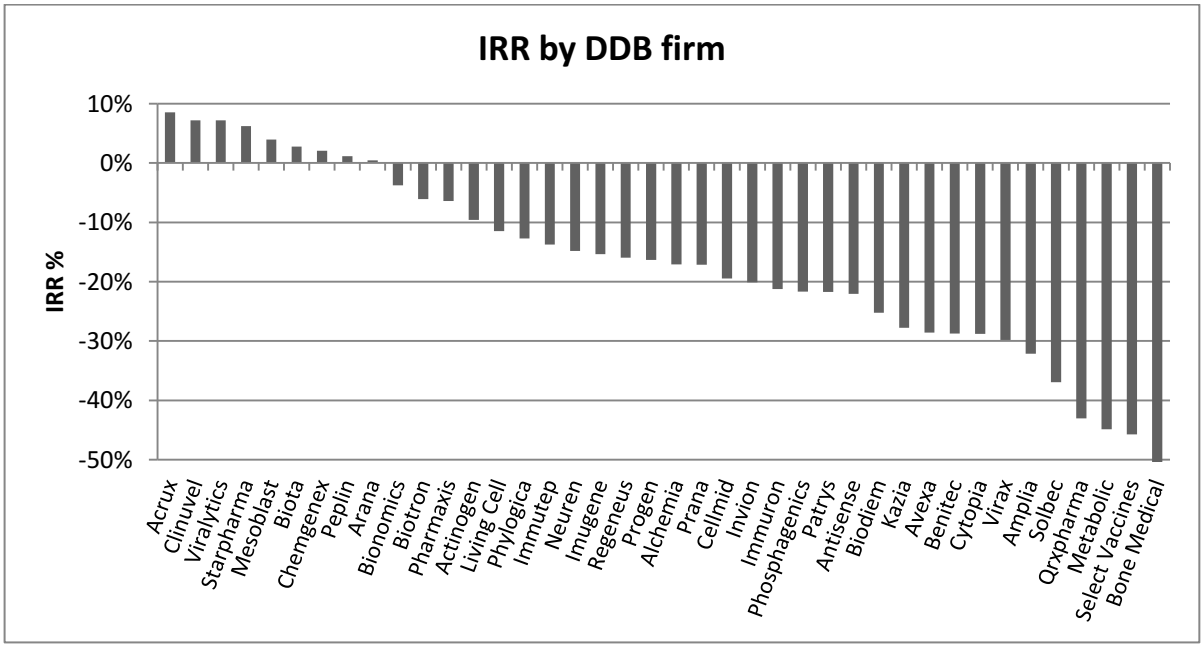


Figure 14. IRR by DDB firm over 15 years



Chapter 10. Discussion of results

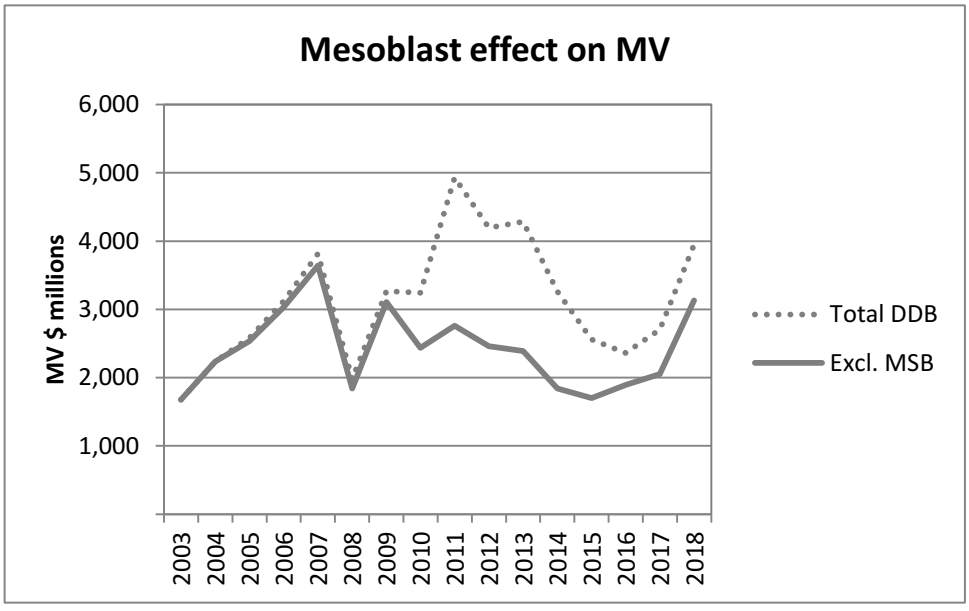
10.1. Analysis of results

10.1.1. Sector development

Mesoblast effect

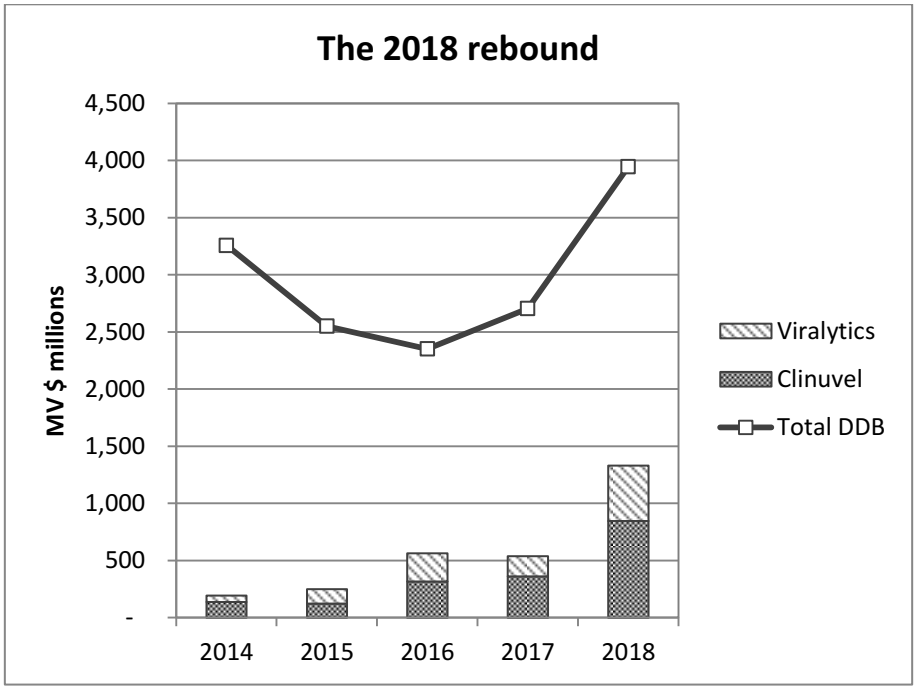
Like most stocks and indices, the total MV of the Australian DDB sector dropped significantly in 2008 during the global financial crisis (GFC), but rebounded in 2009, as shown in Figure 11. The sector's MV (based on the 40 firms in the dataset) reached a peak of $4.93 billion in 2011, but by 2016/17, it had retreated back to 2005 levels (around $2.5 billion). The extraordinary 2011 peak was due to the fortunes of one firm, Mesoblast, a DDB firm developing stem cell therapeutics. In late 2010, Mesoblast announced a license agreement with US-based Cephalon, which carried a US$130 million upfront payment and the prospect of US$1.7 billion in future milestone payments. Mesoblast's MV jumped to $2.2 billion, almost doubling the value of the DDB sector overnight. However, as revealed in Figure 15, the Mesoblast effect was temporary.

Figure 15. Sector MV adjusted for Mesoblast effect



Excluding Mesoblast, the MV of the DDB sector apparently did not grow between 2010 and 2017. Rather, it appeared to have been in decline since the 2009 recovery. However, in 2018, the sector did show significant improvement, as shown in Figure 16. The 2018 recovery was mainly driven by the dramatic growth in the MVs of two DDB firms, Clinuvel (CUV) and Viralytics (VLA). The performance of these firms is discussed in more detail later.

Figure 16. The 2018 sector rebound in market value

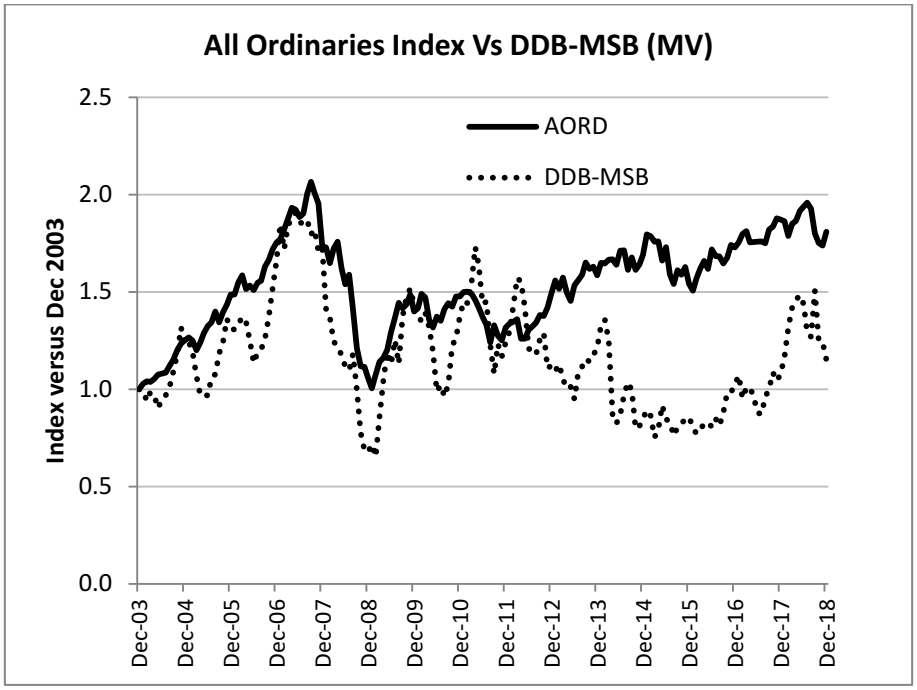


Impact of stock market sentiment

It was interesting to assess the extent to which the overall market sentiment may have affected DDB results and whether or not DDBs were more sensitive to market sentiment changes than other stocks, which might be expected, given their riskier nature.

Figure 17 shows a comparison of the monthly (end-of-month) DDB sector aggregate MVs – excluding Mesoblast – with the monthly Australian All Ordinaries Index (AORD), using 2003 as a baseline. It should be noted that the two are not entirely comparable, because the AORD is based only on the 500 largest firms on the ASX by market capitalisation, whereas the DDB sector index shown is the aggregate MV of all firms in the sector at any point in time. Therefore, DDB index is subject to movements in aggregate MV as a result of entrants and exits. Still the comparison is worthwhile as it indicates some general trends.

Figure 17. DDB sector MV and AORD since 2003



The chart suggests that the DDB sector tracked reasonably closely to the overall market through 2012, although it appears that when the GFC hit in 2008, DDB stocks were hit harder than other stocks, but then rebounded in 2009 as overall sentiment started to turn around. From 2012, the charts diverge, indicating a period of relative depression in the DDB sector, from which the sector recovered in 2018 with the Clinuvel-Viralytics rebound.

The chart suggests that overall stock market sentiment does affect the DDB sector and that the sector may be more sensitive to negative market movements. In addition, however, there is evidence of a significant depression in DDB sentiment in 2013-2016, that appears to be unrelated to overall market sentiment. The specific reasons for this DDB depression are discussed later in this chapter.

Current sector value

As reported in these results, the total MV of the public DDB sector in 2018 was $3.95 billion. However, of the 40 firms selected for analysis, only 26 remained in operation by 2018, due to exits. Since 2014, another 12 DDBs have entered the sector, but these were not included in the analysis because did not meet the inclusion criterion of five years of operations during the 15-year period.

To more validly assess the development of the sector and determine the current value of the public DDB sector in Australia, I added the MV of the 12 new entrants since 2014, as shown in Table 25. For simplicity, I used the MVs at 30 June each year from 2014 through 2018 (rather than calculate volume-weighted averages over six months).

Table 25. MV of new entrants excluded from DDB sector analysis

DDB name	ASX code	MV ($ Millions) at 30 June				
		2014	2015	2016	2017	2018
Prescient	PTX	5.5	3.4	15.1	11.0	23.3
Paradigm	PAR		10.7	12.0	19.6	80.0
Dimerix	DXB		4.7	10.3	18.3	14.7
Opthea	OPT			74.4	150.4	106.4
Recce	RCE			8.6	7.2	17.0
Vectus	VBS				20.8	19.9
Botanix	BOT				16.6	66.1
Noxopharm	NOX				14.0	45.8
Adalta	1AD				21.6	28.6
Zelda	ZLD				31.0	47.8
Telix	TLX					87.1
Neuroscientific	NSB					0
Total new DDB firms		5.5	18.8	120.3	310.4	536.6

Adding the MV of these 12 new entrants, the total MV of the listed DDB sector in 2018 was $4.48 billion. In 2003, the MV of the selected DDB dataset was $1.68 billion. However, there were three DDB firms in existence in 2003 that were not included in the performance dataset of 40 firms, because they exited the sector before 2008 and did not meet the five-year inclusion criterion. The MV of these three firms in June 2003 was $99 million; adding the MV of these brought the total value of the sector in the baseline year to $1.78 billion.

On this basis, the 2018 value of $4.48 billion represented a sector growth of 152% over 15 years, which on a compounded annual basis, represented an annual growth of around 6%. However, over the same period, the ASX Healthcare Index (AXHJ) grew from 3231 to 30913, an annualised growth of 16% pa, and the US NASDAQ Biotech Index (NBI) grew from 733 (July 1, 2003) to 3666 (July 1, 2018), an annualised growth of 11% pa. Therefore, the growth in total market value of the ASX DDB sector was modest by comparison.

Moreover, the 152% growth in MV was mainly due to the larger number of firms in 2018 compared with 2003 (38 versus 24). The average MV of the 38 firms operating in 2018 was $118 million, which is a 59% increase over what it was in 2003 ($74 million). This translates to a 3.2% compounded annual growth rate in the average value of firms. If the sector had been maturing over the 15-year period, one might have expected a larger annual growth in the average MV of public DDB firms.

Sector value versus US

At $4.48 billion, the Australian public DDB sector is small. A comparison of various sector parameters with the 2016 US data from Table 11 (converted to AUD) is shown in Table 26.

Table 26. US versus Australia: Public DDB sector

	US (2016)	Australia (2018)
Number of firms	177	38
Firms per capita (/mill.)	0.55	1.52
MV A$ millions	160,907	4,480
Ave MV	909	118

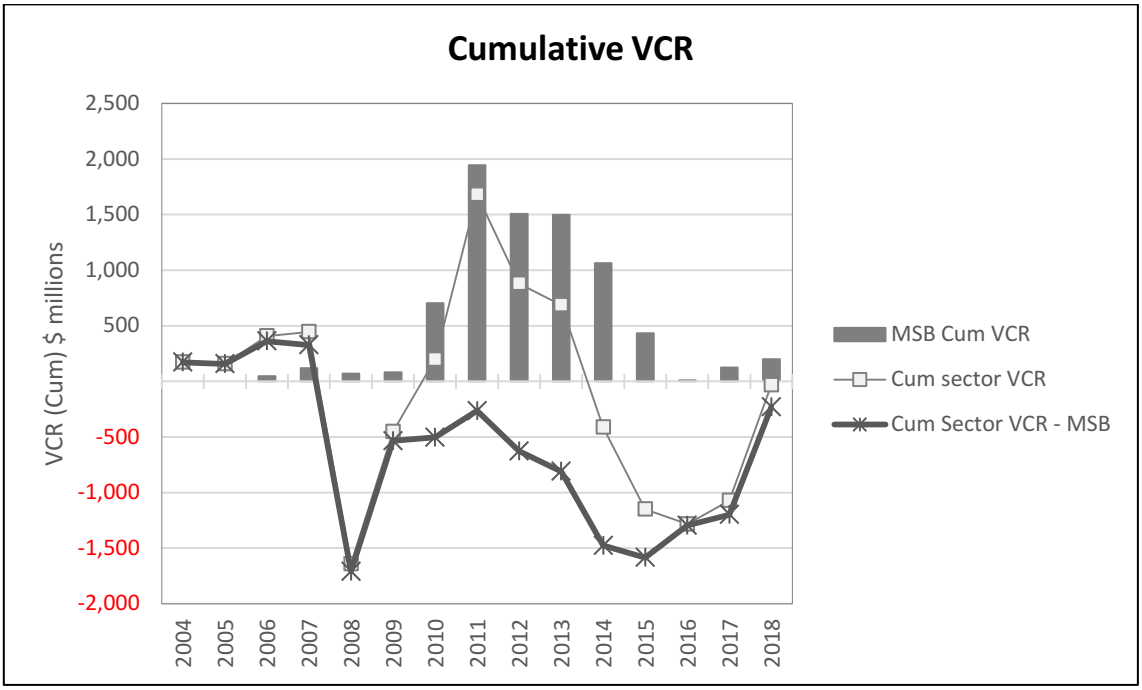
Ignoring the two-year disparity, the value of the Australian DDB sector is less than 3% of the US sector, which is less than half of what would be predicted on a pro-rata population basis. Australia has more public DDBs per capita, but their average value is only 13% of their US counterparts. This comparison ignores the fact that in the US, there are also 20 commercial-stage firms that have evolved from DDBs (DDCs) and that are worth an average of $34 billion each. Australia has none. It also ignores the fact that the US data are two years older than the Australian data and that if 2018 US data were available, the comparison probably would be even less favourable.

10.1.2. Value creation

In total, the DDB sector burned $2.85 billion in investor funds over 15 years to create only $1.59 billion in new PV (excluding acquisitions). In other words, it destroyed $1.27 billion in investor value or an average of $85 million each year for 15 years. Considering the potential alternative uses for the $2.85 billion, the failure of the DDB sector to create value constitutes a substantial added opportunity cost for investors. If that cost were assessed as the return obtainable by keeping the funds in a low-risk, investment account earning 3% p.a., which would have delivered 56% value growth over the 15 years, then the 'real' value loss was close to $3 billion.

It is also worth noting that the value destruction would have been greater if 2017, 2016 or any other recent year had been selected as the terminal year for the VCR assessment. It was only the $1 billion in aggregate VCR added by Clinuvel and Viralytics in 2018 that reduced the overall VCR loss to $1.27 billion. This is depicted in Figure 18, which reveals that apart from the transient spike in VCR caused by Mesoblast in 2010/11, on a cumulative basis, the Australian public DDB sector has been in negative VCR territory since 2007.

Figure 18. Cumulative sector VCR at each year



The VCR rebound in 2018 was a positive development for the sector and suggests that it might start to create value from 2019 on a cumulative basis. However, with Viralytics removed from the numbers going forward – due to its sale in 2018 – it seems that future sector growth and value creation will be reliant on Clinuvel's continued success, unless Mesoblast rebounds or one of the 12 recent entrants creates significant value. However, if Clinuvel is also sold in the near-term and thereby disappears from the numbers, then it is likely that continued value destruction will be the overall outcome in the sector.

10.1.3. Investor returns

The sector investor return, as measured by the portfolio IRR, was -6.2%. Like VCR, the IRR was not improved by selecting any recent year other that 2018 as the terminus year. Table 27 shows the portfolio VCR and IRR outcomes, based on 2014 to 2018 as terminus years.

Table 27. Total VCR and portfolio IRR with different terminus years

	Terminus Year				
	2014	2015	2016	2017	2018
VCR ($ millions)	-1,056	-1,978	-2,386	-2,305	-1,266
IRR (%)	-7.3%	-9.1%	-7.4%	-8.3%	-6.2%

For at least the last five years – and likely many years prior – the Australian DDB sector overall has been a very poor investment. Moreover, not one of the 40 firms generated double-digit returns over the 15 years ending in 2018.

10.1.4. Individual firm performances

In terms of individual firm performances, only 10 of the 40 firms created value. The top-10 firms in terms of VCR over the 15 years, and the 10 worst firms in terms of VCR, are shown in Table 28. Also shown are their individual IRRs.

The most successful firm based on VCR was Clinuvel, generating $662 million in VCR. Viralytics posted a VCR of $356 million before it was acquired in 2018, while Starpharma generated $284 million and Mesoblast finished the period with $199 million in cumulative VCR – down from its cumulative VCR peak in 2011 of nearly $2 billion.

Table 28. VCR top-ten leader and losers

Leaders	VCR $m	IRR %		Losers	VCR $m	IRR %
Clinuvel	662	7.2%		Kazia	-702	-27.7%
Viralytics	356	7.2%		Metabolic	-283	-44.9%
Starpharma	284	6.2%		Avexa	-256	-28.6%
Mesoblast	182	4.0%		Pharmaxis	-220	-6.4%
Acrux	119	8.5%		Qrxpharma	-172	-43.0%
Chemgenex	79	2.1%		Prana	-161	-17.1%
Biota	64	2.8%		Alchemia	-147	-17.1%
Biotron	19	-6.1%		Benitec	-147	-28.7%
Phylogica	18	-12.7%		Phosphagenics	-142	-21.7%
Invion	1	-20.1%		Progen	-117	-16.3%

These 20 firms contributed overwhelmingly to the aggregate sector results. The seven best VCR performers and the five worst VCR performers are each discussed below.

Clinuvel

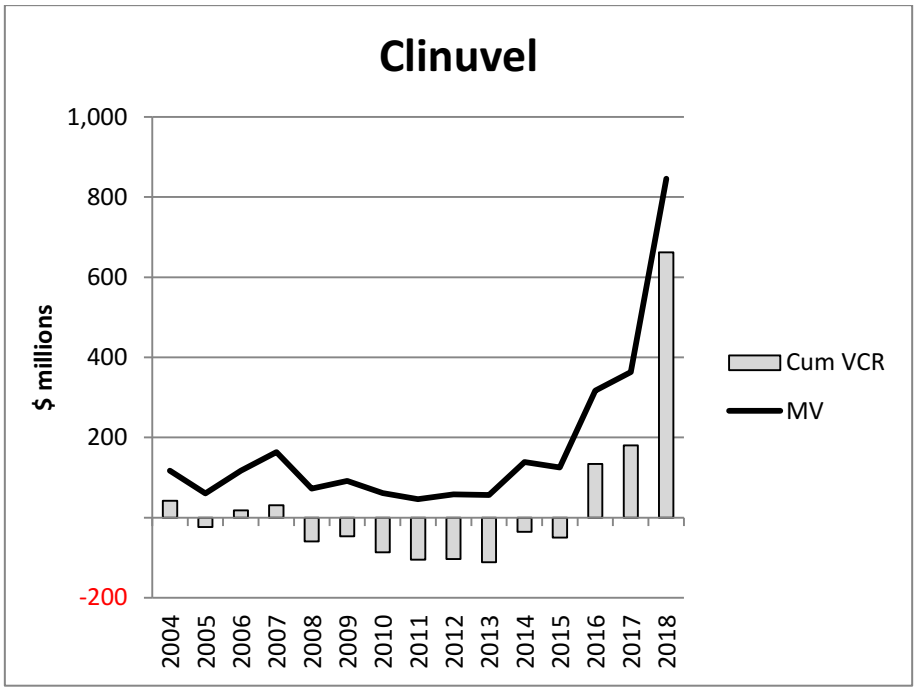
Clinuvel started life as Epitan, a DDB dedicated to developing and commercialising a natural tanning drug, called melanotan or afamelanotide, as a tanning agent that would avoid the risk of skin damage and cancer caused by UV radiation. By 2004, it was apparent that the regulatory pathway for the drug as a tanning agent was too challenging and the company brought in a new CEO and moved the drug's positioning to a niche therapeutic indication, polymorphous light eruption (PLE). In 2006, another CEO came on board, Dr Philippe Wolgen, a Switzerland-based, former cranio-facial surgeon and financier. The company changed its name to Clinuvel and the lead indication for the drug moved to another niche photosensitivity condition, called erythropoietic protoporphyria (EPP).

The company announced positive clinical results against EPP during 2009 and commenced a confirmatory Phase 3 study of the drug, then called Scenesse, reporting positive results in 2010. In 2011, although not yet approved in Europe, the company reported its first sales, made under 'special access' schemes in Italy and Switzerland, which allow doctors to obtain access to unregistered drugs

when needed for patients. In 2014, Scenesse received marketing approval in Europe for EPP, allowing Clinuvel to expand sales beyond special access arrangements. In 2017, Clinuvel posted its maiden profit and in 2018, declared a dividend.

As shown in Figure 19, Clinuvel's MV reached $846 million in the second half of 2018, surpassing Mesoblast as the largest Australian DBB, based on market valuation. In fact, in the month of December 2018, Clinuvel's MV reached $1.1 billion, while Mesoblast's MV was around $600 million. Clinuvel is now Australia's second home-grown DDB to pass the $1 billion market valuation threshold. Further, unlike Mesoblast, its MV growth does not hinge on a single precarious deal and appears to be more sustainable. Therefore, one could realistically envisage continued MV growth in the future or a sale of the company that delivers a substantial return to investors.

Figure 19. Clinuvel MV and cumulative VCR



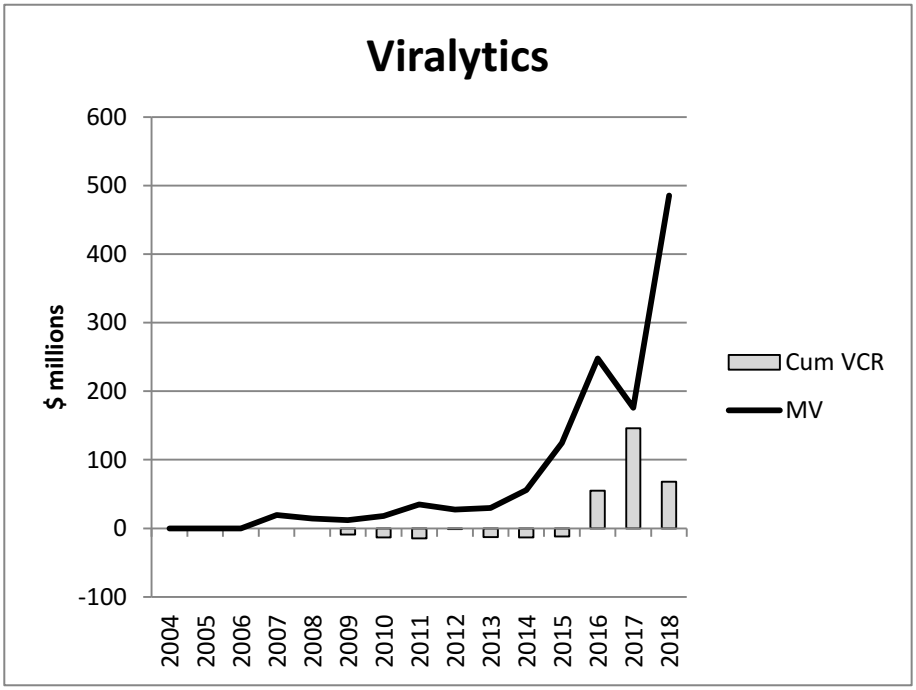
Based on value creation, Clinuvel is already the DDB sector leader, having produced $662 million in VCR, most of it ($482 million) in 2018. To create this $662 million in value, Clinuvel only spent $78 million in RDE and had a total BR of only $84 million. Its PVG/RDE ratio was 9.55, making it the highest R&D productivity in the sector over the 15 years. Despite all this, its IRR was not that impressive (7.2%). Like many DDB firms, a strong VCR performance failed to translate into IRR, because of dilution due to serial fundraisings earlier in its life as a DDB. Between 2003 and 2018, the shares on issue (adjusting for a 10:1 consolidation) grew by more than 500%. However, in 2019, Clinuvel has positive cash flow, so its IRR will improve as it continues to grow VCR without needing to issue new shares.

Viralytics

The other 2018 success story was Viralytics; this was a DDB developing an oncolytic virus (a virus that attacks cancer cells) called Cavatak, as a treatment for cancer. Viralytics was born at the end of December 2006, when ASX-listed Psiron acquired the license to Cavatak from the University of Newcastle and dedicated its business activities to Cavatak, changing its name to Viralytics[6].

In many ways, Viralytics represented the quintessential DDB: It in-licensed an early-stage technology from a local university, then dedicated itself to moving a candidate drug towards a Phase 2 study with the clear plan to attract a pharmaceutical partner. In early 2018, it succeeded, when it was acquired by the Big Pharma firm, Merck, for US$394 million (approx. $500 million). In so doing, Viralytics created $356 million in VCR and it also delivered a positive, albeit modest IRR of 7.2% over the 11 years of its life.

Figure 20. Viralytics MV and cumulative VCR



From a DDB value creation perspective, Viralytics was a genuine success. It spent $58 million on RDE ($61 million total BR) to create added value of $356 million, representing an R&D productivity ratio of 7.18, just slightly behind Clinuvel. However, like Clinuvel and many other Australian DDBs, it suffered from substantial dilution due to fundraisings at relatively low valuations, earlier in its corporate life. Over the 11 years Viralytics existed, its shares on issue grew from 247 million to 2.8 billion (after adjusting for a 10:1 consolidation in 2011). Like Clinuvel, it was impossible for Viralytics' SP growth to keep up with the dilution and still deliver an attractive IRR.

[6] Conflict declaration: I was a non-executive director of Viralytics from 2008 to 2014.

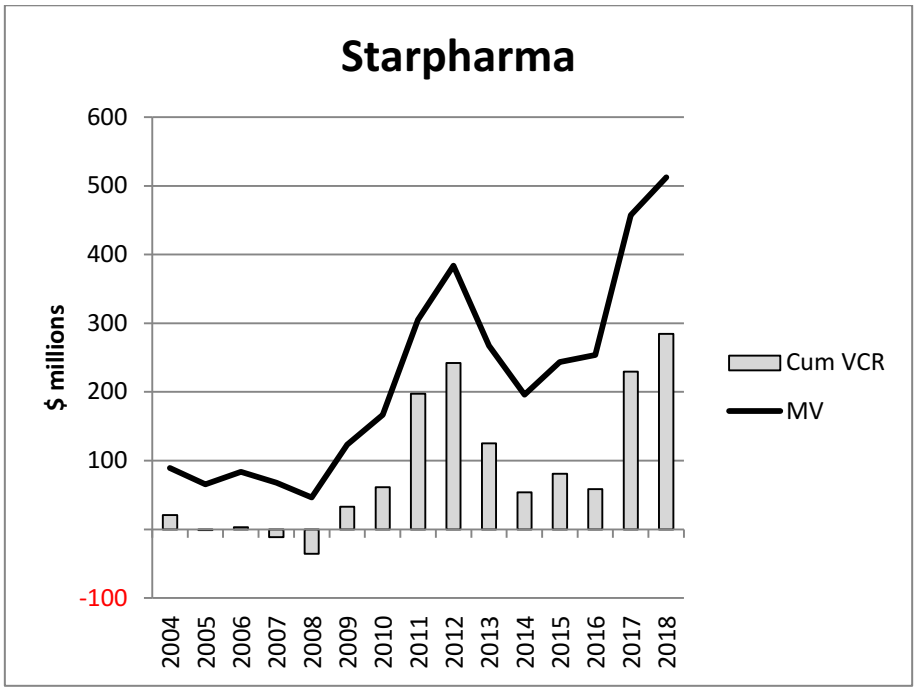
Despite this, by creating substantial value and monetising that value in a Big Pharma trade sale, Viralytics must be considered an important proof-of-principle for the DDB model in Australia. In 2007, its MV was $27 million; in 2018, it was sold for $500 million.

Based on the stock options disclosed in the 2017 annual report, there were 12.8 million unexpired options at the time the Merck acquisition closed, which had a net value (deducting their exercise prices) of around $14 million (average net value of $1.12 per option). The options were distributed to the scientific staff, management and board. The Chief Scientist and two other scientific staff held 4.6 million options between them. Clearly, all did well financially, which should offer encouragement for Australian scientists intending to work in a DDB firm – another reason to applaud Viralytics' achievement.

Starpharma

Third on the VCR top-ten leaders list was Starpharma. Listed in 2000, Starpharma had been developing therapeutics based on dendrimers, which it described as 'synthetic nanoscale polymers'. Its lead product was VivaGel, a dendrimer-based, vaginal gel originally developed for preventing sexually transmitted infections (STIs) caused by HIV and hepatitis C virus infections.

Figure 21. Starpharma MV and cumulative VCR



By 2011, it had executed a license agreement with a condom manufacturer to make and sell VivaGel-coated condoms. In parallel, it had essentially abandoned the STI positioning for the product and was focused on its use as a treatment for bacterial infections of the vagina (bacterial vaginoses). It had also executed a deal with Eli Lilly to develop new drugs based on its dendrimer technology and was

developing its own docetaxel-based (a cancer drug) candidate drug. Finally, it was developing a dendrimer-based version of Monsanto's weedicide, Roundup, for agricultural use.

Unfortunately, in late 2012, Starpharma announced that the Phase 3 clinical trial for VivaGel in bacterial vaginoses had failed to meet its primary endpoint, leading to a significant fall in the Starpharma share price and negative VCR in 2013 and 2014. However, as shown in Third on the VCR top-ten leaders list was Starpharma. Listed in 2000, Starpharma had been developing therapeutics based on dendrimers, which it described as 'synthetic nanoscale polymers'. Its lead product was VivaGel, a dendrimer-based, vaginal gel originally developed for preventing sexually transmitted infections (STIs) caused by HIV and hepatitis C virus infections.

Figure 21, its SP and MV recovered after 2014, making it one of the few Australian DDBs that has seen its fortunes rebound substantially after a major setback.

Part of Starpharma's resilience seems to have been its strategy to exploit multiple aspects of its technology platform, thereby developing a diversified portfolio of potentially licensable assets, rather than having a single or primary candidate drug. Starpharma was also able to maintain investor support and successfully raise funds when needed, without massive dilution; as a result, it not only created value (VCR = $284 million), but also produced a positive, albeit modest, IRR of 6.2%. In terms of R&D productivity, Starpharma spent $157 million on RDE to create PVG of $414 million, which translated to a PVG/RDE of 2.64. This placed Starpharma well behind Clinuvel and Viralytics and in a group of four DDBs with PVG/RDE ratios of between 2.00 and 3.00, including Cellmid, Chemgenex and Invion.

Mesoblast

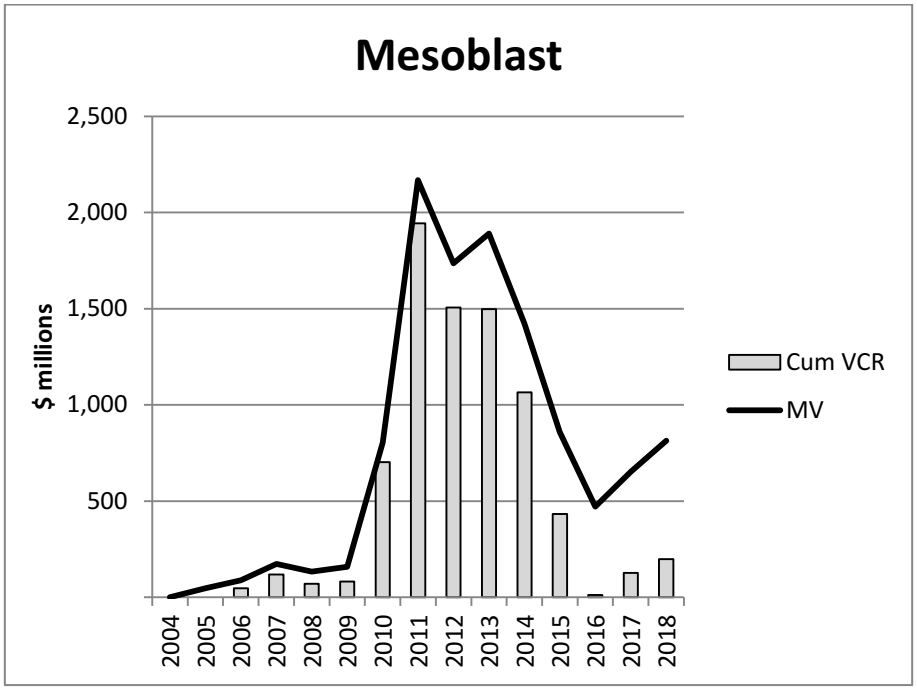
Mesoblast listed on the ASX in 2004 and by 2009, had a MV of around $150 million, placing it the fifth largest ASX DDB, based on MV. In 2011, Mesoblast was dramatically re-rated, adding a staggering $2 billion to its MV as a result of its license agreement with Cephalon, as previously noted. In 2011, with a MV of $2.2 billion, Mesoblast appeared to have all the makings of a highly successful DDB – Australia's first – that overnight had created enormous value for its investors through a transformational pharmaceutical deal.

However, Cephalon was acquired by another pharmaceutical firm, Teva, and in 2016, Teva exercised its option to withdraw from the deal with Mesoblast, rather have to fund further clinical trials by Mesoblast. By the end of 2016, Mesoblast's MV had dropped to around $500 million, representing a $1.7 billion decline in market value from its peak. While the Teva decision in 2016 triggered a large decline in Mesoblast's MV, the MV had been drifting downward since 2013.

In 2018, Mesoblast's MV recovered slightly, but it was still $1.5 billion below its peak. Notably, this decline in value occurred during a period (2012-2018) when the company burned $550 million in net

operating cash outflow (BR). Overall, Mesoblast's cumulative VCR was $182 million and its IRR was 4.0%. The firm spent a massive $496 million on RDE to generate this VCR, and its overall R&D productivity ratio was only 1.48.

Figure 22. Mesoblast MV and cumulative VCR



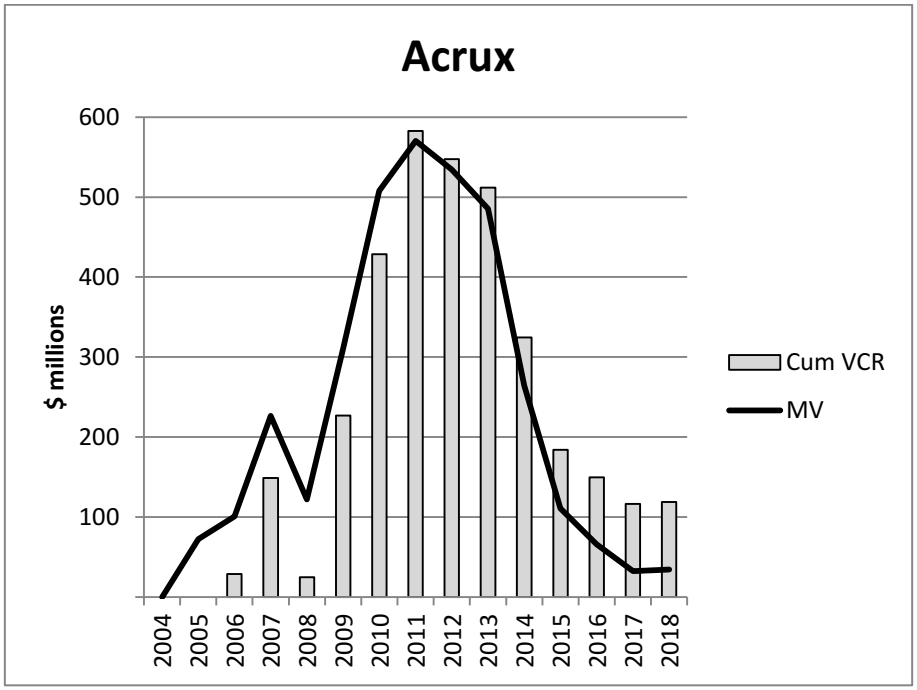
Acrux

Acrux was fifth on the VCR leader-board. Acrux started as a private biotech firm in 1998 with technology from Monash University in Melbourne that allowed enhanced penetration of drugs through the skin. Acrux's mission was to develop a range of transdermal drug products based on the proprietary technology and license them to pharmaceutical partners. Six years later, in September 2004, Acrux successfully listed on the ASX to become a public DDB, with its first drug candidate already in clinical development. In March 2010, Acrux signed a licensing deal with the Big Pharma firm, Eli Lilly, for the commercialisation of its transdermal testosterone spray, called Axiron. The deal was valued at more than US$335 million in milestone payments, plus royalties. By November 2010, Lilly had secured FDA approval for Axiron and then launched it in 2011. The deal and subsequent launch of Axiron in the US triggered a growth in Acrux's PV to over $500 million; so, with negative BR in 2010 and 2011 – due to positive cash flow from license fees and royalties – Acrux produced more than $500 million in total VCR between 2009 and 2011, as shown in Figure 23.

From 2012, its MV and PV started to decline slightly and despite ongoing low or negative BR due to the cash flow offset of royalties from Lilly, the VCR turned negative, dropping significantly in 2014 and 2015. Contributing to this was a patent challenge in the US by a generic firm in 2013 and a

subsequent invalidation of Acrux's US patent on Axiron in 2016, allowing multiple generics to enter the market. However, as early as 2013, Axiron's US market share had already started to flatten out at and sales started to decline from their peak level, indicating a limited market acceptance for the product. More recently, the decline was exacerbated by rapid generic market share growth. In the face of this, in September 2017, Lilly terminated the licensing agreement with Acrux.

Figure 23. Acrux MV and cumulative VCR



The various events were devastating for Acrux. Acrux's royalty revenues peaked in 2014 at $54 million, but by 2018 had declined to only $2 million. By 2018, Acrux's MV has dropped to only $34 million from its peak of $570 million in 2011. Despite these challenges, over the years, Acrux benefitted substantially from the ongoing Lilly royalties and was profitable every year from 2011 to 2017, issuing dividends each year from 2011 to 2016. As a result, Acrux generated significant VCR ($119 million) and posted an overall positive IRR of 8.5% over its 14-year life as a DDB, which was still the highest in the sector, despite its recent reversal of fortune. Unlike many other firms, Acrux consistently generated revenues to fund its BR and was not forced to undertake highly dilutive fundraisings, so its IRR was positive.

From an R&D productivity perspective, Acrux's performance was poor. Its VCR was generated by negative BR (positive cash flow) and not by growth in pipeline value (PVG). Acrux only spent $33 million on RDE but failed to produce any positive PVG. Fortunately for Acrux, much of its PV had been generated prior to its listing on the ASX, so once it was listed, it was quickly able to exploit the licensing potential of its existing pipeline, without substantial additional RDE. However, Acrux failed to use its licensing funds to invest in follow-on pipeline (PVG) that might have otherwise

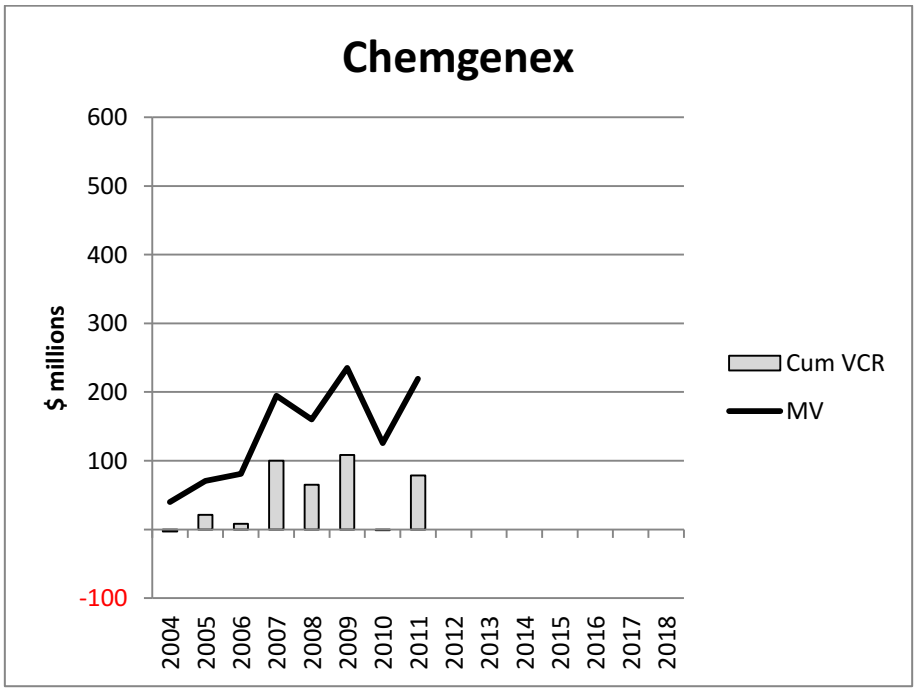
supported the portfolio and the firm's prospects when the initial product failed in the market. Instead, Acrux seemed bent on reporting profitability and distributing profits to shareholders. At the end, all of this was to no avail, with shareholders deserting the stock as soon as the dividends dried up and Acrux was left with little residual TAQ on which to build new PV.

Chemgenex

Chemgenex is worth noting, because it was a trade sale exit, like Viralytics. However, it generated a much smaller VCR ($88 million) and an IRR of only 2.1%.

Chemgenex was originally known as AGT and changed its name to Chemgenex Pharmaceuticals in June 2004, after acquiring a private US DDB firm of the same name. After the GFC, the US pharmaceutical firm, Cephalon, made several cash acquisitions, including two Australian DDBs, Arana in 2008 and Chemgenex in 2010. It also did the lucrative deal with Mesoblast. Ultimately, Cephalon was acquired by Teva in 2011 for US$6.8 billion, but because Cephalon had several marketed products and reported 2011 sales of nearly US$3 billion, it is difficult to say what the Arana and Chemgenex pipelines may have contributed to Cephalon's overall value.

Figure 24. Chemgenex MV and cumulative VCR



However, like Cytopia, Chemgenex sold at a time of relative MV weakness, so that the premium paid by Cephalon barely restored its VCR to previous levels. Like many Australian DDBs, Chemgenex also suffered from dilution, with its SI growing more than five-fold during its eight years between 2004 and 2011. As a result, its IRR was small (2.1%), despite the positive final VCR. In terms of R&D productivity, Chemgenex spent $68 million on RDE to generate its $169 million in PVG, which translated to an R&D productivity ratio of 2.49.

Biota

Among the VCR leaders, Biota[7] is important to discuss, because of its long history, its success in getting the first Australian developed drug to market, and its success in generating pharmaceutical partnerships. Yet despite all this, it failed.

Listed on the ASX in 1985, Biota was the oldest DDB in Australia in 2003, and for many years, was considered the sector leader. Biota was the first Australian DDB to achieve the historic milestone of having its candidate drug, Relenza, reach the market. Relenza was a breakthrough drug for influenza, with the original research conducted at CSIRO and then licensed to Biota. In 1990, Biota signed a global license agreement with the Big Pharma firm, Glaxo, under which Glaxo would fund and manage all the clinical development and then commercialise the drug. Glaxo succeeded in the development program and nine years later in 1999, Glaxo-Wellcome, as it was known at the time, gained FDA approval and launched Relenza in the US. At the same time, Roche launched its own flu drug, Tamiflu, which it in-licensed from a US DDB, Gilead. The competition in the first year was fierce, but Relenza held its ground. However, the same year, Glaxo-Wellcome merged with the UK Big Pharma, SmithKline Beecham, to become GSK. The merger also brought in new management, who after a portfolio review and rationalisation, decided to deprioritise a number of products, including Relenza. The promotion of Relenza was abruptly halted and Relenza sales and market share dropped to near zero by 2002, leaving Tamiflu to dominate the market.

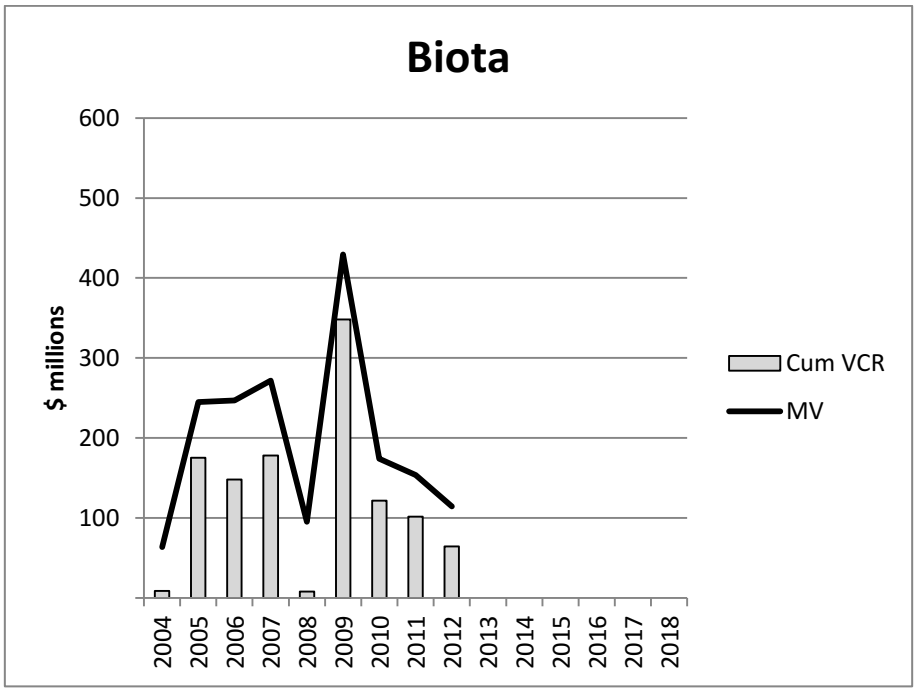
In the meantime, the Biota SP had dropped from a peak of $7.85 (MV of $500 million) in 1999, to less than $0.50 (MV of $40 million) by 2002. The Relenza disappointment and SP collapse led to sweeping changes to the board and management, and a plan to revitalise the firm. By the end of 2005, Biota had refocused R&D on new antiviral drug development programs, moving forward with a series of antiviral candidate drugs for Respiratory Syncytial Virus (RSV) infection (bronchiolitis), Human Rhinovirus (HRV) infection (the common cold) and Hepatitis C Virus (HCV) infection (liver disease). It had also obtained rights to 'Ivanir' – an improved flu drug to replace Relenza – from the Japanese Big Pharma, Daiichi-Sankyo.

In 2004, Biota initiated a law suit against GSK for breach of contract in their failing to promote Relenza. Coincidentally and ironically, the US and several other governments started stockpiling Relenza in anticipation of a potential bird-flu pandemic, which led to a large increase in Relenza sales for GSK and a major boost in royalty income for Biota in 2005. In the same year, Biota executed a license agreement with Medimmune (now AstraZeneca) for its RSV program and in early 2006, signed an agreement with Boehringer-Ingelheim for its HCV program. By early 2006, Biota's prospects looked good: The SP was approaching $2 and the MV was $245 million and both would stay around those levels for the next two years.

[7] Conflict declaration: I was CEO and managing director of Biota from July 2002 through December 2005.

However, during 2008, Biota investor sentiment collapsed, no doubt exacerbated by the GFC, but mostly driven by a disappointing outcome in the GSK lawsuit. The company had spent $40 million on legal fees and then settled for a $20 million payment from GSK, not even covering its legal costs. When it was revealed that Biota had turned down an offer of $100 million from GSK two years earlier in 2006, the backlash from shareholders was severe. By the end of 2008, the share price was down to a low of $0.34 and all the previous VCR eliminated, as shown in Figure 25. There was a brief resurgence in 2009, due to another round of Relenza stockpiling in response to the swine-flu scare in the US, but by 2010, Biota entered a terminal decline. By 2012, the HCV and RSV license agreements had been terminated by their respective partners and the company had failed to progress its HRV and Ivanir programs, despite having consistently large cash reserves.

Figure 25. Biota MV and cumulative VCR

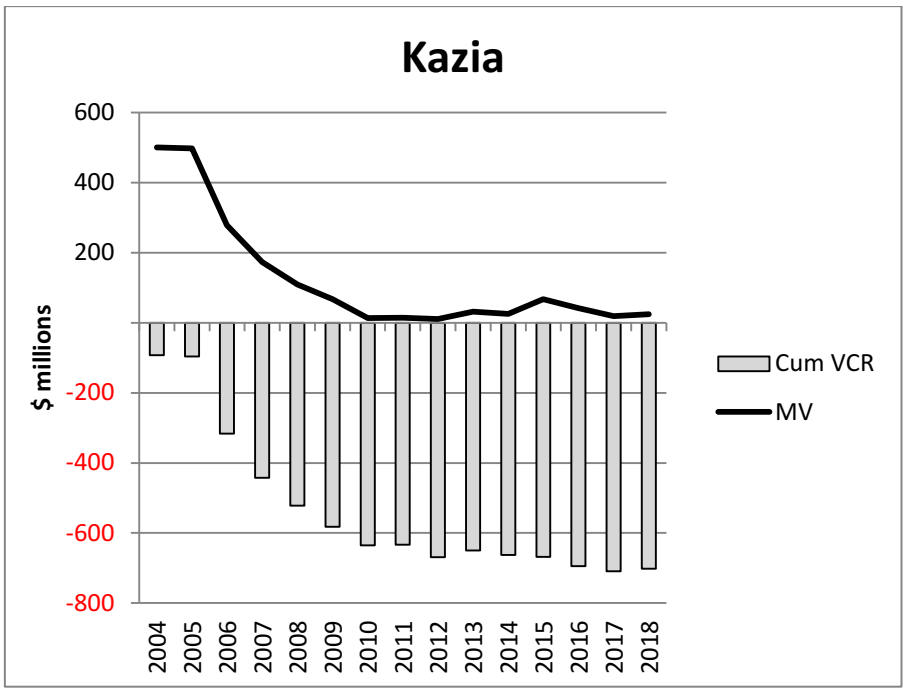


Biota exited in October 2012, via a reverse-merger into a US NASDAQ-listed shell, Nabi Pharmaceuticals, with the explicit goal of getting better value appreciation by US investors for the Biota pipeline. The goal was not achieved. In 2018, Nabi (renamed Aviragen) merged with Vaxart, crystallising a cash return to any former Biota shareholders who had decided to hold onto their shares. The return was an effective share price of only $0.085, less than 10% of the share price at the time of the Nabi merger (Langsam, 2018). Because the current study measured performance up to Biota's delisting from the ASX in 2012, Biota delivered a positive VCR of $64 million and a small positive IRR (2.8%) during the assessment period. The company spent $114 million on RDE and generated only $35 million in PVG (PVG/RDE = 0.31), with the additional VCR and positive IRR driven by positive cash flows rather than R&D productivity.

Kazia

Among the VCR 'losers' in Table 28, Kazia single-handedly destroyed $702 million in value (negative VCR), more than half the total negative VCR of the entire sector. The MV and VCR data over the 15-year period are shown in Figure 26.

Figure 26. Kazia MV and cumulative VCR



Kazia first appeared on the ASX in 1994 as 'Norvet', a DDB developing human and veterinary therapeutics. It changed its name to 'Novogen' in 1997, focusing on human therapeutics, and in 2017, changed its name to Kazia Therapeutics.

By 2003, Novogen was the sector leader based on market value, with a MV of $554 million and carried high investor hopes for the success of its cancer drug candidate, phenoxodiol. In 2005, it announced plans for a Phase 3 trial. However, the share price and MV declined nearly 50% during 2006, as the start of the trial continued to be delayed; the trial finally started in 2007 and then in June 2010, the company announced that the trial had failed to meet its primary or secondary endpoints, leading to a collapse of the share price. By 2012, the MV was below $10 million, a massive decline from its peak.

Over the following several years, Novogen cut its expenses, in an attempt to preserve cash, and refocused it development on other cancer candidate drugs in its portfolio, with Cantrixil for ovarian cancer as the lead program. In 2015, it also hired a new CEO. By 2016, the lead program had shifted to another cancer drug candidate, GDC-0084, for glioblastoma multiforme (a type of brain cancer).

Over the 15-year timeframe of this study, Novogen burned through $175 million in investor funds, $137 million of which was RDE, while consistently producing a declining MV and negative PVG (and consequently, negative VCR). Its IRR for the 15-year period was -27.7%, effectively losing 100% of its early shareholders' funds. Naturally, its PVG/RDE ratio was very negative (-3.85).

It is perhaps surprising that shareholders would continue to fund such a company. However, this perhaps points to an important phenomenon in biotech: In the highly financialised investor-relay model, investors may move in and out of stocks rapidly and regularly, based on the potential for shorter-term gains in the share price. Investors can also have short memories and ignore past failures to invest or re-invest in a stock, based on a renewed narrative and potential for revitalised growth in the share price. For those with longer memories, the abysmal failure of Novogen/Kazia must have had a negative impact on their future willingness to invest in any Australian DDB.

Metabolic

Although a long way behind Kazia in terms of the scale of its value destruction, Metabolic's failure possibly did as much to damage overall investor sentiment towards the DDB sector in Australia. In 2004, it boasted a MV of $322 million and was the second largest DDB behind Novogen (Kazia) at the time. By the end of 2007, the MV was down to $10 million, and it later abandoned drug development altogether and became a diagnostics business. Its failure was also prominent, because it was the first high profile DDB failure in Australia.

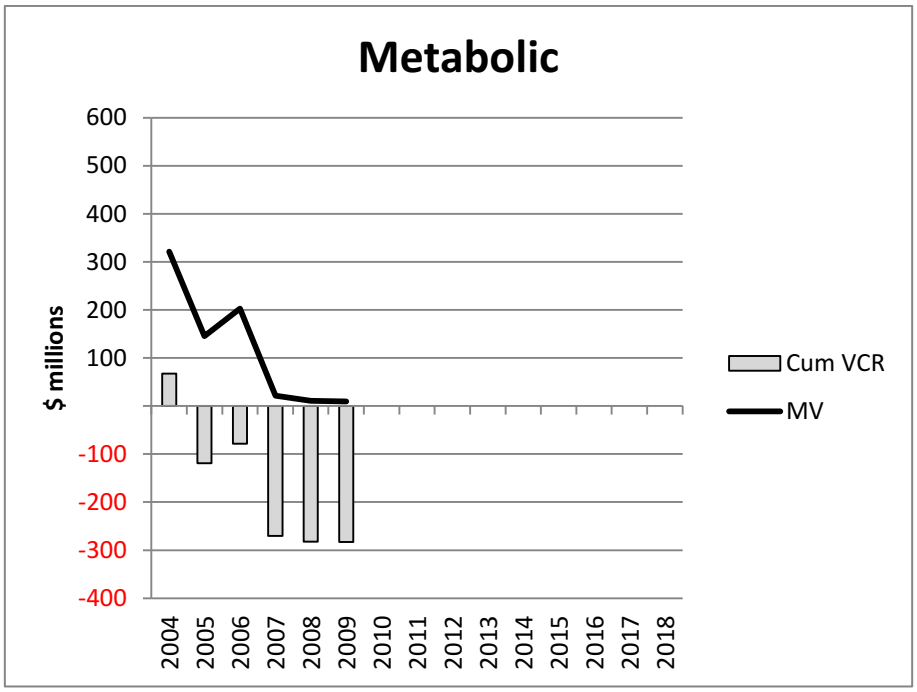
Metabolic listed in 1998 with in-licensed technology from Monash University and much excitement around the possibility that this Australian DDB had found a treatment for obesity, considered by many to be a 'holy grail' of drug development. Based on animal studies, Metabolic's drug candidate, AOD9604, was believed to act directly on the body's fat cells to enhance the breakdown of stored fats and inhibit the synthesis of new fat. The result was purported to be an effect similar to the slimming effects of physical exercise.

In 2003, Metabolic started a Phase 2 clinical trial of the drug in more than 300 subjects. The company announced that the completion of the trial was scheduled for late 2006, with results available in early 2007. Along the way, the anticipation was maintained by several announcements heralding various milestones in the trial. However, in February 2007, the company announced that the trial had failed and the project was being terminated. The share price and MV immediately collapsed and never recovered.

Metabolic lived off its cash reserves for the next two years and then in 2009, reinvented itself as a diagnostics business, 'Calzada', exiting the DDB sector. During its six years of operations, Metabolic burned $52 million in investor funds; by 2009, its MV and PV were approximately zero, as shown in Figure 27. Overall Metabolic reported both a large negative VCR and IRR (-$283 million and -

44.9%), while spending $37 million on RDE. With a PVG/RDE ratio of -6.20, it represented the worst R&D productivity in the sector.

Figure 27. Metabolic MV and cumulative VCR



Pharmaxis

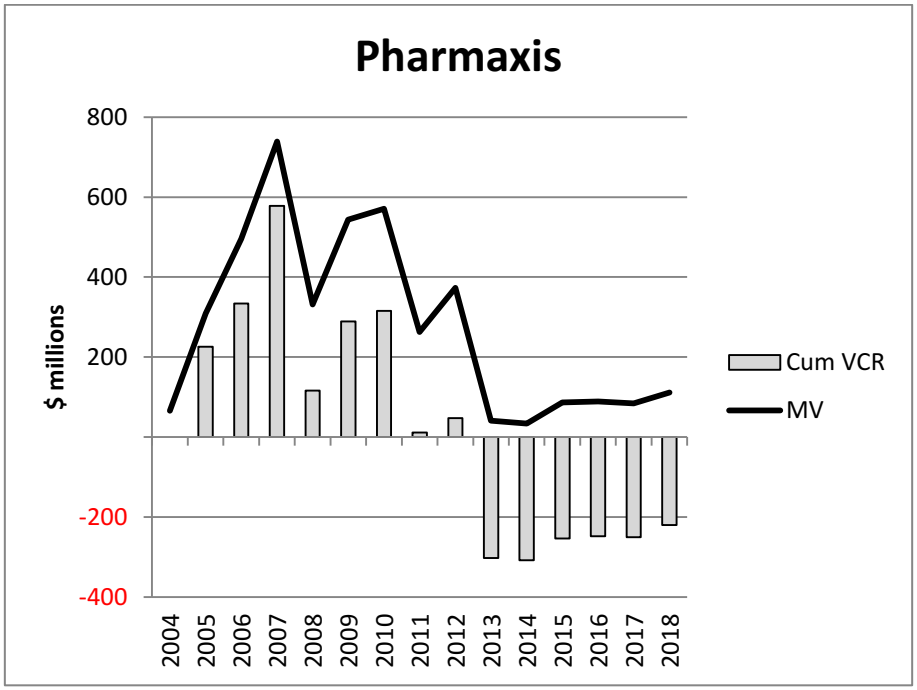
The third largest VCR 'loser' in Table 28 was Pharmaxis, producing -$220 million in VCR and an IRR of -6.4% across its 14-year life from 2003 to 2018. The RDE was $278 million to generate only $40 million in PVG (PVG/RDE = 0.14). Pharmaxis is important, because it was heavily promoted by investment bankers and brokers, had strong analyst and professional investor support and then led a number of high-profile failures in the post-GFC period.

Pharmaxis was born as a spin-out from the Australian National University in Canberra in 1998, and as a private firm, attracted significant VC funding. Pharmaxis listed on the ASX in November 2003, boasting a high-calibre management team, a diversified, late-stage pipeline and what appeared to be a commercial-ready product, complete with finished product packaging ('Investor Presentation' released to ASX November 17, 2003). It had the other advantage of having been selected by VCs for investment and presumably, had been diligently evaluated and guided by them. Further, unlike many other DDBs that were interested in licensing their candidate drugs to pharmaceutical firms, Pharmaxis boasted that it would take its products all the way to the market on its own.

Its lead candidate drug was Bronchitol, a treatment for cystic fibrosis (a respiratory disease). Bronchitol was based on the idea of repurposing a well-known sugar molecule, called mannitol. At listing, Bronchitol was already in a Phase 2 trial; the listing was strongly supported by investors and it raised $23 million at its IPO. Following the IPO, its MV steadily increased over the next four

years, reaching $739 million in 2007, making it the clear sector leader. With $76 million in cash reserves at June 30 2007, Pharmaxis's PV of $663 million was the highest ever achieved in the Australian DDB sector. Not unexpectedly, the MV and PV declined somewhat through the GFC, but buoyed by a stream of promising announcements, it rebounded in 2009 and by the end of 2010, its MV had returned to around $600 million.

Figure 28. Pharmaxis MV and cumulative VCR



Unfortunately, in May 2011, it announced that the Committee for Medicinal Products for Human Use (CHMP), which is the body that recommends approval of a drug to the US FDA, indicated that it would not vote to approve Bronchitol. The Pharmaxis share price dropped immediately, causing a $400 million overnight loss of MV, as shown in Figure 28. There was some good news in Europe, where Bronchitol was approved in early 2012, and that stabilised the MV at $300-400 million during 2012. Based on the EU approval, the company announced it was going to go ahead and file for approval in the US, despite the earlier CHMP vote. In early 2013, the US application failed, leading to a terminal collapse of the Pharmaxis share price and by the end of 2013, its PV was negative (-$23 million) and its MV stood at only $41 million. The PV and MV did not recover in 2014.

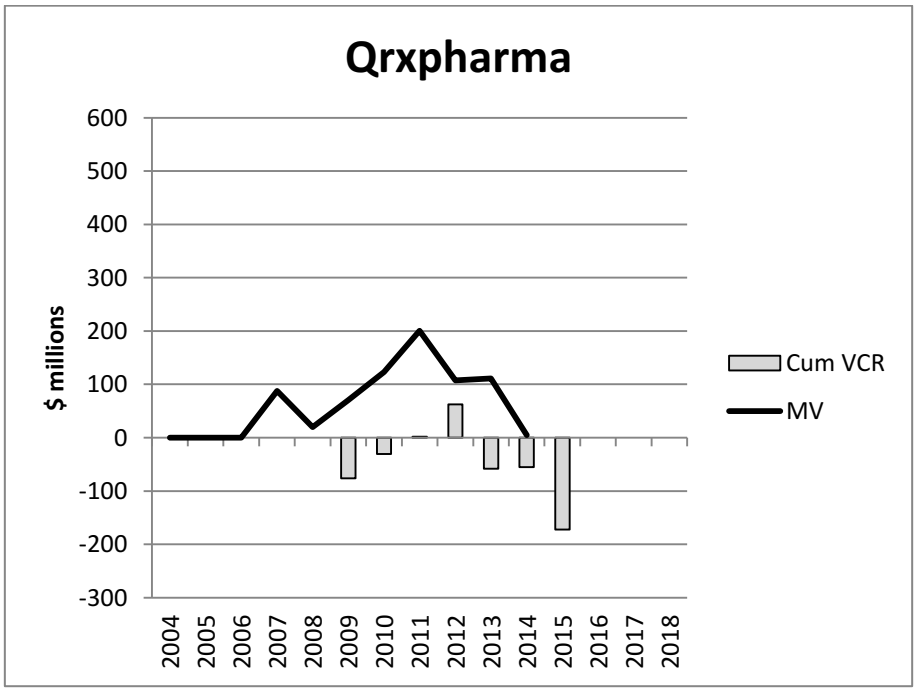
On May 19 2015, under a new CEO, Pharmaxis announced a restructure and change in strategy, acknowledging that their strategy of attempting to take a drug all the way to market without a partner was flawed (Gardner, 2015).

Qrxpharma

Pharmaxis was not alone as a high-profile failure in 2014. Right on its heels was the failure of Qrxpharma, another DDB that had promised much to investors and then failed at FDA approval. Qrxpharma was a spin-out from the University of Queensland with technology for pain management, its lead program being a 'dual opioid' drug for the treatment of moderate to severe pain. Scientists at the University of Queensland had postulated that the opioid, oxycodone, acted through a different set of neural receptors to other opioids, like morphine and hydrocodone, and thereby, the combination of morphine and oxycodone could represent a valuable synergy in pain management.

Qrxpharma benefited from some early VC funding and then listed in 2007. Their prospectus promised the completion of a Phase 3 trial by 2009 – to be fully funded by the IPO fundraising – and then approval and marketing in 2010. Like Pharmaxis, Qrxpharma was intent on proceeding all the way to marketing approval without a pharmaceutical partner and becoming a "commercial success" in its own right (ASX listing prospectus 2007, p. 2). These timelines were not achieved and the company was forced to raise significant additional capital, including from US investors.

Figure 29. Qrxpharma MV and cumulative VCR



Nevertheless, Qrxpharma broke the $100 million MV barrier in 2010, climbed to a MV of $200 million in 2011 and peaked in May 2012 at a MV of $265 million, based on anticipation of a positive result at FDA approval. However, in June 2012, they received advice from the FDA that the drug would not be approved based on their current data. This caused a significant slide in the SP in the second half of 2012. The company attempted a refiling of its application, but in April 2014, it received a final rejection from the FDA, causing the stock to collapse and its MV was only $4

million by the end of 2014. The company shuttered all drug development, reduced its BR to near zero and became a shell. Over its seven-year life, Qrxpharma had burned through $114 million in investor funds ($81 million in RDE) and delivered a negative VCR of -$172 million and an IRR of a staggering -43%.

Unlike other 'shells', such as Virax and Bone Medical, Qrxpharma was not able to stay alive long enough to find a new technology to vend into its existing ASX shell. The primary reason is that in 2015, its US investors launched a class action suit (in the US) against the company's directors and its CEO, which ultimately forced the company into administration.

Alchemia

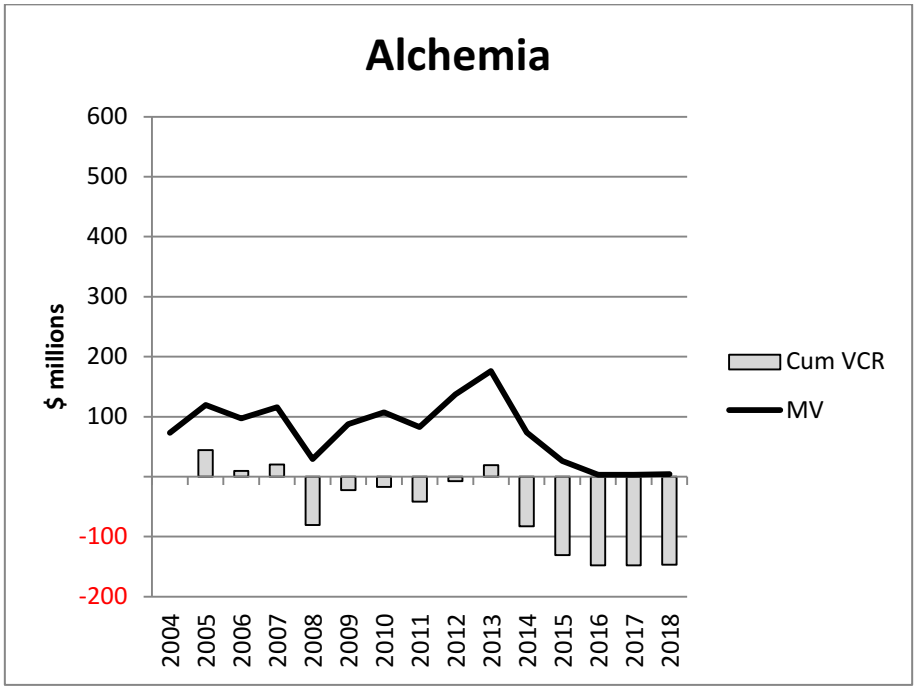
The final VCR 'loser' highlighted here is Alchemia. This DDB was founded in 1995, as a spin-out of the Institute for Molecular Bioscience at the University of Queensland. It was supported by VC funding, before it listed on the ASX in December 2003. Its technology was around the synthesis of carbohydrates for potential therapeutic use as drugs, with an initial focus on a synthetic heparin (fondaparinux).

By early 2006, its MV had grown to around $150 million, driven by a series of positive announcements around the fondaparinux program and drug development programs in cancer and eye disease. In 2006, Alchemia executed an agreement with the Indian generic pharmaceutical firm, Dr Reddy's Laboratories, allowing Dr Reddy's to manufacture and market fondaparinux in the US as a generic product against GSK's established heparin product, called Arixtra. In 2011, Dr Reddy's was granted approval to market the drug in the US as a generic version of GSK's drug.

In 2013, Alchemia described itself as a "Well financed biopharmaceutical company with balanced pipeline and partnerships with global pharmaceutical companies" (*Investor Presentation*, released to ASX on May 22, 2013). In the 2013 year, it reported $24 million in revenues, mostly from US fondaparinux sales from its profit-share agreement with Dr Reddy's.

However, by 2014, the sales started to decline and the company pinned its future and value creation on its cancer drug development program, HA-irinotecan, which was in a Phase 3 trial. Unfortunately, in October 2014, Alchemia announced that the Phase 3 trial had failed to meet its primary endpoint; as a result, the MV dropped overnight from $200 million to $30 million. In September 2015, the company sold its fondaparinux interests to Dr Reddy's for $17.5 million and subsequently distributed $30 million to shareholders as a capital return. After the return of capital, its MV dropped to $3 million and it effectively became a shell, having shuttered all drug development activities, while looking for new opportunities to acquire. Four years later, in 2018, Alchemia was still a shell, with $1.5 million in cash and trading at a MV of $3 million.

Figure 30. Alchemia MV and cumulative VCR



Over the 15-year period, Alchemia spent $77 million on RDE and created negative PVG of -$50 million. Its VCR was -$147 million and its IRR was -17.1%.

Like Pharmaxis and Qrxpharma, Alchemia had been funded by VCs prior to its listing, had gone on to generate significant promise, only to fail emphatically. The impact on investor sentiment of these failures and the overall poor performance of the sector are discussed further below.

10.1.5. Investor sentiment

Under-achievers

There were several DDBs that never reached any significant heights of investor expectation over the 15-year period, instead surviving at relatively low MVs. Setting an MV threshold of $100 million, the list of these 'under-achieving' firms is quite long, as shown in Table 29.

Table 29. Under-achievers in the DDB dataset

	Max MV $ millions	2018 MV $ millions	RDE $ millions	PVG/RDE	BR $ millions	VCR $ millions	IRR %
Actinogen	35	30	21	0.50	21	-11	-10%
Antisense	43	5	35	-0.33	39	-50	-22%
Benitec	94	38	44	-0.91	107	-147	-29%
Biodiem	21	-	21	-0.14	25	-28	-25%
Biotron	27	10	32	1.75	36	19	-6%
Bone Medical	27	-	12	-0.36	13	-18	-51%
Cellmid	31	24	7	2.57	29	-11	-19%
Cytopia	54	-	46	-0.57	38	-65	-29%
Immuron	42	24	23	0.00	43	-43	-21%
Imugene	44	44	19	1.09	23	-3	-15%
Living Cell	62	43	29	-0.00	50	-50	-11%
Patrys	45	15	51	-0.26	47	-60	-22%
Phylogica	90	90	38	1.65	45	18	-13%
Regeneus	62	26	23	-0.98	15	-38	-16%
Select Vaccines	14	-	6	-1.28	12	-19	-46%
Solbec	27	-	5	-3.93	8	-26	-37%
Virax	28	-	9	-0.87	19	-27	-30%

These 17 firms, representing 43% of the DDB dataset by number, never achieved much at all, despite burning a total of $421 million in RDE and $568 million in total BR over the 15 years. They all generated negative investor returns, although two of the firms – Biotron and Phylogica – had positive

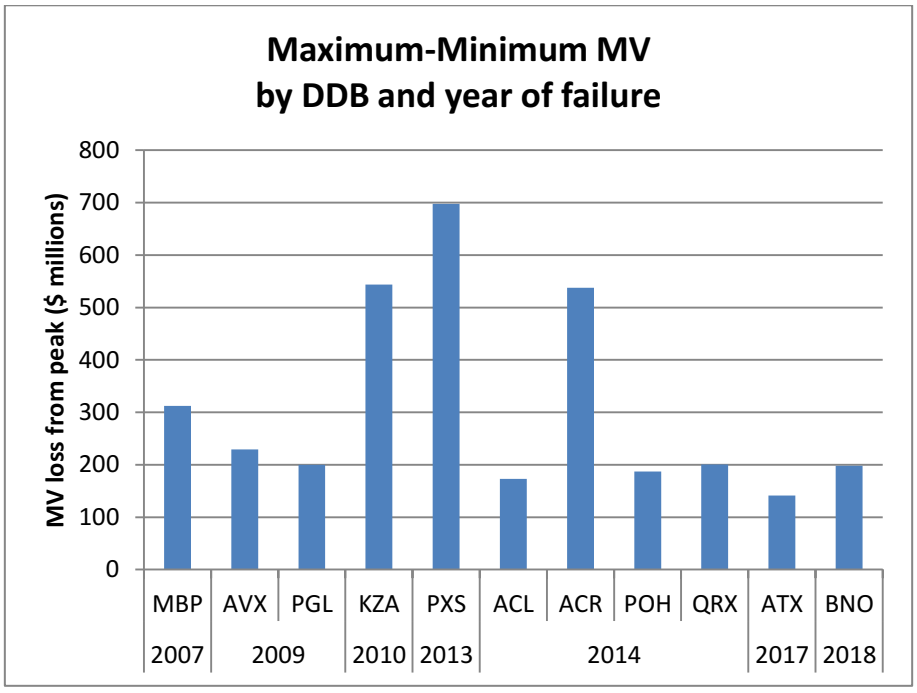
R&D productivity and managed to produce small, positive VCRs. Interestingly, Cellmid had a high PVG/RDE ratio (2.57), yet produced negative VCR. The reason is that its RDE was only 25% of its BR, so the small PVG generated from its RDE was overwhelmed by NRDE costs and the VCR was negative.

Dilutionary effects were also a significant problem for most of these firms. From an investor perspective, it would have been disconcerting that nearly half of their 'bets' on DDBs would fail to yield positive returns and destroy so much value. However, this realisation was likely overshadowed by the procession of high-profile failures that built up huge investor expectations and then shattered them.

The parade of failures

PV is fundamentally a measure of the optimism ('hope') of investors about a firm's prospects. High-profile failures would be expected to dent that optimism. Therefore, it is interesting to consider the timing of the various failures and the size of the MV losses that ensued from their highest level of optimism (peak MV) to their lowest level, after the failure. This is shown in Figure 31 for the major firms that announced clinical trial failures, regulatory failures or other major setbacks.

Figure 31. Peak-low MV declines by DDB and year of failure



Metabolic's clinical failure immediately preceded the global financial crisis (GFC) in 2008. As the first high-profile DDB failure, one could expect that it might have soured investors' taste for biotech investments in the short-term. However, the GFC may also have reset expectations for all stocks and the Metabolic effect may not have lasted into 2009. Coming out of the GFC, however, both Avexa and Progen announced failures in 2009. Like Metabolic, they crashed after promising much and

building up investors' expectations. Both firms later exited the sector. On the heels of those, Novogen announced its clinical trial failure in 2010; however, arguably most of the optimism for that firm had evaporated over several years prior.

By 2011-2012, it was likely that investor sentiment had improved. Acrux, Mesoblast, Starpharma, Pharmaxis and Qrxpharma were all on the ascendancy and between them, were worth $3.5 billion in MV. It looked like the Australian DDB sector was finally going to deliver and produce some winners (Dean, 2013). That perception, however, was short-lived.

Pharmaxis was the first domino to fall in early 2013, failing at registration and losing 90% of its MV by the end of 2013. The Pharmaxis failure likely did enormous damage to DDB investor sentiment. It showed that even with curation by VCs, a lower-risk 'repurposing' drug development model, allegedly good management and plenty of funding, the company had still failed and destroyed more than $260 million in investor funds over 10 years (2005-2014) with little to show for it. For the analysts and brokers in the sector, it had also damaged their reputations, one broker commenting to me in 2015 that his firm had 'burned' so many investors on Pharmaxis that they were loath to go back to those investors about any more biotech deals.

Soon after, Phosphagenics ran into trouble, although not due to a clinical or regulatory failure, but something far worse for its impact on investor sentiment. In late 2013, it was discovered that nearly $6 million had been misappropriated by the firm's management. The firm's high-profile CEO – who had been chair of the Australian Biotechnology Victorian Committee and a member of the Victorian Biotechnology Council – had personally embezzled nearly $4m, which had been spent on jewellery, clothing, household expenses and duty-free goods; in late 2014, the CEO was sentenced to six years' gaol.[8] In 2012, Phosphagenics' MV was above $200 million; by December 2018, it was down to $8 million. However, the impact of the Phosphagenics scandal on investor sentiment likely was much greater than the value of its MV loss.

The train wreck continued: The next major firm to fall was Qrxpharma, in April 2014, after its failure at FDA approval. This led a 90% decline in its MV, which triggered a lawsuit in the US against the firm's former directors and CEO, ultimately forcing the Australian firm into administration – an unheard-of demise for an Australian DDB. The threat of an investor lawsuit by US investors and its catastrophic effects on a small Australian firm must have made ASX investors a little nervous about investing in any Australian biotech firm with US investors.

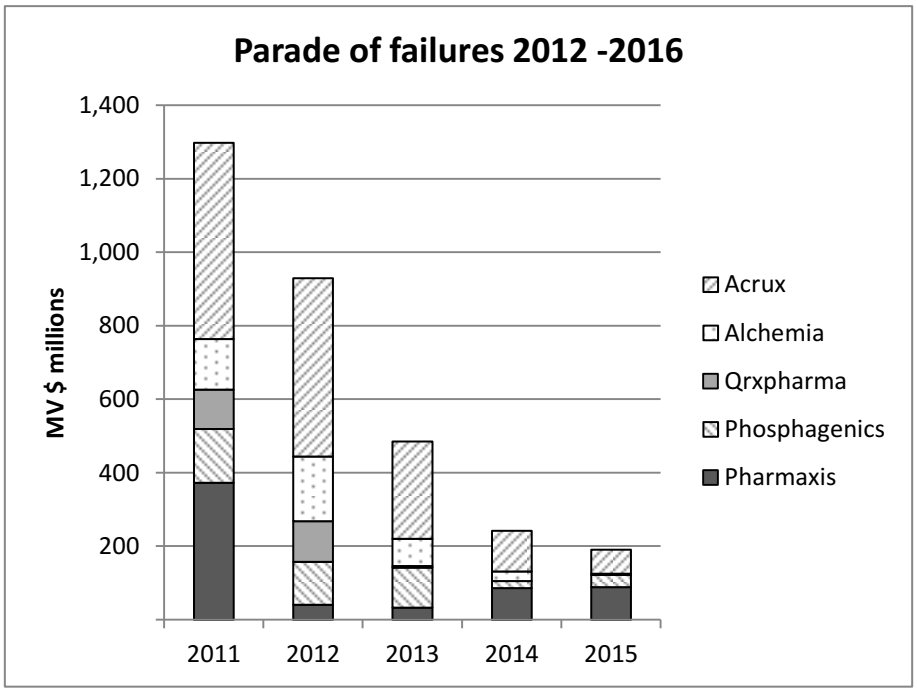
Then in October 2014, Alchemia announced its clinical trial failure, also triggering a 90% decline in its MV. In parallel, by late 2014, Acrux was in rapid decline – its MV dropping more than 60%

[8] https://www.theaustralian.com.au/business/news/six-years-jail-for-phosphagenics-biotech-fraudster-esra-ogru/news-story/c0571b1a183142b93fc297f4620362e7

compared with mid-2013, after its patent challenges in the US and with its rapidly declining sales. Acrux's decline told investors that even when an Australian DDB secures a solid pharmaceutical deal, gets a product to market and achieves profitability, it can still fail.

The total loss in MV from these five firms – between 2012 and 2016 – was a staggering $1.1 billion, as shown in Figure 32. Understandably, 2014 was described as the sector's '*annus horribilis*'[9].

Figure 32. DDB failures 2012-2016



Against all this, Mesoblast was in a slow decline from its 2011 peak – a decline no doubt exacerbated by the pall over the sector since 2012 – and then in 2016, when Teva cancelled its license agreement, it dropped another $400 in MV in one year. Cumulatively, by the end of 2016, Mesoblast had lost $1.7 billion from its peak MV, indicating to investors that even a billion-dollar pharmaceutical deal will not assure success of an Australian DDB.

Meanwhile, Biota – Australia's oldest DDB – entered a terminal decline in 2010, losing more than $250 million in MV after its ephemeral revival in 2009. Its subsequent reverse-merger into Nabi Pharmaceuticals destroyed all the remaining PV of the former sector leader and demonstrated that a DDB with 25 years of history, plenty of cash, pharmaceutical partnerships in place and a drug on the market, could still fail and deliver zero return to its investors.

[9] https://www.theaustralian.com.au/business/business-spectator/australias-biotech-wallflowers/news-story/136e3534e6aa4d42b53d3aaf2baaa611?nk=884d0132f0f641743d0e3ee44fa580b6-1548622395

The only offsetting positive news in 2014 was the growth in the MVs of Clinuvel and Neuren, both of which surpassed $100 million for the first time in 2014. Investors also saw the recovery of Starpharma after its 2012 clinical trial failure.

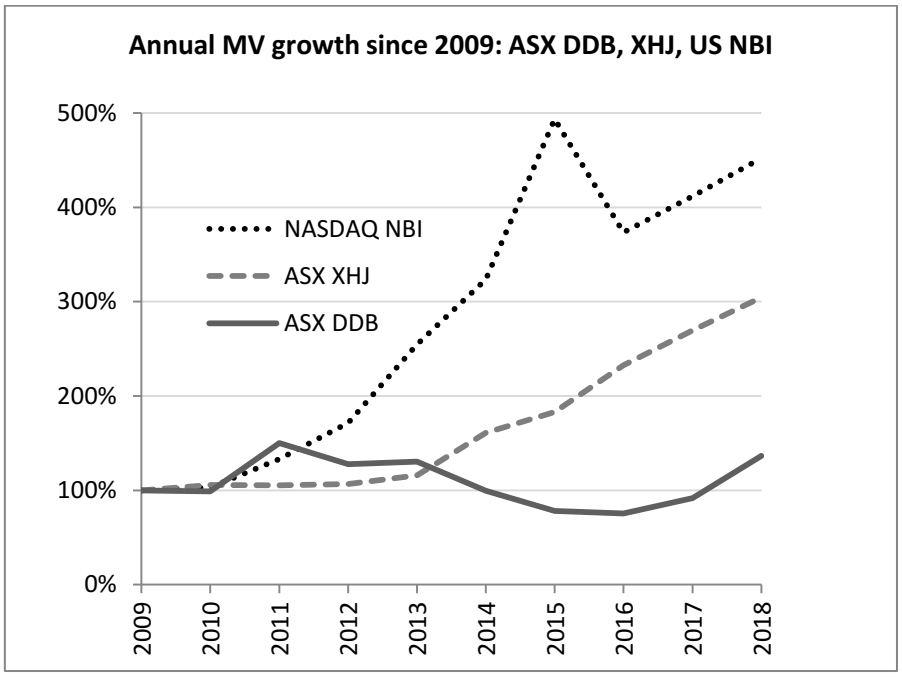
Finally, there was the ongoing strength of Bionomics, the 15-year-old DDB stalwart that had shrugged off the GFC and steadily increased its MV over the previous 10 years to above $200 million in both 2014 and 2015. However, in October 2018, Bionomics announced that the Phase 2 trial of its lead drug for PTSD (post traumatic stress disorder) had failed to meet its primary endpoint. This led to a collapse in its MV by December 2018 and the departure of its high-profile CEO, who had led the company for more than a decade and previously been the chair of AusBiotech, a member of the Australian Government's Biotechnology Advisory Council and a member of the Prime Minister's Science Engineering and Innovation Council.

Despite the Bionomics failure, by 2018, investors must have taken heart from the success of Clinuvel and Viralytics, and the apparent resilience of Starpharma. Perhaps the passage of time had also allowed them to forget the 2014 train wreck and earlier failures.

GFC inflexion

If the GFC was indeed an inflexion point in investor sentiment and memory, then it would be interesting to assess the overall impact of the negative sector developments in the nine years since then. Figure 33 shows a comparison of the growth in the total MV of the Australian DDB sector (including the new firms since 2014) with the growth of the Australian Healthcare Index (XHJ) and the NASDAQ Biotech Index (NBI), using 2009 as the index year.

Figure 33. NBI and XHJ versus AU DDB since 2009



While the NBI grew more than fourfold and the XHJ threefold since 2009, the total market value of the Australian DDB sector grew only 37%, with all the growth since 2017. In fact, if the Mesoblast effect in 2011 were removed, then the picture shows a clear and consistent depression in the value of the Australian DDB sector between 2009 and 2017. Given the unrelenting parade of failures since 2012, it is not surprising.

In the financialised, investor-relay model of biotech investing, investors would be expected to move from one stock to another to take advantage of short-term rises in that stock's fortunes. However, the eight-year pall over the sector since 2009 may indicate that investors have longer memories than implied by the investor-relay model, and potentially have been irreversibly scarred by the poor performance of DDB stocks. Alternatively, even those investors that did jump horses may have found that their new horse was just as lame as the previous one.

The overall negative sentiment generated by the high-profile failures after 2009 would have affected the MVs of all firms. For example, it is possible that the slow decline of Mesoblast's MV since 2011 may have been partly due to the weight of the overall sector gloom. Indeed, the sector gloom after 2009, may have resulted in poorer VCR and IRR performance for a number of other firms, such as Starpharma and Clinuvel, which without the weight of the negative overall sentiment, may have recorded more positive VCRs and IRRs. However, both performance constructs are ultimately determined by the terminal year's results and in that year, 2018, the sentiment appeared to be positive. The depressed earlier years, however, may have contributed to more dilution than might have occurred in more bullish times, due to the impact of fundraisings at depressed share prices. Regardless, the overall sentiment argument has no real bearing on the large number of abject failures, for which the VCRs and IRRs were so negative that sector sentiment was an inconsequential factor.

The walking dead

If investors needed reminding of the failure of the Australian DDB sector, then the persistent presence of dormant, former DDB corporate shells must have served as an enduring reminder. These 'zombie' firms, which typically remained ASX-listed, were almost always co-opted by entrepreneurs or brokers who then sought to use the ASX listing as an asset; they scouted for a new technology to vend into the shell and thereby achieve a 'back-door' ASX listing, also known as a reverse takeover. Recent ASX rule changes have sought to supress this practice, but during the period of this analysis, it was certainly prevalent.

Of the 40 DDBs, 10 (25%) failed in their original drug development mission and became non-operational shells at some stage. Five of these were later reborn outside the DDB sector: Progen, Metabolic, Solbec, Select Vaccines and Avexa.

One recent addition to the 'walking dead', Alchemia, had yet to be reincarnated at time of writing, but doubtless will be at some stage. The other four shells were reborn back into the DDB sector. Bone Medical was a non-operating entity as early as 2011 and the company spent the next five years looking for the right new technology to vend into its ASX-listed shell. It was not until 2016, that it succeeded and was reborn as Noxopharm, with the mission to resurrect the failed Novogen/Kazia drug, phenoxodiol, using a new formulation.

Virax was another persistent zombie firm that was non-operational from as early as 2011. More than three years later, it was reborn as Prescient Therapeutics, after it vended in a cancer drug technology from Yale University in the US. Actinogen was essentially a shell for seven years, from as early as 2008. Finally in 2015, it vended in an Alzheimer's disease candidate drug from the University of Edinburgh (UK) and was reborn with new funding and a new mission.

Imugene was another small DDB that was a shell from 2011. In December 2013, it vended in a cancer drug candidate developed by the University Medical School in Austria. For both Virax (Prescient) and Imugene, an Australian private firm had been set up to hold the option to the license from the overseas PRO, with the specific goal of an obtaining an ASX back-door listing. This allowed the ASX shell to simple acquire the private firm and in so doing, acquire the license to the technology.

In almost all cases, whether the shells were reborn as DDBs or in other fields, there was a recapitalisation, partly due to the equity cost of the acquired technology and partly to compensate the brokers or promoters. Generally, there was little residual value for previous investors after the rebirth. The rebirth of public shells has been a common practice in Australia and not just in the DDB sector. For example, eight of the DDBs in the current dataset were born from dormant mining or other shells, as shown in Table 30.

Table 30. Australian DDBs born from shells

ASX DDB	Previous shell (ASX code)	DDB rebirth year
Virax	Rancoo Ltd (RAN)	1998
Solbec	Britannia Gold NL (BNA)	2002
Immutep	Prima Resources Limited (PRR)	2002
Imugene	Vostech Limited (VOS)	2003
Benitec	Queensland Opals NL (QOP)	2003
Phosphagenics	Vital Capital Limited (VIT)	2000
Chemgenex	Australia Wide Industries Ltd (AWI)	1999
Bone Medical	Aerodata Holdings Limited (ADH)	2005

10.1.6. Why they failed

Funding

Many have claimed that the paucity of funding in Australia is a major reason for Australia's inability to translate perceived great science into commercial success stories (Herpin et al., 2005; Jens, 2007; Lavelle, 2012; Marot et al., 2005; Wood, 2011). However, is cash really the problem? Given that in this research, the 40 DDBs spent $2.9 billion on RDE and still failed to deliver any overall value, might suggest otherwise. Indeed, some of the biggest cash burners and R&D spenders were among the biggest losers as shown in Table 31, which lists the top 20 DDBs by total RDE over the 15-year period.

Table 31. RDE, cash, BR, VCR and IRR

DDB name	Total RDE $ millions	Ave Cash $ Millions	Total BR $ millions	Cum. VCR $ millions	IRR %
Mesoblast	487	102	536	199	4.0%
Pharmaxis	278	62	260	-220	-6.4%
Bionomics	195	17	103	-42	-3.7%
Starpharma	157	25	130	284	6.2%
Kazia	137	26	175	-680	-27.7%
Biota	114	55	-29	64	2.8%
Peplin	109	17	101	-12	1.1%
Neuren	108	7	92	-1	-14.8%
Immutep	97	12	126	-48	-13.7%
Prana	89	16	122	-161	-17.1%
Avexa	81	22	125	-135	-28.6%
Qrxpharma	81	19	114	-172	-43.0%
Clinuvel	78	16	84	662	7.2%
Alchemia	77	11	97	-147	-17.1%
Chemgenex	68	11	91	88	2.1%
Viralytics	58	18	61	356	7.2%
Progen	56	22	89	-117	-16.3%
Phosphagenics	51	10	108	-142	-21.7%
Patrys	51	6	47	-54	-21.7%
Cytopia	46	10	38	-65	-28.8%

These 20 firms accounted for 84% of total RDE in the sector and 87% of the total cash burn (BR). The most successful firms – Clinuvel and Viralytics – were not even in the top 10 R&D spenders. The availability of cash and ability to spend on RDE were not the reasons for their success, just as lack of cash was not the cause of the failures of Pharmaxis or Kazia, which were two of the largest R&D spenders, yet delivered negative VCR and IRR outcomes.

For all 40 firms, the correlation between total RDE and VCR was weak (r = 0.05). The failure of RDE to translate into PVG and VCR suggests that TA quality may be the problem and that investor cash was directed into programs with relatively poor value creation prospects.

In contrast, RDE was significantly correlated with IRR (r = 0.40), suggesting that cash, at least as represented by the value of RDE, is needed to drive IRR. Given the VCR relationship, it might indicate that high cash reserves – to which RDE is highly correlated (r = 0.74) – allow the firm to avoid highly-dilutive fundraisings, which would otherwise undermine IRR. The correlation coefficient between average cash reserves and IRR was 0.45, suggesting that this may be the case.

Strategic errors

In some cases, it appears that Australian DDBs failed to understand 'market demand' as partnering demand. Instead, they restricted their market conception to the 'medical need' and defined their market opportunity based on the incidence of the disease targeted by their drug. I will refer to this as the 'commercial' market to distinguish it from the partnering market.

For example, Avexa's lead program, ATC, was aimed at HIV treatment, which had (and still has) a large commercial market. However, the partnering market is almost non-existent, because HIV is well-managed by existing drugs; moreover, in third world countries, the commercial market is low-priced, making innovation in the field even less attractive to Big Pharma. One way or another, it was apparent that Big Pharma had lost interest in licensing new HIV drugs as early as 2005, around the time Avexa acquired ATC from the UK-based pharmaceutical firm, Shire. Possibly Shire already realised the change in the market, but apparently Avexa did not, and over the next five years, it spent $81 million in RDE and burned a total of $112 million in investor funds, before it realised (as disclosed in its 2010 annual report) that no pharmaceutical partner was interested in ATC. Unfortunately, the mistake destroyed the firm and after four years as a dormant shell, including a failed attempt to be reborn as a mining company, it exited the sector in 2015 to become a diagnostic business. I will refer to this misunderstanding of the real marketplace as 'market definition' failure.

Other firms, like Pharmaxis and Qrxpharma, decided to take their drug all the way to the commercial market, making their strategy and ambitions clear in their prospectus and annual reports. They then drove their programs all the way to regulatory approval without a pharmaceutical partner and failed at the approval step. Arguably, that failure was not unexpected, given the enormous infrastructural

challenge, portfolio breadth and time needed for a DBB to become a commercial-stage firm. Partnering with a larger pharmaceutical partner reduces the risk of failure for the drug development program at all stages, because of the additional capabilities, funding and guidance on clinical development that the partner brings. The partner also brings extensive expertise in the regulatory process and relationships with regulatory authorities that help reduce regulatory risk. The 'go it alone' strategy may have been motivated by the desire to demonstrate commercialisation, but it would seem to be a precarious and ill-advised strategy for a small Australian DDB. I will refer to this as 'commercial focus' failure.

Some firms were obsessed with producing short-term profits, possibly in the belief that this constituted demonstrable commercial success for Australian investors. Acrux almost certainly fitted into this category, extracting as much profit as possible from its first product and distributing dividends to shareholders, while apparently failing to invest in a robust pipeline of follow-on opportunities that would have buoyed its value in the face of the lead drug's ultimate commercial failure. Between 2007 and 2010, Biota appeared to make the same mistake, generating profits while failing to invest in its key antiviral drug development programs. I will refer to this as the 'profit means success' misconception, which is arguably a variant or extension of the 'commercial focus' failure.

As previously noted, DDBs can become profitable for several years and potentially indefinitely, without becoming commercial-stage firms (DDCs). Biota, Acrux and Arana are Australian examples of this. However, because they lost sight of their primary role as intermediaries, instead they were content that they had achieved commercial success and failed to use the funds to build a stronger TA and portfolio of candidate drugs to secure their long-term futures as DDBs. Being 'content' is not a viable state for DDBs, because of a phenomenon that I call the 'Red Queen' effect.

The Red Queen

The Red Queen is a reference to the character from Lewis Carroll's *Through the Looking Glass*, who had to run as fast as possible, just to stay in one place. Evolutionary biologists have borrowed the character to form the 'Red Queen hypothesis' wherein evolutionary equilibrium is characterised by constant development to keep pace with predatory threats. It has been applied to drug development in the sense that constant increases in regulatory hurdles imposed by regulators (the predators) force biotech firms to constantly innovate just to keep pace (Warren, 2011). It has also been invoked in relation to biotech firms that are growing rapidly, but struggle to keep pace with the growing complexity that is associated with that growth (Khilji et al., 2006; Wells et al., 2003).

My invocation of the Red Queen effect is different again. Time is the enemy of DDB firms, because its passage degrades the value of static TA and unless the DDB is strengthening its TA and moving candidate drugs forward at an urgent and fully-funded pace, it loses the battle against time. One

reason is the patent 'clock'. Patents last for 20 years and pharmaceutical partners typically want 8-10 years of intact patent life at the projected date of product launch, in order to recoup their development and licensing investment and then deliver an attractive commercial return. This means that at the typical Phase 2 licensing point, which is still up to 4 years away from product launch, a candidate drug needs to have 12-14 years of patent life remaining (Scheel et al., 2013). Thus, those DDB firms that do not (or are unable to) fund their programs aggressively enough to complete Phase 2 and partner their program within eight years after the completed patent is filed (when the patent clock starts ticking), may miss the window for a pharmaceutical alliance. They could then find themselves unable to secure a partner and condemned to watch the patent clock run down on their drug pipeline and the PV shrink inexorably to zero.

Potentially, this happened to Biota. Between 2006 and 2011, Biota had average annual cash reserves of $72 million, but over this time, it sat on the cash instead of aggressively driving forward its two lead antiviral drug programs, Ivanir for influenza and vapendavir for rhinovirus infections (the common cold). By 2012, when the company exited to NASDAQ, neither program had progressed to Phase 3 (or been partnered) and by then, both patents had less than 10 years of patent life remaining. Not surprisingly, six years later in 2018, neither program had been partnered and now must be considered valueless, both victims of the Red Queen.

Biota's drugs were all 'small molecule' drugs and as such, would have been exposed to low-price generic competition as soon as the patent expired. This patent exposure is less of a threat for biologic drugs – protein-based drugs, in contrast to synthetic, small-molecule drugs. As noted previously (7.4 Technology asset), the US Biologics Price Competition and Innovation Act (BPCI Act) of 2010 extended the commercial protection of biologic drugs well-beyond the life of their patents. Under the BPCI Act, biologic drugs are protected from competition for 12 years after FDA approval, regardless of their patent status. Similar legislation in Europe, grants biologic drugs an eight-year exclusivity period after approval. In this way, biologics have a degree of Red Queen immunity, as least with respect to patents.

Regardless of any Red Queen immunity on patents, TA value can decline over time because of evolution in the medical need. As an example, in the early 2000s, candidate drugs for hepatitis C (HCV) infection were in demand for licensing by Big Pharma. However, by 2015, there were several effective HCV drugs on the market and the medical need was no longer considered unmet; as a result, Big Pharma lost interest in HCV. DDB firms that were working on HCV drugs and did not progress them quickly enough to do a pharmaceutical deal, apparently missed the window to do so. This is another example of the Red Queen at work.

R&D productivity

The concepts of TA quality and R&D productivity were discussed in sections 7.4 and 7.5. High quality TA (high TAQ) theoretically will lead to a high PVG/RDE ratio and more efficient generation of PVG and VCR. A PVG/RDE ratio of less than 1.0 cannot lead to any PVG or VCR.. One would predict that only those firms with positive R&D productivity (PVG/RDE > 1.0) would have any chance of being successful, while those with the highest PVG/RDE ratios would report the highest VCR and IRR results. This was generally the case, but there were some notable exceptions. Table 32 shows those DDBs that produced PVG/RDE ratios of greater than 1.0. The full list of DDBs and their PVG/RDE ratios is shown in Table 24.

Table 32. PVG/RDE leaders

DDB name	RDE $ millions	PVG $ millions	PVG/RDE	VCR $ millions	IRR
Clinuvel	78	746	9.6	662	7.2%
Viralytics	58	417	7.2	356	7.2%
Starpharma	157	414	2.6	284	6.2%
Cellmid	7	18	2.6	-11	-19.4%
Chemgenex	68	169	2.5	79	2.1%
Invion	20	46	2.3	1	-20.1%
Biotron	32	55	1.8	19	-6.1%
Phylogica	38	63	1.7	18	-12.7%
Mesoblast	496	732	1.5	182	4.0%
Imugene	19	21	1.1	-3	-15.3%

In the case of Cellmid and several other unsuccessful firms (based on VCR and IRR), the level of RDE was simply too low to be a driver of any PVG. Biota and Acrux, which are not shown in the table because their PVG/RDE ratios were less than 1.0, produced positive VCR and IRR, despite low R&D productivity. The reason for this is that they generated profits and disbursed dividends, rather than investing in RDE to grow PVG.

What is particularly notable is that 30 of the 40 firms had PVG/RDE ratios less than 1.0, indicating that their TAQ was never capable of generating any PVG. It should be remembered that, as shown in Figure 5 in section 7.4, TAQ is conceived to be a multidimensional construct that incorporates not only technical aspects of a drug development program – efficacy and safety – but medical need, market demand, commercial protection and development risk. For some of the failed firms, the TA deficiency may have been in 'efficacy and safety', such that their drug development program never had the technical potential to generate drugs that would attract a pharmaceutical partnership, regardless of other factors. This may be indicated where clinical trial failures caused the firm's demise, such as in the cases of Kazia, Metabolic, Alchemia, Bone Medical and Amplia. In other cases, the TA problem may have been around patents (commercial protection), as appears to have been the case with Biota, or lack of market demand, as was the case with Avexa. As per the model in

Figure 6, it is also possible that the moderating effects of management were part of the TA translation problem.

A detailed analysis of the causes of failure for each firm, in the context of the TAQ model, is beyond the scope of this research. However, the low R&D productivity of most of the firms is undeniable and is likely related to some aspect of the TAQ model as broadly conceived.

Is Australian science the problem?

The view that Australia has high quality R&D capabilities and produces high-quality R&D output has long been held in Australia. The problem has always been seen as ineffective management with poor commercialisation skills, as epitomised by this 2005 quote from an article in the *Sydney Morning Herald*, titled "We've the brains but not the managers":[10]

> Brain for brain, Australia is up with the best in producing world-beating technologies. Ideas surge from university laboratories, from small back rooms and, especially, from the CSIRO, the Commonwealth Scientific and Industrial Research Organisation. But turning those ideas into money-making companies, capable of competing in a market that, increasingly, is global in its nature is, in many cases, harder than developing the technology. And, according to some executives who have gone through the fire, Australia does not produce enough executives qualified to take such enterprises to commercial success.

While strategic missteps, management competencies or other factors, such as the 'tyranny of distance' (Gilding, 2008), may have influenced the productive conversion of TA into positive investor outcomes, it is not reasonable to attribute the failure of most of the DDB sector to these forces. A more likely culprit is the quality of the TA. If so, how does this reflect on the quality of Australian R&D?

Rarely has the view been expressed that Australia's drug discovery prowess may not be up to the standard needed to give DDBs programs of sufficient quality to compete with US biotech firms. On the contrary, the views from government bodies and the peak industry body, Ausbiotech, have been unwaveringly celebratory about Australia's biotechnology standing in the world, with Australia's top five ranking on the *Scientific American* 'Biotechnology Worldview Scorecard' often cited as evidence (Dalidakis, 2015; Lavelle and Rathjen, 2014; Nogrady, 2018). However, this ignores the fact that that ranking has been inflated by the inclusion of CSL – a 100-year-old pharmaceutical manufacturer – as a 'biotech' firm.

[10] https://www.smh.com.au/business/weve-the-brains-but-not-the-managers-20050711-gdlnxc.html; July 11, 2005 article by Garry Barker.

In the face of this positivity, there have been few dissenting voices against the view that Australia produces great research and the problem is cash and managers, not the PROs. In 2004, in an unpublished research study, Vitale observed (2004, p. 6):

> Venture capitalists claim that there is plenty of money to invest, but a shortage of investment-worthy propositions. If so, serious questions must be asked about the focus of Australian research and the capability of Australian research establishments to create realistic business plans.

This was amplified in another unpublished study for the US Studies Centre (Barlow, 2010), which compared Australian cities with San Diego and directly challenged the prevailing views about the quality of Australian technology (Barlow, 2010, p. 1):

> The view that predominates in Australia, as confirmed by a range of participants in Australia's biotechnology sector whom we surveyed, is that we have failed to leverage our research base in biotechnology because of problems in Australia's industrial system. These include the lack of a "flagship" company that can act as a repository of talent when start-ups fail, a lack of access to patient venture capital funding, and a lack of sustained government policy support for biotechnology industry development at both the state and federal levels. Our analysis, however, suggests a more worrying problem: that Australia's research base is not as outstanding as is popularly imagined

The study went on to identify a lack of investment intensity and a shallow, clinically-oriented research portfolio, with a relatively low level of investment in biological sciences – the heart of drug development. Further, the study reported that Australian PROs generated "research outputs of low average quality compared with San Diego" and "research outputs of lesser commercial significance" (Barlow, 2010, p. 2). However, it needs to be noted that the study was not published in any peer-reviewed journal and could be criticised legitimately on a number of grounds.

Regardless, the results of the current research, notably the PVG/RDE ratios and the high rates of failure, must add some volume to the voice that perhaps Australian technology – at least that exploited by its public DDBs – may not be world-class after all.

Are VCs the problem?

The lack of venture capital in Australia has been blamed repeatedly for the DDB sector's problems. As noted above, however, Australian VCs have reportedly blamed the lack of investable firms, not the absence of capital.

The Australian Venture Capital Association Limited (AVCAL) website provides an investee map that lists all the firms that have received investment by Australian VC firms

(https://www.avcal.com.au/documents/item/968; accessed February 15, 2019). A list of 65 firms is shown as having received Australian VC funding; of these, only seven were DDBs. Based on another source (Herpin et al., 2005), the list of private DDBs that received VC funding was a little longer, with an additional four DDBs identified.

Based on Herpin et al. (2005), there were only three DDBs that were VC-backed and went onto become ASX-listed, as follows (listing year in parentheses): Alchemia (2003), Pharmaxis (2003l) and Qrxpharma (2007). On this basis, it appears that Australian VCs have only rarely invested in DDBs that have matured into public companies and listed on the ASX, and have not done so in more than a decade. Investments by Australian VCs in already-listed DDBs are even rarer. The only case appears to be a funding round for Peplin in 2008 that was led by GBS Ventures (Herbert, 2008); again, this was more than decade ago.

Given the failures of Pharmaxis, Qrxpharma and Alchemia, VCs could be forgiven for snubbing the ASX as an exit for their private investments. Apart from the poor performances of these three marquis DDB investments by VCs, there may be other reasons why VCs have avoided the ASX in the last 10 years. For one thing, the ASX now imposes a two-year escrow on early investors after an IPO, during which time, the escrowed investors are unable to sell their shares. Even after escrow expiry, because of the relatively low valuations and often limited liquidity of listed DDB firms in Australia, the VC firm may find itself owning a large share of the firm and unable to sell into the market without driving down the share price.

Whatever the reason, instead of pursuing ASX IPOs, it appears Australian VCs have been more inclined to fund firms privately and then exit via a trade sale. Indeed, between 2014 and 2016, there were three high-profile trade sales of VC-backed DDB firms that never listed on the ASX. These are shown in Table 33.

Table 33. VC-funded private DDBs that have executed trade sales

DDB Firm	Therapeutic area	Founding	VC investors	Trade sale exit
Hatchtech	Head lice	2001: University of Melbourne spin-out	Uniseed, OneVentures, QIC, GBS, Blue Sky	2016: Dr Reddy's Laboratories paid $10m upfront, $50m in pre-commercial milestones, and undisclosed royalties
Spinifex	Neuropathic pain	2005: University of Queensland spin-out	GBS, Brandon Capital, MRCF, Uniseed, UniQuest	2015: Novartis paid $200 million upfront, milestone payments up to US$600m
Fibrotech	Diabetic nephropathy	2006: University of Melbourne spin-out	MRCF, Brandon Capital, Uniseed	2014: acquired by Shire for US$ 75 million upfront, plus up to US$600m milestones

One implication of these successful sales might be that higher-quality Australian DDB projects get 'cherry-picked' by VCs, developed for a period of time and then sold off to international firms, without ever reaching the ASX. It might be argued that this leaves the lesser-quality programs to compete for an ASX listing, obtaining their 'venture capital' from less-discerning retail investors (Sparling and Vitale, 2003). However, this latter point must be regarded as speculative only at this point, the verification of which is beyond the scope of this research. Whatever the case, the relatively low proportion of VC-backed DDB firms and the relatively modest trade sale values obtained for the private firms tends to support the idea that Australian technology – at least when it comes to drug development – may not be that investable or valuable, at least to VCs.

Regardless of the investability or value argument, the fact is that investments by VCs in DDB firms have not contributed to the development of the ASX DBB sector in the last decade. It could be argued that the public DDB sector has been deprived of the potential contribution of VC-backed firms to overall sector development. In this sense perhaps, the VCs *are* part of the problem.

Is the ASX the problem?

The US public listing process is long and complicated, typically involving multiple rounds of venture capital followed by at least one round of institutional funding, prior to the IPO (Shimasaki, 2014c). This torturous, VC-curated pathway tends to ensure that any DDB that reaches IPO is mature, has proven technology, has solid funding in place, boasts a valuation of at least US$200 million, and has

the potential to become a multi-billion firm in the future. Unlike the ASX, the process and scale of a US listing allows VCs to exit without difficulty.

In contrast, the ASX is a much easier exchange on which to list. The valuation thresholds are low and the IPO pathway can be expedited, potentially without the involvement of VCs or institutional funds prior to listing. In Australia, the valuation threshold was $10 million for much of the last 15 years and was recently increased to $15 million. However, as the valuation includes the intangible value of the equity (PV for DDBs) plus the value of the cash raised at ASX listing, the threshold increase likely has not stifled the listing opportunities for most private DDB firms.

These attributes of the ASX have allowed early-stage firms that could not attract, or did not want VC funding, to get access to funding through the public market. In some ways, an ASX listing and public funding provides the venture capital needed for early-stage Australian firms (Vitale and Sparling, 2004). This has created a local stock market with a much larger number of public biotech firms per capita than the US and most other countries, a statistic celebrated by some as indicative of Australia's biotech strength (Lavelle, 2012); however, it may be a key cause of the sector's weakness.

Because of the low valuations and early stage of the newly-listed firms, the amount of funding raised at the IPO is typically very modest, leaving firms with a short cash runway and the need to raise additional funds in the near term (Herpin et al., 2005). As noted by Herpin et al. (2005, p. 116): "On average, Australian biotech companies go public at a tenth of the valuation of their US counterparts and also raise a tenth of the amount."

This means that, even if the PVG/RDE ratio is large, most firms are condemned to poor investor outcomes because of serial dilution effects on IRR. So, potentially the ASX *is* part of the problem. In the case of DDBs, the investors (and the DDB firms) might be better served by the ASX's demanding that the funds raised at listing are provably sufficient to support the firm's projected BR through to a realistic partnering milestone, not necessarily profitability. This would largely avoid the dilution problem and force prospective public firms to focus on partnering and carefully map out their value creation pathway. However, this would also require an in-principle commitment to the PCI view and an understanding of the real market for Australian drug development output.

Are expectations the cause?

As noted already, several Australian DDBs seemed to have viewed early 'commercial' success as a strategic imperative, by generating revenues, profits and dividends. Perhaps this was driven, at least in part, by the prevailing narrative that Australia has great technology, but lacks commercialisation skills. It may also be that Australian retail investors are impatient, expecting the rapid achievement of value-accreting milestones that generate equally rapid share price growth. For drug development, that's a real challenge.

However, given the hype around the high quality of Australian R&D, perhaps retail investors can be forgiven for being impatient. Unfortunately, even the most patient investor would not have seen a positive return from a portfolio of DDB investments in the last 15 years.

10.1.7. Why some succeeded

So far, the analysis has focused on why DDBs failed. Admittedly, the failure of the sector has been so widespread and emphatic that that focus has been appropriate and necessary. However, it is also important to learn from the success stories. In that regard, the VCR performance analysis points to two clear successes: Clinuvel and Viralytics.

Clinuvel

In some ways, Clinuvel succeeded against the odds. Its initial focus was on a drug to promote artificial tanning. It was thwarted in that plan, but was able to pivot and refocus the drug on a niche drug therapeutic indication, called EPP. By 2014, this provided a pathway to an approval in Europe, yielding some early revenues through limited distribution to a handful of European treatment centres. Even with limited sales, because the drug sells for between €56,000-84,600 per treatment course, it was able to generate $46 million in sales in 2018 and is projected to generate $133 million in 2019, based on a recent analyst report[11]. This continued sales growth, combined with the possibility of FDA approval in the US during 2019, puts Clinuvel in a strong position for future success.

Clinuvel's drug, afamelanotide (Scenesse), is one of the few Australian-developed drugs ever to succeed in a Phase 3 trial, gain regulatory approval and generate sales. That alone is a mark of success. However, it is now also succeeding from an investor returns perspective. In September 2015, Clinuvel was trading under $3.00 per share. Three years later in September 2018, Clinuvel became the first Australian DDB to traverse $20 per share, breaking the $1 billion MV barrier. In a 2018 analyst report, it was predicted to reach a price of $31.70 per share in 2019, which would imply a valuation of $1.5 billion[11]. By April 2019, its market value was already approaching $1.2 billion and likely by the end of 2019, Clinuvel likely will be heralded as an unequivocal DDB success story.

Perhaps one of the reasons for Clinuvel's success has been its leadership and culture. Dr Wolgen started as CEO in 2006 and implemented the strategic pivot that saw the company successfully pursue a niche therapeutic indication over the subsequent 10 years. In a 2009 'Open Briefing' interview (Clinuvel ASX release, April 16, 2009), Dr Wolgen stated: "The key competency of my team is its resilience in professional adversities when encountered." Finding ways to navigate

[11] Analyst report by Sphene Capital 25 June 2018, titled "Clinuvel: NDA for the treatment of EPP in the US is a key milestone." Online source: http://www.more-ir.de/d/16649.pdf

setbacks has certainly been a feature of Clinuvel over the years. In a recent article, Dr Wolgen reportedly described Clinuvel's pathway to success as "tortuous"[12]:

> "Rather than traversing along the fastest imaginable and plotted route to success, we have frequently been impelled to take tortuous avenues to achieve our objectives," he told shareholders recently...Unlike the majority of ASX-listed drug plays, at least Clinuvel (ASX: CUV) has navigated these tortuous routes. It actually has a drug on market — to treat a rare skin intolerance to sunlight — which makes the company a rarity in itself.

The article went on to give Dr Wolgen much of the credit for the success of the firm. As an exercise, I calculated the IRR since 2006, when Dr Wolgen started; it was 10.6%. If Clinuvel achieves the projected $1.5 billion MV in 2019, that figure grows to 16%, which starts to approach a meritorious performance for a biotech firm.

In its 2015 annual report, Clinuvel declared the firm was making the transition to a 'commercial' firm. However, Clinuvel is still a DDB and far from being a commercial-stage DDC. Based on the 2016-2018 annual reports, it was evident that the focus was still on R&D, with commercialisation limited to generating a low volume of direct sales to 44 EPP 'expert centres' in Europe. Indeed, in its 2018 profit and loss statement, 'business marketing & listing', which was the only expense category that approximated commercialisation expenses, accounted for only 8% of the firm's expenses, with the bulk of expenses associated with R&D and personnel.

Successful DDBs in the US have gone down the same path – using a niche market opportunity to generate early revenues to establish commercial proof-of-concept and make the product attractive to global commercial partners. While the EPP approval is a great regulatory breakthrough for Clinuvel and generates modest but useful sales, EPP is only one small indication for the drug. Its successful adoption by doctors for EPP will signal reduced risk as the company pursues much larger therapeutic opportunities in the future, such as vitiligo – the skin-whitening disease that affects up to 2% of the world's population and is a significant unmet medical need in the US, especially among African Americans.

What Clinuvel is currently doing with EPP is effectively a pilot-commercialisation program that is logistically manageable for a small firm with limited real pharmaceutical commercialisation capability. Going forward, that capability may be tested, especially once FDA approval is obtained. Nevertheless, in the short-term, it has allowed the company to deliver to the sceptical Australian market a 'commercial' success story, even to the extent of posting a profit in 2018 and extracting a dividend to underscore the narrative. In terms of growing future shareholder value, it could be argued

[12] *Stockhead* article September 11, 2017, by Tim Boreham, titled: "Clinuvel's tortuous avenue to solve rare skin condition," Online source: https://stockhead.com.au/health/clinuvels-tortuous-avenue-to-solve-rare-skin-condition/

that that dividend may have been better invested in more R&D to expand the future indications of the drug.

Over the next few years, as the indications grow for Scenesse, along with its potential launch in the US and the massive logistical challenge that represents, Clinuvel is going to need to rapidly expand its commercial capabilities. As noted in the 2018 analyst report: "Turning Clinuvel from a research driven company into a commercial global entity entails certain organizational risks, which could endanger the profitability of the company and therefore our price target"[11].

The 2018 analyst report projected a dramatic growth in commercial costs from 2019, assuming a US approval. While it is feasible for a small Australian firm with no commercial experience or infrastructure to manage a handful of customers in Europe and without the help of a pharmaceutical partner or distributor, marketing in the US is a much more challenging proposition. Add to this, the potential expansion of the use of the drug beyond the extremely narrow condition of EPP to broader indications, and the challenge is amplified. As previously noted, infrastructure, management skills and culture are substantial barriers for a DDB seeking to migrate to a DDC. Life is much more complex at the commercial interface of the pharmaceutical industry and a large, multinational and highly-functional regulatory, logistical and marketing infrastructure is needed. Clinuvel may be able to make the transition to a DDC in the future, but to attempt it could represent a strategic 'commercial focus' error and might even threaten the survival of the firm. If it succeeds, it will take many years and Clinuvel would become a rare DDC transition success outside the US. More likely, Clinuvel will realise the capabilities challenge in front of it and seek a global licensing partner to manage international commercialisation. It may even choose to be acquired by that partner, monetising a multi-billion valuation for its shareholders.

Fortunately, Clinuvel has found a way to avoid the Red Queen, despite its aging patent portfolio. The original patent on afamelanotide expires in the early 2020s, which is theoretically an insufficient 'runway' to attract a pharmaceutical partner. Moreover, because the drug is a small-molecule, it does not have the Red Queen immunity enjoyed by biologic drugs (see section 10.1.6). So far, Clinuvel has circumvented this problem by selling the product itself for EPP in Europe, rather than relying on a pharmaceutical partner. It has also filed a number of follow-on patents covering specific uses of the drug and its specific drug delivery system. The other commercial protection it has is that afamelanotide is not a simple pill that can be easily copied, but a drug delivery device that is implanted under the skin and slowly releases drug over time.

On top of that, EPP is also commercially-protected by its 'orphan drug' status in Europe and the US. This is another measure to avoid the patent Red Queen. In order to stimulate pharmaceutical industry development of drugs for rare (orphan) diseases, the US FDA and the equivalent authority in Europe (EMA) introduced orphan drug legislation, which gives post-approval commercial protection for a

drug's use in a specific 'rare disease. In the US, the orphan drug exclusivity is for seven years after approval, while in Europe, it is 10 years. This confers a relatively weak form of Red Queen immunity, because it is limited to the first approved indication of the drug.

Again, Clinuvel's other patents and its delivery system may provide adequate protection for the other indications, but once a drug is approved in the US and starts to generate substantial sales, patents are typically challenged by competitors and such challenges are encouraged and rewarded by the FDA. While competitors will probably avoid EPP, because it is a very limited indication and is protected by orphan drug exclusivity, they will almost certainly challenge the use patent for vitiligo and if that patent falls, Clinuvel's long-term value proposition may fall.

Regardless of these challenges, the Clinuvel experience doubtless could provide some valuable lessons for other DDB firms. That would require a detailed case study analysis, which is beyond the scope of the current research. However, it would be a worthwhile future research project.

Unfortunately, the Clinuvel story cannot be held up as an example of successful Australian science, as afamelanotide was not the product of Australian research. It was licensed from the University of Arizona (Hadley and Dorr, 2006).

Viralytics

In contrast, Viralytics' success *was* the product of Australian technology. The idea of using a virus to attack cancer cells and the original development of the strain of cocksackievirus (CVA21) that would do the job were undeniably the creation of an Australian PRO – The University of Newcastle. The virus became known as Cavatak. In line with the classic US DBF model, the principal scientist behind the project at the University, Associate Professor Darren Shafren, became the chief scientist of Viralytics in 2006 and drove the development program at Viralytics until its sale to Merck in 2018.

From 2007 through 2009, the company struggled financially, its cash reserves rarely above $2 million. The company had no institutional shareholder support and survived on share purchase plans, which allow existing shareholders to buy stock at a discount, plus a convertible note from a controversial US funding entity, La Jolla Cove Investors. Meanwhile, by 2010, the drug had not progressed beyond a series of Phase I studies in Australia.

One of the key challenges for Viralytics was that oncolytic virotherapy – the idea of using a virus to treat cancer – was a novel idea that had yet to be adopted by Big Pharma, so there was not much interest in licensing such a drug. Because Cavatak was a biologic drug, the 2010 BPCI Act gave it Red Queen patent immunity, making it potentially more attractive to partners. However, the real breakthrough was in 2011, when a US oncolytic virotherapy DDB, called Biovex, was acquired by the big biotech firm, Amgen, for around US$1 billion. Suddenly Big Pharma started to take notice of oncolytic virotherapy and Viralytics had found a 'market' for its program.

Moreover, Shafren believed that Cavatak was at least as good as the Biovex program. In 2011, the board undertook a strategic review and developed a plan to drive Cavatak into Phase 2 studies, with the clear goal of finding a pharmaceutical partner to acquire it. The idea was that Cavatak would emerge from a successful Phase 2 study just around the time that Big Pharma's interest in oncolytic virotherapy was peaking. In 2012, to support this plan, the board also hired a new CEO, Dr Malcolm McColl, who was the former head of business development at Starpharma and whose core expertise was licensing. On the back of the Biovex deal and on the back of a surge in US biotech investor sentiment in early 2014, Viralytics was able to raise $27 million in US funding – more than enough to complete the Phase 2 study, with an initial focus on melanoma.

Fortunately, the plan worked. The Phase 2 melanoma study yielded positive results and key opinion leaders (KOLs) started to endorse Cavatak. McColl and Shafren embarked on a partnering program to find a pharmaceutical partner for the drug and in 2018, they succeeded, with Merck paying around $500 million for the company. During its 12 years of ASX life, Viralytics generated VCR of $357 million and an IRR of 7.2%. However, if the IRR were calculated from the time McColl joined the firm in 2012, it was 30.6%, a level of investor return that is unequivocally attractive and globally competitive.

One of the reasons for Viralytics' success was possibly that the firm never had any illusions about becoming a 'commercial' business. Instead, it had a clear understanding of its role as an intermediary in the pharmaceutical drug development process and a mission to find a pharmaceutical partner – preferably one that would acquire it.

It was also fortunate to have the market evolve in a timely fashion, such that the acquisition could occur. If the Biovex acquisition had not happened in 2011, Viralytics may have ended up as another shell on the Australian DDB scrapheap. But good firms also make their own luck; the shift in pharmaceutical interest towards oncolytic virotherapy was not just a product of the Biovex deal, but also years of hard work by Shafren attending countless international cancer conferences to recruit KOLs, build the research credentials of Cavatak and gain the attention of pharmaceutical R&D personnel, the ultimate gatekeepers to a pharmaceutical deal. Doubtless, there are other reasons that could be distilled from the Viralytics experience but, like Clinuvel, such an analysis requires a detailed case study that is beyond the scope of this research.

10.2. **Validation of VCR as a performance measure**

Under the investor captaincy paradigm, the IRR of a DDB firm is the ultimate measure of its performance. However, IRR is a long-term, single-endpoint measure, which is not practical for regular or ongoing measurement of firm performance. Based on the general model previously proposed in Figure 6 in section 7.8 and the foregoing analysis, it is proposed that VCR may be a useful annual measure of firm performance, which is easier for management, boards and investors to operationalise than IRR.

However, one needs to establish that VCR is a valid surrogate of IRR. First, as previously discussed (section 7.8), to conceptually align the two measures, VCR needs to be determined on an annual basis, since IRR is a compound annual measure. Second, VCR is largely unaffected by dilution, while IRR is significantly affected by dilution. Therefore, dilution needs to be incorporated as an explanatory variable and needs to be calculated on an annualised basis to align with IRR.

I conducted a multiple regression analysis of the data for all 40 DDB firms, using IRR as the outcome variable and VCR per year (VCRPY) and dilution per year (DILPY) as the predictor variables. DILPY was measured as the average annual growth in SI (shares issued). Technically, I should have used the compounded annual growth in the volume-weighted SI rather than a simple average, but the calculation was complex and the average growth was deemed to represent an acceptable approximation for the analysis. The analysis revealed a high correlation between VCR and IRR (r = 0.63), with VCRPY explaining 39% of the variance in IRR (R^2) and with a highly significant P-value. By adding DILPY to the regression, the explanatory power was enhanced, with the two variables accounting for 51% (adjusted R^2) of the variance in IRR, as shown in Table 34.

Table 34. Multiple regression of IRR on VCRPY and DILPY

Regression Statistics	
R^2	0.534
Adjusted R^2	0.508

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	-0.100	0.022	-4.501	0.000065
DILPY	-0.028	0.008	-3.330	0.001975
VCRPY	0.006	0.001	5.810	0.000001

As predicted, the VCRPY regression coefficient was positive and the DILPY coefficient was negative. The small size of the coefficients is reflective of the small relative value of the outcome variable. Both predictor variables displayed a highly significant relationship with IRR, based on the P-values.

In conclusion, VCR appears to have validity as a measure of public DDB firm performance that is investor-relevant (i.e., related to IRR). VCR is highly-correlated with and predictive of long-term IRR. If dilution per year is added as a variable, the predictive power is improved, adding support for the validity of the general model in Figure 6.

VCR embeds managerially-important performance variables. First, it embeds the growth in the perceived pipeline value (PV), which reflects clinical progress and the efficacy of management's narratives about that progress. It also embeds the cost to achieve that PV growth, in the form of BR, which embeds RDE. PV growth is a positive development, but achieving it while keeping cash burn under control indicates positive management performance. One important way to keep BR low and maximise VCR is to generate non-dilutive revenues, such as grants and licensing revenues, rather than issuing new shares. In this way, VCR also embeds partnering performance and pursuit of grant income. In summary, VCR offers boards, management and investors of DDBs a useful performance metric that is a surrogate of IRR, but can be measured in the short-term (e.g., annually), whereas IRR has to be calculated over several years.

Chapter 11. Limitations, implications and conclusions

11.1. Limitations

11.1.1. Concepts and constructs

The rationale for restricting the analysis to only those biotech firms involved in drug development has been extensively elaborated in Chapter 5. Further, because there are no commercial-stage firms (DDCs) in Australia born from DDBs, the restriction to pre-commercial firms was not limiting.

IRR is a well-established metric for measuring investor performance of individual firms and portfolios of firms, and is widely used by venture capitalists as a primary performance metric. I have proposed an additional metric, VCR, which I have sought to operationalise in this research and validate against IRR. Based on its relationship with IRR, there seems to be a basis for its validity and utility as an annual measure of firm performance; however, its managerial utility has yet to be tested.

A clear limitation of the VCR concept, along with its subordinate construct, PV, is that it is not an objective measure, but a measure of value as perceived by investors. It is unlikely that investors would quantitatively measure the rNPV of a firm's pipeline in forming their perception of PV, although some may be guided by rNPV analyses in research reports, which are available for most DDBs. Therefore, the perception may not represent a valid measure of the 'true' value of a firm's pipeline. Further, that perception – to the extent that it does constitute a value assessment of a firm's pipeline – may be influenced by many factors, notably the narratives from CEOs about pipeline progress and their perceived credibility (Andersson et al., 2010; Birch, 2016).

A further limitation of the PV/VCR concept is that is not restricted to the value of candidate drugs in the firm's drug development pipeline. As noted in Chapter 7, PV embeds all the aspirations of investors for the realisation of future value by the firm. While the principal way for DDBs to grow their PV is to advance candidate drugs from one phase of drug development to the next, PV is not restricted to clinical trial progress. The aspirational value of future monetary gain for investors could be increased by the firm's receiving royalty revenues or other cash flows unrelated to its drug development technology. This was the case with Arana, for example. However, I believe that this type of PV growth, while not as sustainable or of the same value potential necessarily as candidate drug progress towards a pharmaceutical deal, is a legitimate endeavour and a way to build short-term value for DDBs.

An overarching factor and one that perhaps moderates the extent to which DDB narratives translate into PV growth, is the overall market sentiment towards biotech and drug development. This may be affected by trends in the broader stock market in Australia and very likely, it would be affected by the performance of high-profile firms in the sector. In the latter regard, this research suggests that the

perceived value of the whole sector may have been tainted by the unrelenting procession of high-profile failures after 2012. As a result, the PVs of other DDB firms may have been negatively affected at the time of their terminal assessment. However, by the same reasoning, those firms that still existed in 2018 would have been positively affected by the sector's revival in that year. Going forward, it is possible that the successful sale of Viralytics and the ongoing success of Clinuvel could improve overall sentiment; this might bolster the valuations of other DDB firms that offer persuasive narratives for investors, thereby improving overall sector VCR in the short-term. Because of the relationship between PVG and IRR, if VCR improves, then so would IRR to some extent, although the long history of dilution for most companies could continue to suppress their IRRs.

Perhaps an argument exists for looking at the sector, from 2015 onwards, after the 2014 'train-wreck'. To explore this, I assessed the IRR results for the three-year period to 2018, using 2015 as a baseline; this left 26 surviving firms for analysis. The portfolio IRR on these survivors increased significantly to +9.8% and individual firms performed much better, with IRRs as follows: Clinuvel (85%), Viralytics (38%) and Starpharma (23%). However, the IRRs for Acrux and Mesoblast both turned negative, due to weaker performances in recent years. It also helped several smaller firms with previously negative IRRs, turn into positive IRRs, notably Imugene, Biotron, Patrys, Invion, Regeneus and Phylogica. By starting at 2015, the surviving firms were able to discard their earlier history of dilutive fundraisings and have their IRRs assessed on their current value growth; given the greater maturity of the surviving firms, this growth was achieved without the massive dilution of their earlier lives. Overall, however, there were 16 DDBs (62% of the firms) that still produced negative IRRs.

Clearly, there is a survivor bias problem with such an analysis, which eliminates all of the failed firms that exited the sector prior to 2015. Regardless, it may point to an improvement in investor sentiment, which could help achieve a brighter future for the sector. On the other hand, the exercise also smacks of a fishing expedition for a specific timeframe that finally makes the sector performance look acceptable, after many years of failure. Unequivocally and for many years, the returns from the public DDB sector have been disastrous. With Viralytics gone and possibly quickly forgotten in 2019, and if Clinuvel is also sold and/or if US biotech sentiment wanes – as it has several times in the past – then the improving DDB sentiment and sector performance could prove to be short-lived.

11.1.2. Methodology

There are aspects of the dataset and the inclusion and exclusion criteria that could be questioned. The dataset excluded those firms that were classified as medical devices, even if their application was therapeutic. A notable exclusion was Sirtex, which is discussed in more detail below.

I excluded several other firms for other reasons, as outlined in section 8.1, including 12 DDB firms that listed in the last five years. However, based on Table 25, none of these has been so successful during the period that their inclusion would have changed the results in any material way. In the same vein, the requirement that firms be listed for at least five years during the 15-year period was arbitrary, but reasonably based. Apart from the 12 new DDBs, the others excluded because of the five-year rule were Zenyth, Meditech, Australian Vaccine Technology and Evogenix. Again, none of these would be considered a success or would have changed the overall results.

There are aspects of the data handling that could be questioned, including (a) the timing of 'exit' events for calculation of metrics, (b) the differences in timing and calculations for MV, C and BR calculations and (c) the fact that monthly MVs were based on the end-of-month closing share price, not a monthly average. Each of these is addressed below.

For those six firms that were acquired, the exit timing was not problematic. In addition, one firm, Biodiem, voluntarily delisted to become a private firm, so the exit timing (delisting) in that case was reasonably clear. It becomes more questionable in relation to the eight firms that exited for other reasons (refer Table 19. Summary of exits in the DDB dataset). For these firms, specific decisions were made about the exit date, as described in Chapter 8, usually around the date of the announcement that the firm was moving into another field (Progen, Avexa, Metabolic, Select Vaccines and Solbec). In all cases, the firm had effectively shut down their DDB operations and the announcement about exiting came later. In a variant of this, Bone Medical effectively stopped all drug development during 2011 and did not announce an exit to another field (initially by acquiring a geospatial technology) until 2015. However, I deemed the firm to have exited in 2013, when it undertook a massive recapitalisation and diluted out all previous shareholders.

Arguably, all these firms could have been considered to have exited as DDBs, when they shut down their drug development, rather than when the exit announcement actually occurred, or the recapitalisation, in the case of Bone Medical. While this would not have appreciably changed the VCR calculation, it may have improved the IRR slightly by reducing the number of years over which the IRR was calculated. However, because all these firms generated such negative IRRs (and VCRs), it would have had a negligible effect on the individual firm and overall sector results.

The second issue relates to the timing differences between the calculations of MV, C and BR. MV was based on a volume-weighted average (VWA) over the six months after June 30 each year, while C (cash reserves) was calculated as a single value at June 30 of the same year and BR was the operating cash burn over the year ending June 30 each year. The rationale for the timings is detailed in the Chapter 8.

The rationale for using the cash figure from the June 30 annual report was that this is the figure at the forefront of the minds of investors as they reviewed the annual performance of the firm's performance in the lead-up to the annual general meeting of shareholders, where the CEO and chairman explained the firm's performance and prospects to shareholders. Arguably, the cash reserves (C) could have been determined as an average over the full year, rather than at a single date. This could have been done by collecting the quarterly cash data for each firm (for those firms that reported quarterly) and determining a simple average of the four quarters. This may have changed some of the PV calculations slightly for some firms in specific years, but given there was not a large year-to-year variation in overall cash levels for the sector, it would have had negligible impact on individual firm or sector performance.

MV was calculated as a VWA of the MV over the six-months from July to December each year, with a few exceptions for exits, as noted in Chapter 8. This could have been handled differently; for example, the MV could have been calculated as the VWA over a shorter period, such as September to November (three months), which would more closely reflect the period over which investors are exposed to – and likely to react to – the annual report and the annual shareholders' meeting.

This may have affected the terminal MVs for some firms, due to specific events or SP movements during the last six months of 2018. To assess this, I redid the calculation of MV for all firms in 2018 based on September-November, rather than July-December. For most firms it had little impact, affecting the terminal MV by less than ± 5% and had no measurable impact on IRRs, especially those firms with negative IRRs. Where the impact was greater than 5%, the majority of firms' MVs were negatively impacted (reduced). However, in a few cases of firms with positive IRRs, the impact was positive. For example, Mesoblast's IRR was slightly improved from 4.0% to 4.3%, Starpharma's IRR increased from 6.2% to 7.0% and Clinuvel's IRR performance increased from 7.2% to 7.9%. However, the improvement in the case of Mesoblast was because its SP declined late in the year following a clinical trial failure and the recalculation de-emphasised that event. If the December MV alone had been used for Mesoblast's IRR calculation, the final IRR result would have been only 1.1%. Similarly, Starpharma saw a significant fall in its SP in December; if that month had been used for its IRR calculation, its IRR would have been reduced to 5.2%. In summary, because of the month-to-month variation in share prices (and MV), the six-month VWA assessment for MV is appropriate.

Finally, a clear, but not significant limitation of the data was that monthly MVs were based on the end-of-month closing SP, not a volume-weighted monthly average SP. This could not be avoided using *DatAnalysis* as the data source, but as noted in Chapter 8, using the end-of-month MV was unlikely to significantly distort the results, especially when the MV was calculated over six months.

11.1.3. Time period

The 15-year period from 2003 to 2018 was selected to provide a long enough period of time for drug development programs to reach their full potential. The rational for using 2003 as a baseline is elaborated in Chapter 8, notably that many new firms were born after 2003 and that 2002 was a recessionary year in the sector, the inclusion of which could have biased results to the positive.

An argument may exist for shifting the baseline from 2003 to 2002, on the basis that 2003 was a bullish year in the sector and as a baseline, may have negatively biased results. To test this, I created a new dataset, using 2002 as a baseline, instead of 2003. To avoid significant additional data collection, I limited the dataset to the 40 firms and focused only on IRR, at both a portfolio level and individual firm level. At the end of the 16-year period, the $40,000 portfolio was worth $32,559 including dividends; this representing a principal loss of 18.6%. The overall portfolio IRR was 'improved' to -1.9% (from -6.2%), indicating that – as expected – using 2002 as a baseline helped the results. An alternative interpretation is that even including this positive bias, the portfolio returns were still negative.

As discussed in Chapter 10, the GFC may have been an inflexion point in investor sentiment and memory. Therefore, an argument exists for setting the baseline at 2009, immediately after the GFC. To explore this, I re-assessed the performance of the DDB sector, using 2009 as a baseline, instead of 2003. This removed five firms from the analysis: Solbec, Peplin, Cytopia, Metabolic and Arana. The sector VCR and portfolio IRR were then calculated using the surviving 35 firms. At the end of 2018, the total investment of $35,000 was worth $27,213 including dividends. This represented a principal loss of 22% over eight years and an IRR of -3.2%. The VCR from 2010 to 2018 was -$583 million, an improvement over -$1,266 million for the whole 15-year period, but it was based on fewer participating years and fewer firms. In summary, the overall negative performance of the sector was not significantly improved by changing the baseline to 2009. However, changing the baseline to 2009 did push Clinuvel's IRR up to 22% and Viralytics' IRR up to 19%, amplifying their successes.

11.1.4. Portfolio IRR

In relation to the method of calculating the portfolio returns, I used a simple approach whereby a naive investor placed $1,000 'bets' on each of the 40 firms, regardless of the firm's value at the time. I outline the rationale for this the methodology chapter (Chapter 8) and argue that the approach mimics a VC portfolio investment approach.

I also argue against a value-weighted investment approach on conceptual grounds. Further, because two of the three largest firms at the start of the period – Kazia and Metabolic – destroyed so much value, a value-weighted portfolio approach anchored in 2003 seemed unlikely to generate better results.

Regardless, in order to explore this question, I re-calculated the portfolio IRR with individual firm holdings in the portfolio based on the share price (SP); in all cases, the SP had been adjusted for any reverse-splits. Using this method, firms with higher SPs in their baseline year represented a greater share of the overall portfolio. The share prices in 2003 ranged from $0.14 (Solbec) to $5.77 (Kazia). This SP-weighted portfolio approach offered a simple value-weighting model that avoided the complexities and extensive calculations needed to allocate the portfolio based on a fixed percentage of MV. The results were not substantially different to the $1,000 bet approach. The portfolio IRR was -5.9% compared with -6.2% for the approach used in the research.

11.1.5. Dataset exclusions

Medical devices

The current research is focused on drug development biotech firms. Drug development is the dominant form and paragon of biotech industrialisation in the US, and the DDB is the most common type of biotech firm in Australia, so the focus is legitimate. However, despite its prominence, perhaps drug development is not the best exemplar of biotech industrialisation in Australia.

Australia has a reputation for producing successful medical device firms. Resmed developed the CPAP device for treating sleep apnoea and Cochlear pioneered the bionic ear. The two companies have been unequivocally successful on the global stage, now with a combined market capitalisation of greater than $30 billion. According to a recent Austrade report (Austrade, 2016), Australia's medical devices industry employs over 19,000 people, generates around $12 billion in annual revenue and contributes to annual exports of greater than $2 billion.

In contrast, the market capitalisation (MV) of the DDB sector in 2018 was only $4.5 billion (including the 12 new entrants since 2015). Further, assuming an average of 50 people employed by each DDB firm – likely a high estimate – the 40 DDBs in the current dataset employ no more than 2,000 people, and in 2018, generated total revenues under $100 million. Perhaps Australia is simply better at developing and commercialising medical devices than drugs; viewed another way, perhaps the cost and risk profile of medical devices is better suited to the Australian funding environment.

The 'Medical devices' category embraces a wide array of products, with the boundaries defined by their regulatory treatment. Medical devices include everything from tongue depressors to complex equipment, such as CAT scanners and X-ray machines (Shimasaki, 2014a). Compared with drugs, medical devices have a much lower time, cost and risk of development. According to Shimasaki (2014a), medical devices cost $15 to $100 million to develop, compared with drugs at $250 million to $1.5 billion. The time to market for medical devices is 3-5 years, compared with 12-15 years for drugs. The development risks for devices are also much lower, with a greatly reduced clinical trial burden and reduced regulatory hurdles.

While the commercial payoff for medical devices may be lower than drugs, they may represent a more realistic field for Australian R&D endeavour than drugs, especially in a country with low levels of high-risk capital and impatient and risk-intolerant investors. A blockbuster drug may deliver a massive payoff to a DDB firm, but Australia may simply never be able to afford the *ante* – both financially and technologically – to seriously play in that game, instead failing in the attempt or forced to be content with niche opportunities. This view is not proposed as a conclusion of the current research, but merely informed speculation at this stage, which may form the basis for some future research.

Sirtex

As noted in Chapter 8, the 40-firm DDB dataset excluded Sirtex, because its therapeutic product was classified as a medical device. Sirtex started in 1997 with technology from a cancer research institute affiliated with the University of Western Australia. The technology was called SIR-Spheres – tiny, radioactive microspheres that could be injected into the liver to treat liver cancer. It listed on the ASX in 2000. The technique was shown to work in clinical trials and due to the faster regulatory pathway for medical devices, by 2003, Sirtex was generating $10 million in sales per annum. By 2018, sales had grown to more than $200 million per annum; in the same year, Sirtex was acquired by a Chinese pharmaceutical firm for $1.9 billion. If an investor had put money into Sirtex in 2003, instead of DDBs, and then sold in 2018, they would have enjoyed an IRR of 15% – a better outcome than any DDB.

Sirtex is not only a financial success story. It is the story of Australian technology delivering a genuine breakthrough in the treatment of cancer. Fortuitously, its product was classified as a medical device and not a drug, even though its use was solely therapeutic. However, the fact is that even if Sirtex had been included in the dataset, the portfolio IRR still would have been negative. However, perhaps the Sirtex experience adds weight to the argument that Australia performs well in medical devices, but not so in drugs.

Private DDB firms

A clear limitation of the research is that the dataset was limited to ASX-listed firms and excluded private firms. Hodgson (2006, p. 635) states that "The performance of publicly quoted companies is a rough proxy for the current status of a given country's biotech sector" and the Swinburne DBF Dataset supports the view that the ASX-listed firms represent the majority of the DDB sector value and employment. However, there is also evidence that VCs have cherry-picked many of the better projects for development as private firms that then end up in trade sales, not on the ASX. This may be an Australian-specific issue that limits the number and quality of ASX-listed DDBs. On the other hand, many of the recent ASX DDB listings are based on foreign-born, not Australian-born technologies.

PRO partnering

The research excludes drug development by Australian PROs that was not spun out into a new private or public firm, but directly partnered to a foreign pharmaceutical company. The most prominent example of this is the cancer drug, venetoclax, a leukaemia drug that targets a cancer-survival protein called BCL-2. The original discovery of BCL-2 and its role in cancer cell survival was made at the Walter and Eliza Hall Institute (WEHI) in Melbourne, from 1988 through 2005 (https://social.shorthand.com/WEHI_research/nge4mUouhGc/venetoclax). In 2006, WEHI also discovered a series of compounds that would block BCL-2 and filed a patent, which was licensed to the US big biotech firm, Genentech, giving WEHI a claim on future royalties. In 2007, the US Big Pharma, AbbVie, joined the collaboration with Genentech.

All preclinical and clinical drug development and registration was funded and conducted by Genentech and AbbVie. In 2017, after the US approval of venetoclax, WEHI announced the sale of its royalty rights on the drug for US$325 million, delivering a large payday for the WEHI, with the funds slated to be invested in more research and various projects at WEHI.

Recently, venetoclax was approved for marketing in Australia and on February 23, 2019, the Australian Health Minister announced the listing of venetoclax on the Pharmaceutical Benefits Scheme (PBS), reportedly saving patients around $250,000 in cost per treatment. On this basis (and without knowing the actual reimbursed price that the Australian government negotiated with Genentech/Roche), if 2,000 patients were treated with the drug over the next decade, then the royalty payment to WEHI would just cover the taxpayer cost of the subsidised supply of the drug.

The minister's announcement (https://twitter.com/GregHuntMP/status/1099466111655895041) also described venetoclax as "Australian discovered and developed". Clearly, it was not 'developed' in Australia, with the message apparently designed to reinforce the belief that Australia is a world-leading drug innovator.

In partnering directly with Big Pharma, WEHI had arguably deprived Australian DDB firms of the opportunity to participate in the value creation that would have accrued from further development of the drug prior to partnering. Potentially also, WEHI's and Australia's share of the value chain would have been dramatically improved by doing so. Given the likely commercial value of venetoclax, had the technology stayed in Australia and been developed through to Phase 2, the potential share of the value chain captured in Australia could have been 10 or 20 times the royalties pocketed by WEHI. Moreover, a partnership could have been negotiated that would have seen Australia receive a greatly-reduced price for the drug – a great social payback for the country – instead of burdening Australian taxpayers with a hefty PBS-subsidised cost. Finally, it may have created an Australian big biotech and allowed Australian politicians to honestly boast about Australian drug development prowess.

11.1.6. Other limitations

Investor relay

The analysis of firm performance over a 15-year period does not reflect the real world, where people do not hold stocks for 15 years, but sell in and out of stocks at will. Day traders are common in speculative ASX biotech stocks, as they are in mining stocks. However, other investors can also have a short-term perspective on their investment. Someone who bought Biota at 35 cents in 2002 and sold at $1.80 in 2005 was extremely satisfied with their investment return. Investors since 2015, especially in Clinuvel and Viralytics, will have enjoyed a handsome return, probably because they were not the same investors who invested when the firms first listed on the ASX, many years earlier.

Sentiment is capricious, personal and potentially short-lived. However, given the negative long-term results, it would have been extremely difficult for any investor – even the most nimble and well-informed – not to have had some memorably negative experiences from investments in Australian DDBs over the last decade or more. However, as indicated by the post-2015 analysis, perhaps things are turning around for the sector.

Australia only

Clearly, one limitation is that the study results and conclusions apply to Australia only. Australia may present unique challenges for biotech firms and the results and conclusions may not be generalisable to other countries. It would be valuable to conduct a similar study, focused on DDBs, in the UK, Germany and Canada, which have all found it difficult to replicate the US experience and build a robust drug development biotech sector (Hopkins et al., 2013; Momma and Sharp, 1999; Moustakbal, 2014; Smith et al., 2009). Sadly, one answer may be that drug development is best left to the US DDBs and big biotech firms; they have bottomless VC funding, a $30+ billion NIH budget, deep-pocketed pharmaceutical firms in their backyard and so much more going for them – not to mention an unassailable head-start. It is possible that Australia, like Canada and Europe, could never hope to be competitive.

Investor captaincy

A limitation of the study is that its concepts, constructs and central ideas are all squarely based on the notion that the investor perspective is paramount. I have argued for this perspective, because without investors, DDBs will never get started and never be able to build value and deliver high investor returns. This contrasts with commercial-stage biotech firms that may be self-funded from profits and thereby, have the option of prioritising stakeholders other than their investors. For such firms, maximising shareholder value (MSV) may only be one of several perspectives for the firm to consider, including a societal responsibility to develop life-saving cures for diseases, a responsibility to build sustainable employment and a public responsibility to return value to the taxpayers and the

governments that funded their genesis and early development (Lazonick, 2014, 2018; Lazonick and Tulum, 2011).

The societal responsibility and the obligation to 'give back' for all the direct government funding to DDB firms – such as R&D tax credits and grants – are entirely valid perspectives for governments and taxpayers to use in assessing the overall performance, value and contribution of the sector to Australia. Further, there is little doubt that the potential to create a life-saving treatment or cure for a disease is in the minds of DDB boards, employees and CEOs, and that it represents an important attraction to working in the sector. The need to give back to society and see Australian innovations turned into real benefits for all Australians must also be a consideration and an underlying driver for people working in the sector.

However, for the CEO of a loss-making DDB firm that can only continue the firm's operations and have any chance of staying ahead of the Red Queen if it is able to raise another round of investor funds, the most pressing consideration must be the perspective of investors. Accordingly, the performance of the board and CEO of that DDB firm is almost always framed by sector analysts, commentators and other CEOs, in terms of success in fundraising and achieving share price growth.

11.2. **Implications for theory, policy and practice**

11.2.1. Theory implications

The PCI paradigm

One of the goals of this research was to unravel the Gordian conceptual knot that has strangled biotech firm performance and led to the generation of largely meaningless biotech 'industry' reports. This thesis achieves that goal and exposes the challenges and forces that have contributed to and perpetuated the confusion and definitional chaos. This represents a contribution of this thesis as it may lead to useful redefinition of terms such as biotechnology, biotech firm and the biotech industry.

However, a more substantial contribution to existing theory is the re-conceptualisation of biotech firms as intermediaries in an industrial value chain. This PCI (pre-commercial intermediary) view of the biotech firm – including the distinction between DBFs and DDCs and the proposed subtype classification within DBFs – offers a new basis for classifying biotech firms for research purposes. This does not, in my view, constitute new theory, but rather an important refinement of the definition of the unit of analysis, which in conjunction with the empirical results of the current research, could lead to productive new research and the potential development of new theory. It could be considered a modification and extension of current theory that offers a significant departure from current thinking that may alter scholars' extant views and may alter research practice in the field (Whetten, 1989).

New performance metrics

The PCI view also brings with it the concepts of PV and VCR, which at least for public firms, represent the first non-generic metrics for assessing the performance of DDB firms. DDB firms are pre-commercial and cannot be evaluated by standard financial metrics; for the first time, VCR provides a financial metric on which their performance can be evaluated. Potentially, VCR can also be applied to other DBFs, but that has yet to be evaluated.

Emerging from the PCI paradigm and within the framework of the DDB definition, the concept of TA is an important one. It relates to and emerges from the unique role of DDBs as intermediaries and seeks to capture all the elements that constitute the firm's foundation of technological opportunity, from which it can create investor-relevant value. Related to this is the proposed PVG/RDE metric, which seeks to represent the investor-relevant output from R&D expenditure, which is moderated by management.

Research opportunities

Virtually all of the 'biotech' datasets used for biotech firm and industry research have co-mingled commercial and pre-commercial firms. By separating out the pre-commercial firms and further classifying by DBF sub-type – perhaps focusing on DDBs – much of the DBF research could be revisited.

A study similar to the current one could be conducted on public biotech firms in Canada, UK and other countries. As already noted, there is evidence that these and other countries may suffer from similar challenges to Australia in building a viable DDB sector. It would be interesting and valuable to assess that idea using the constructs and concepts developed in this thesis. It would also be interesting and valuable to conduct the same exercise in the US.

From the Australian perspective, it would be insightful to conduct a case study research project on Viralytics and Clinuvel to better understand what may have been the critical success factors for these firms. This could be helpful to other DDBs, both private and public, and possibly contribute to sector policy.

Given that there have been signs of improvement since 2015, it would be useful to extend the current performance analysis to 2019 and beyond, using 2015 as a base. This may deliver a much more positive performance assessment and sector prognosis.

Further, from an Australian perspective, it would be interesting and valuable to replicate the current study in the medical devices sector. Is Australia simply better at medical devices? Do medical devices represent a more productive focus for Australian research rather than drug development?

It would be interesting and valuable to elaborate and test a theoretical model of the drivers of value creation for DDB firms. This is beyond the scope of the current research, but the model in Figure 6, which primarily seeks to elaborate the complex relationship between VCR and IRR, may provide a useful starting point for development of such a theory of the drivers of value creation. As suggested by the analysis of some of the individual firm performances in this study, such a model would need to incorporate 'management' as a predictor variable; however, that variable needs to be conceptualised and specified. The number and value of pharmaceutical license agreements may be another important variable and predictor of IRR and VCR. In Australia's case, the 'tyranny of distance' may be another variable that needs to be defined and incorporated.

11.2.2. Policy implications

The illusory vision of biotech policy

One way or another, building a successful and sustainable bioeconomy has been at the core of most state or federal government biotechnology policy in Australia, over the last two decades. This research, however, suggests that those policies have not succeeded, at least with respect to pharmaceutical drug development – the gold standard of biotechnology industrialisation.

However, attempting to build a bioeconomy based on DDBs may be a frustrated ambition in any case, because DDBs are by their nature ephemeral: Viralytics is now gone; Clinuvel and any other successful firms may follow; Fibrotech, Spinifex and Hatchtech were sold off before they had a chance to contribute to the bioeconomy, at least as public firms. Sustainable innovation is a real challenge when early investor value extraction is the driver.

Implied in most biotech sector policy, in Australia and elsewhere, is the desire to create a biotech sector similar to the US, where a growing number of big biotech firms act as anchor tenants and provide a model for younger firms to emulate and a source of expertise and partnerships for younger firms. While some of these US big biotechs disappear in acquisitions by Big Pharma, there are others waiting in the wings to fill their shoes. Moreover, the sale of big biotech firms, such as Genentech and Alexion, spin out new firms, as scientists and entrepreneurs are released to explore new ideas for value creation. Australia is a long way from that scenario and it seems unlikely that it will ever build anything approaching it, given the experience of the last 15 years.

An optimist might say that with the turn-around in Australia's DDB sector since 2015 and the vibrancy of the US biotech sector in recent times, the Australian DDB sector may be on the cusp of finally creating the long-awaited, virtuous cycle that spins out a couple of big biotech anchor tenants and leads to a sustainable sector. It is a possibility, but frankly, it seems a remote one at this point. Potentially and hopefully, some of the conclusions, ideas and observations in the current research may help avert future failures and the optimistic view will be proven prophetic.

On the other hand, it may be that the US is a unique setting, inimitably bringing together massive forces with such energy that critical mass is achieved and DDBs are spun out with the realistic ambition of becoming billion-dollar big biotechs. These forces include the world's most lucrative pharmaceutical market, the presence of the world's largest pharmaceutical companies, a massive NIH research and grants budget, research institutions of unparalleled capability and an unfettered entrepreneurial culture that bridges academia and the private sector. Combine these forces with the fuel provided by the largest venture capital funds in the world and critical mass is achieved. It is difficult to imagine that Australia could ever generate the TA mass or quality to compensate for the

lack of the other elements needed to reach critical mass. The same problem may apply in the UK, Germany and other countries.

The public cost

In the meantime, based on the total annual RDE expenditure of the firms in the dataset of this research – around $230 million p.a. – the Australian government is providing up to $100 million a year in public funds to the DDB sector through the R&D tax credit system alone. On top of this, firms can receive Australian government grant funding through the Accelerating Commercialisation program.

The R&D tax rebate system was only introduced in 2011, so it is not valid to apply the tax credit rate (43.5%) to all RDE across the 15 years of the current research. However, prior to 2011, there were more generous grant schemes in place and a less-generous R&D tax concession system. Therefore, for the purposes of roughly estimating the public investment in the sector over the 15-year period, it seemed reasonable to apply the 43.5% rate on all RDE over the 15 years. On this basis, the public contribution to the sector was around $1.25 billion. Add this to the negative VCR of $1.27 billion and the sector actually destroyed $2.5 billion in private and public funds, with half of the value destruction absorbed by taxpayers. Regardless of the actual figure, it seems clear that the public investment in the sector has been substantial, and to date, it has not helped create a successful and sustainable DDB sector.

This is not to suggest that the system should be scrapped. The axing of the Commercial Ready scheme in 2008 was seen as a body-blow to the sector; and indeed, it may have contributed to the depressed sector results after 2009, although this is speculative. Regardless, it was replaced by the R&D tax rebate scheme in 2011, which has been described by AusBiotech as a "game-changer" for Australian biotech[13]. If the sector is to have any chance of building on its current positive trend, the tax rebate needs to stay in place to give it a chance.

Australian content

The other significant policy implication relates to the translation of Australian research. Biotech academics and policy-makers generally think of the success of local biotech firms – in this case DDBs – as a reflection of the quality of scientific output by local PROs. However, as is clearly the case with Australia's most successful DDB, Clinuvel, and many of the more recent listings in the DDB sector, the technology came from overseas, not Australia. The resurrections of Actinogen, Patrys, Avexa, Invion and Imugene were all based on acquisition of foreign technology. Of the 12 ASX listings of DDBs since 2015, at least four were based on foreign technology. Two others were drug repurposing stories that only had a shallow foothold in Australian research.

[13]https://www.ausbiotech.org/policy-advocacy/about-the-policy

The sourcing of foreign technologies to package into ASX-listed shells or to list on the ASX as a *de novo* IPO has become increasingly common in recent years. This fact should lead to some rethinking about how to measure the productive translation of scientific output from local PROs. It may also bring into question the quality of Australian research output as a basis for drug development, given the paucity of real Australian research breakthroughs forming the basis for new firms. Of course, one notable exception is Viralytics.

Finally, it should cause the Australian Government to question its investment in ASX firms through R&D tax credits and grants, in those cases where the listed firm is merely a vehicle for funding of foreign technology. Perhaps the tax credits and grants should only be available to DDBs that are employing core technology that is the product of Australian research.

Fostering sustainable success and Australian value capture

Another policy consideration relates to private firms and technologies that never reach ASX listing. If it is the case that VCs cherry-pick the best firms, develop them for a number of years and then 'flip' them in a trade sale, it really only benefits the VC fund managers and the small number of high net worth individuals who invest in the VC funds. There are few, if any, enduring social, financial, employment or other benefits for Australia. Meanwhile, the VC fund managers and investors would have benefited from the R&D tax credits and grants received by the firms prior to their sale. Perhaps there is an opportunity for policy changes to encourage the longer-term growth and further development of these firms, rather than simply seeing them sold off at the earliest opportunity to overseas buyers. However, specific policy proposals are beyond the scope of the current research.

As suggested by the venetoclax example, it would be helpful for future policies to ensure that Australian PROs are dissuaded from directly partnering drug discovery breakthroughs. Given the cost of new drugs to taxpayers, the Australian government has a substantial incentive to ensure that Australian drug discovery breakthroughs are developed in Australia through to Phase 2, before partnering, rather than sold off at the earliest opportunity, leaving Australian taxpayers to pick up the bill later.

ASX policy changes might help to better curate the quality of firms listing on the ASX and avoid the subsequent dilution problems that create the vicious cycle of negative investor returns. As already suggested, Australian investors might be better served by the ASX's demanding that the funds raised at listing are credibly sufficient to support the firm's projected cash needs through to a partnering milestone. This would largely avoid the dilution problem and force prospective public firms to focus on partnering and more carefully map out their value creation pathway.

Reporting and performance monitoring

At the very least, I would recommend that the Australian government adopts the classification concepts proposed in this thesis when reporting on the metrics of the biotech sector, such as employment and market value. Ideally, I would also recommend that the metrics proposed in this thesis – VCR and IRR – also be used in reporting the performance of the public DDB sector (and other public DBF sectors, such as medical devices).

Above all, I would strongly recommend that governments, Ausbiotech and consulting firms that report or comment on the Australian biotech sector, stop including CSL in the Australian biotech figures. CSL is a 100-year-old pharmaceutical manufacturer that did not evolve from a DDB or any other biotech firm. It is not a biotech firm, except in the most lax and negligent application of the term. Its inclusion serves no legitimate purpose, other than to inflate the reported performance of the Australian biotech sector and occlude the real performance and the real issues that need to be addressed.

11.2.3. Management implications

VCR as a performance metric

Dilution has a significant effect on IRR, but whether dilution occurs is a board-level decision, generally outside the borders of management's responsibility. On the other hand, VCR can be viewed as a product of management's interface with the firm's TA. The value and utility of VCR is that it measures the productive translation of RDE and TA into investor-relevant value outputs. Therefore, it has potential for use by boards of public DDBs as an annual measure of management performance. Based on published salary surveys, a majority of the CEOs of ASX-listed biotech firms receive part of their compensation in the form of an annual incentive or bonus that is tied to performance against KPIs (key performance indicators). ASX guidelines and corporate governance practice preclude using share price *per se* as a KPI, even though IRR is the ultimate measure of performance for DDBs. VCR presents an alternative potential KPI that embeds share price growth as a result of efficient and effective R&D management and the delivery of value-accreting development milestones.

In the same vein, the subsidiary metric of PVG/RDE could be used, not only to measure the effectiveness of the firm's R&D management of its TA, but for making strategic portfolio decisions aimed at improving the quality and mix of its TA.

11.3. **Conclusions**

This research has sought to address the question: Do Australian drug development biotech firms create value and deliver attractive investor returns? The answer is an unequivocal "no".

Over the last 15 years, the Australian public DDB sector has destroyed value and delivered extremely poor investor outcomes overall. No individual firm has delivered an attractive investor return and most firms have lost virtually all their investors' funds. Overall, the sector used ('burned') $2.9 billion in investor funds and possibly $1.2 billion in public funds. That $4.1 billion investment generated only $1.6 billion in PV growth, representing aggregate value destruction of around $2.5 billion.

There are signs that things may be improving. Since 2015, there have been two success stories and some other firms have started to deliver attractive IRRs, which may signal a better future for the sector. Over the 15-year period of the research, however, Australia failed to create a successful and sustainable drug development biotech sector, as measured by the selected cohort of ASX-listed DDB firms. Moreover, the sector failed to create a single flagship firm that could come close to being considered a 'big biotech' anchor tenant. The repeated reference to CSL as an anchor biotech tenant – at least by some consultants and Ausbiotech – is nonsensical, counter-productive and misleading. The Australian DDB sector is fundamentally small and weak. The view that Australian biotech 'punches above its weight' in drug development biotech is groundless.

Lack of funding has often been cited as a barrier to drug development success in Australia, but this research has not found a relationship between cash or RDE and value creation, although there was a significant relationship between RDE and investor returns (IRR). However, there were several cases, where firms had large cash reserves and RDE, and yet failed to create value or failed completely. It should be emphasised that these data and conclusions apply to public DDBs and it may be that a lack of VC, angel and grant funding is indeed stifling the birth and development of private DDBs.

The other often-cited reason for the lack of success in Australia is poor commercialisation skills; this was not explicitly tested in the research, but the obsession with attempting to prove 'commercial' success – by taking a drug all the way to market or generating early profits – may have actually contributed to individual firm failures. This research, with its conceptualisation of DDBs, suggests that the critical skills needed for successful management of a DDB are not 'commercial', but are effective R&D management and partnering, combined with a clear understanding of the market for DDB firms within the pharmaceutical value chain.

In that regard, a number of strategic errors have been identified as possible contributors to firm failure, including the focus on commercialisation and early profits, as well as the failure to correctly

define the market. In some cases, the root cause of failure may have been ignorance of the time-sensitivity of DDB drug development – a concept referred to as the 'Red Queen'.

The research also calls into question the role of the ASX, both as a contributing factor in DDB firm failure and its appropriation as a vehicle for funding of foreign technology, not Australian technology. The fact that Australian public funds are used to support such firms through R&D tax credits and grants should be of concern to policy-makers and Australian taxpayers.

Although the lack of venture capital may be a constraint on new firm formation and sector development – a long-held view by many in and around the sector – it appears that VCs have been active and have made judicious investments in early drug development projects that are attractive for subsequent sale to pharmaceutical partners. However, this practice does not contribute to public DDB sector development.

The research also calls into question the quality of Australian research output as a platform for drug development. The poor overall R&D productivity of the DDB firms in this study and their high rates of failure may support the view that Australian drug development technology may not be world-class. In framing expectations around biotech policy, Australian governments need to consider this possibility, rather than continue to uncritically accept the premise that Australia is a world-leader in the field and the problems are exclusively in commercialisation. Potentially, Australia has neither the funding ecosystem nor the technology quality to support a globally-competitive DDB sector that can reach the critical mass needed to spin out one or more big biotech firms, and on which a bioeconomy could be anchored.

One important conclusion of the research is that future DBF research should discriminate between DDBs and other DBFs, and exclude all commercial-stage firms from their datasets. It would be helpful if those that author the *Nature Biotechnology* and the Ernst & Young annual biotechnology industry reports, also adopted this frame in their future reporting.

The research also makes several contributions to theory, policy and practice, which have been outlined earlier in this chapter. Notably, the PCI view of the biotech firm offers an important new paradigm for thinking about the role and purpose of biotech firms. The research also presents and tests a potentially valuable tool for measuring the performance of public DDB firms, in terms that are relevant to the role and purpose of DDB firms. This measure, VCR, may represent the first useful managerial tool for short-term performance assessment of DDBs.

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APPENDIX: DATA TABLES

MV, based on VWA for July-December each year ($ millions)																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	MV Gr$
Acrux	ACR			72.3	100.9	226.3	122.0	310.1	507.6	570.2	534.4	485.2	264.4	110.6	66.0	32.2	34.4	-37.8
Actinogen	ACW						2.8	3.6	5.9	4.8	3.6	2.0	13.4	34.8	31.8	30.3	55.3	52.5
Alchemia	ACL		73.0	119.6	97.4	115.8	29.3	87.6	107.0	82.5	137.1	175.9	73.8	25.9	2.9	3.1	4.0	-69.0
Amplia	ATX											32.6	33.8	31.3	151.1	10.0	11.8	11.8
Antisense	ANP	30.7	42.6	16.6	19.0	22.2	33.9	33.5	6.9	21.7	21.3	22.9	17.2	15.1	7.4	5.3	14.5	-16.2
Arana	AAH	234.7	291.2	215.6	270.1	253.0	249.6	321.4										86.7
Avexa	AVX			32.8	111.6	237.4	55.7	109.5	35.2	32.8	19.9	12.1	15.9	8.1				-32.8
Benitec	BLT	73.6	53.1	25.6	9.8	32.9	14.6	17.0	14.6	19.6	15.1	24.9	94.3	68.5	17.7	37.6	49.6	-24.0
Biodiem	BDM		18.2	21.4	12.2	12.1	7.2	13.9	13.3	8.6	5.6	6.7						-11.5
Bionomics	BNO	14.7	17.6	21.1	34.2	80.8	68.5	95.3	96.4	194.2	110.7	293.2	230.1	201.5	183.8	213.8	95.4	80.7
Biota	BTA	47.7	63.5	245.0	247.0	271.8	95.1	429.3	174.1	153.4	114.4							66.7
Biotron	BIT	22.7	15.8	16.1	21.4	18.7	13.0	12.3	12.1	17.6	27.3	20.4	26.2	23.8	17.0	10.1	74.1	51.4
Bone Medical	BNE			7.5	7.7	27.1	21.2	17.3	4.8	1.4	1.1	1.3						-6.2
Cellmid	CDY				8.8	7.5	5.6	7.3	13.5	7.2	8.6	23.6	20.7	28.3	30.8	24.0	26.1	17.3
Chemgenex	CXS	33.8	39.7	70.7	81.0	194.4	160.2	235.3	125.5	219.5								185.6
Clinuvel	CUV	66.5	117.2	60.8	117.3	163.4	72.5	91.9	61.6	45.8	58.0	56.2	138.9	125.1	316.9	363.3	846.0	779.5
Cytopia	CYT	33.8	40.6	54.4	51.4	42.8	15.4	8.8										-25.0
Immuron	IMC	22.2	42.4	35.1	26.0	11.7	7.9	16.0	26.0	18.5	6.1	9.0	18.5	30.6	30.4	24.5	40.6	18.4
Immutep	IMM	21.9	15.1	18.6	10.7	5.8	2.3	67.2	90.3	195.4	153.4	69.3	48.0	101.0	77.8	59.3	121.9	100.0
Imugene	IMU	26.2	33.3	23.6	22.9	26.4	9.0	15.0	9.9	2.7	3.5	6.2	12.7	16.6	27.3	43.8	77.2	51.0
Invion	IVX								20.8	41.9	17.8	40.6	36.0	12.8	4.0	9.1	189.5	168.7
Kazia	KZA	554.3	500.1	498.1	278.2	173.0	109.2	67.3	13.3	14.1	10.7	32.2	25.4	67.7	41.9	19.0	24.2	-530.1
Living Cell	LCT			21.4	25.3	57.0	39.1	61.6	45.8	20.4	17.7	31.3	25.3	20.5	41.9	42.7	25.4	4.1
Mesoblast	MSB			46.2	88.9	173.8	134.1	158.3	804.2	2,168.9	1,736.0	1,891.0	1,420.7	858.9	471.3	652.4	814.3	768.1
Metabolic	MBP	234.9	321.5	145.4	202.5	21.3	10.5	9.4										-225.5
Neuren	NEU			49.5	46.0	37.0	12.4	9.2	7.2	28.1	42.6	149.9	158.3	162.4	93.8	218.6	142.5	93.0

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	MV Gr$
Patrys	PAB					44.5	12.9	23.7	21.4	14.1	18.3	27.3	15.2	7.0	4.8	15.5	39.7	-4.8
Peplin	PEP	58.0	43.7	66.6	134.2	161.6	65.2	162.8										104.8
Pharmaxis	PXS		66.1	309.1	495.7	738.9	331.4	543.6	570.5	262.6	372.7	41.0	33.4	86.3	88.9	84.3	111.7	45.6
Phosphagenics	POH		55.0	134.0	202.6	158.3	51.0	57.7	80.6	161.9	146.3	116.3	108.3	19.1	33.3	23.8	15.6	-39.3
Phylogica	PYC			10.5	32.9	34.0	12.0	21.5	17.1	23.4	12.2	9.6	16.1	23.5	35.9	89.8	71.1	60.6
Prana	PBT	49.6	62.6	25.6	46.8	69.4	80.5	45.4	31.8	43.6	73.7	218.7	110.9	70.3	40.9	33.1	22.5	-27.1
Progen	PGL	47.7	165.7	114.5	204.0	193.7	42.3	14.9	7.9	4.3	6.4	11.5	11.6	10.0				-47.7
Qrxpharma	QRX					87.9	19.9	70.6	123.1	200.7	107.6	111.3	4.9					-87.9
Regeneus	RGS											62.1	32.9	22.4	33.1	26.4	40.1	40.1
Select Vaccines	SLT	14.1	13.9	7.6	3.3	6.1	2.0	1.5	4.3	5.6								-14.1
Solbec	SBP	22.3	26.9	16.3	10.6	10.8	4.0											-18.3
Starpharma	SPL	54.8	89.2	65.4	83.5	68.0	46.5	123.2	166.4	305.2	383.7	267.4	196.1	243.6	253.9	457.2	512.5	457.8
Viralytics	VLA					19.6	14.5	12.1	18.1	34.6	27.1	29.9	55.8	124.4	247.6	176.0	485.6	466.0
Virax	VHL	12.1	27.5	14.6	16.0	10.3	4.1	7.9	5.3	3.5								-8.7
Total MV		1,676	2,235	2,582	3,120	3,815	1,977	3,283	3,242	4,929	4,193	4,282	3,259	2,550	2,352	2,705	3,946	2,270

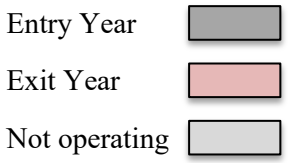
Entry Year

Exit Year

Not operating

Cash held at June 30 of each year ($ millions)																		
Company Name	ASX code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Average
Acrux	ACR			28.1	19.7	17.2	34.4	14.7	58.6	33.2	30.0	22.8	25.8	23.1	29.4	34.0	28.5	28.5
Actinogen	ACW						2.5	1.9	1.1	0.9	0.2	0.1	1.1	9.8	4.8	4.0	13.5	3.6
Alchemia	ACL		20.4	15.8	16.2	9.7	15.6	8.9	17.4	5.6	14.0	13.0	11.1	5.1	1.9	1.9	1.6	10.5
Amplia	ATX											0.1	7.9	4.1	3.2	5.8	2.2	3.9
Antisense	ANP	6.5	14.4	8.8	8.2	7.6	6.4	3.1	1.7	2.3	5.0	4.0	1.3	6.8	4.8	1.9	1.9	5.3
Arana	AAH	10.1	37.6	39.7	41.5	169.0	183.5	181.2										94.7
Avexa	AVX			15.7	20.2	76.9	43.4	18.8	24.3	16.4	12.6	11.9	3.4	1.0				22.2
Benitec	BLT	0.2	4.7	6.1	0.9	5.0	1.8	1.9	0.7	6.7	3.1	1.6	31.4	21.8	18.2	17.4	16.1	8.6
Biodiem	BDM		9.8	5.7	2.9	3.0	5.6	4.0	4.2	2.6	1.3	1.2						4.0
Bionomics	BNO	6.1	8.7	9.0	4.7	12.8	6.3	4.8	12.6	16.1	17.3	22.5	9.6	26.6	45.5	42.9	24.9	16.9
Biota	BTA	21.6	22.9	24.8	46.2	62.2	60.2	86.7	104.9	70.0	52.9							55.2
Biotron	BIT	5.4	2.6	2.1	4.6	1.4	2.1	1.0	1.8	2.1	7.9	4.8	1.8	4.5	3.4	2.0	1.5	3.1
Bone Medical	BNE			1.7	0.2	1.5	0.4	0.0	0.0	0.0	0.0	0.0						0.4
Cellmid	CDY				2.5	1.8	1.0	0.2	2.1	1.6	1.1	1.8	2.5	1.6	2.7	4.0	1.6	1.9
Chemgenex	CXS	3.1	0.9	0.9	15.6	25.4	10.1	17.7	12.8	10.2								10.7
Clinuvel	CUV	2.6	5.5	4.8	8.6	33.8	25.8	21.7	19.4	12.2	12.7	12.6	14.6	10.6	13.8	23.8	36.2	16.2
Cytopia	CYT	2.3	4.0	12.9	19.0	14.1	11.0	4.0										9.6
Immuron	IMC	0.4	0.3	0.2	1.4	0.7	1.1	0.2	1.9	0.8	1.4	1.4	6.1	3.1	2.3	4.0	4.7	1.9
Immutep	IMM	1.6	2.8	7.5	3.2	0.7	1.1	0.9	5.6	45.9	17.0	22.0	14.2	6.8	20.9	12.2	23.5	11.6
Imugene	IMU	2.6	1.0	4.3	2.7	1.1	1.6	2.5	0.8	1.9	1.0	0.6	1.2	2.0	1.6	4.8	7.8	2.3
Invion	IVX								3.4	3.9	4.2	3.1	4.0	2.3	0.4	0.9	2.9	2.8
Kazia	KZA	31.0	58.4	47.3	33.5	39.5	35.4	33.3	15.1	6.0	8.3	2.7	2.5	44.4	33.5	14.5	6.0	25.7
Living Cell	LCT			2.6	3.0	2.5	10.8	2.9	3.1	4.5	3.2	4.5	4.6	5.1	5.3	7.5	6.9	4.7
Mesoblast	MSB			15.1	7.9	12.1	14.1	16.5	32.0	263.2	205.6	315.3	196.4	144.1	109.5	61.9	51.1	103.2
Metabolic	MBP	6.9	17.3	17.1	23.3	20.6	16.5	12.2										16.3
Neuren	NEU			10.1	7.5	4.4	1.7	0.6	2.9	2.9	7.7	3.4	22.5	16.6	8.1	1.3	11.4	7.2

Company Name	ASX code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Average
Patrys	PAB					2.3	15.2	9.6	6.8	6.2	6.2	5.2	8.6	4.6	3.2	1.9	4.6	6.2
Peplin	PEP	6.4	7.6	9.2	22.7	23.8	26.2	21.9										16.8
Pharmaxis	PXS		25.2	33.4	97.8	76.2	111.8	125.0	85.8	44.3	81.5	63.9	34.2	54.1	39.2	21.5	31.1	61.7
Phosphagenics	POH		8.2	4.7	9.0	16.3	15.6	9.3	8.4	6.3	21.6	14.1	7.6	15.8	9.9	4.0	3.3	10.3
Phylogica	PYC			5.5	2.6	3.4	3.2	3.1	2.2	5.2	2.8	1.8		1.5	7.1	9.9	3.1	3.7
Prana	PBT	3.5	29.6	21.5	10.0	7.4	11.2	4.3	5.2	8.8	5.6	13.3	34.2	34.9	28.6	21.9	15.2	16.0
Progen	PGL	12.0	14.3	23.4	15.9	98.2	76.7	28.0	3.9	6.3	1.8	1.4	3.0	2.8				22.1
Qrxpharma	QRX					35.7	29.7	17.8	12.8	7.3	23.0	12.0	10.5					18.6
Regeneus	RGS											0.4	2.5	3.0	0.5	4.1	1.1	1.9
Select Vaccines	SLT	2.5	1.5	1.2	0.9	2.6	0.9	0.1	0.3	1.2								1.3
Solbec	SBP	1.9	2.7	1.4	0.9	3.1	1.5											1.9
Starpharma	SPL	7.9	15.7	8.2	14.3	10.1	7.5	11.6	22.9	18.9	42.8	33.8	24.0	30.8	46.0	61.2	51.3	25.4
Viralytics	VLA					1.9	2.8	1.3	5.1	5.0	5.9	5.1	24.3	21.6	46.1	41.1	50.4	17.6
Virax	VHL	1.5	3.8	4.1	3.6	1.6	1.6	1.1	1.4	0.6								2.1
Total Cash		136	320	393	471	805	796	673	481	619	598	600	515	509	490	410	403	677



Annual BR, for years ending 30 June ($ millions)																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Acrux	ACR				8.2	7.7	2.7	5.8	-48.1	-66.1	2.4	-6.3	-36.4	-10.5	-16.5	-5.4	5.3	-157.2
Actinogen	ACW							0.5	0.7	0.8	0.8	0.1	0.4	3.7	5.0	1.1	7.9	21.2
Alchemia	ACL			7.0	11.9	14.2	8.4	7.2	5.7	11.6	11.8	13.3	1.6	6.2	-2.3	-0.0	0.3	96.8
Amplia	ATX												1.6	4.0	4.7	6.2	3.5	20.0
Antisense	ANP		2.2	5.6	4.0	2.7	3.4	3.3	1.3	1.9	2.4	2.8	3.1	-1.3	2.0	2.9	2.3	38.6
Arana	AAH		-35.5	-27.4	-2.9	-3.1	-6.2	-5.2										-80.3
Avexa	AVX				8.9	15.6	29.3	40.9	16.8	5.2	2.3	2.7	1.7	2.0				125.3
Benitec	BLT		8.8	13.2	8.4	2.0	3.3	2.2	2.4	3.3	3.2	2.7	9.3	9.7	20.2	8.3	9.8	106.7
Biodiem	BDM			4.1	2.8	3.6	4.3	1.5	3.3	2.5	1.2	2.0						25.3
Bionomics	BNO		3.0	3.3	3.8	6.3	6.5	5.0	7.1	9.0	4.0	10.1	12.9	-4.9	15.4	1.4	20.5	103.2
Biota	BTA		6.0	13.0	7.7	-21.0	-4.8	-32.5	-46.6	34.1	15.4							-28.7
Biotron	BIT		2.6	1.7	1.8	3.6	1.6	1.9	1.9	2.0	2.3	3.1	3.0	2.7	3.1	2.8	1.8	35.9
Bone Medical	BNE				3.0	2.8	2.4	1.6	0.9	0.7	1.1	1.0						13.5
Cellmid	CDY					2.9	1.6	1.1	1.2	2.3	1.8	1.5	2.2	3.1	2.5	4.1	4.5	28.8
Chemgenex	CXS		2.2	6.7	8.5	11.9	16.0	24.1	4.8	16.6								90.8
Clinuvel	CUV		6.0	9.2	11.4	8.2	7.2	11.0	11.8	9.5	10.0	6.9	4.8	4.5	5.0	-9.9	-11.7	84.0
Cytopia	CYT		3.4	7.7	5.2	7.6	7.3	7.1										38.4
Immuron	IMC		1.2	1.8	2.8	3.0	2.1	2.1	2.3	2.0	2.5	2.0	2.7	3.0	4.9	7.0	3.5	42.8
Immutep	IMM		5.6	4.7	5.1	3.3	1.6	1.9	6.5	12.8	19.1	16.0	14.2	7.8	11.3	8.5	7.8	126.2
Imugene	IMU		1.5	1.6	1.8	1.7	1.3	-0.9	1.7	-1.1	1.0	1.4	1.1	2.0	3.1	2.7	4.5	23.4
Invion	IVX									13.5	10.6	3.5	4.4	10.1	3.8	0.2	-0.7	45.4
Kazia	KZA		10.5	12.8	14.4	14.6	20.1	20.6	16.6	8.7	7.3	8.8	5.7	5.8	12.0	10.7	6.0	174.7
Living Cell	LCT				6.6	5.5	5.6	5.7	5.9	5.7	2.5	-1.3	0.1	3.6	3.2	3.4	3.6	50.0
Mesoblast	MSB				3.7	9.1	6.2	9.2	9.7	-108.2	62.8	54.1	81.9	121.7	77.1	121.9	101.1	550.3
Metabolic	MBP		8.9	10.7	10.1	13.4	5.3	3.4										51.8
Neuren	NEU				8.4	10.6	11.7	4.7	1.5	2.3	2.6	5.1	7.3	8.4	16.5	8.0	5.2	92.4

Company Name	ASX code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Patrys	PAB						7.5	7.3	7.1	5.1	3.8	2.6	5.1	4.1	1.5	1.3	2.1	47.4
Peplin	PEP		4.0	7.5	11.8	23.1	26.3	28.4										101.0
Pharmaxis	PXS			9.3	13.8	20.7	18.9	26.5	39.7	37.4	37.1	35.4	28.1	-21.8	12.0	15.3	-12.2	260.0
Phosphagenics	POH			3.6	6.1	9.4	9.4	7.0	7.8	9.4	12.0	8.3	6.6	10.7	6.2	5.8	5.4	107.9
Phylogica	PYC				2.8	3.1	5.0	3.9	3.6	2.9	4.2	2.3	3.2	2.5	3.2	1.9	6.7	45.2
Prana	PBT		5.3	11.4	11.7	9.2	9.4	7.0	4.7	4.6	6.8	8.0	13.5	10.9	7.4	5.9	6.2	122.0
Progen	PGL		5.3	5.3	6.5	9.8	15.6	15.8	12.9	4.7	5.3	2.6	2.5	2.5				88.8
Qrxpharma	QRX						14.1	17.0	25.4	22.2	11.7	11.7	12.2					114.4
Regeneus	RGS												6.2	5.9	2.3	-3.6	4.2	15.1
Select Vaccines	SLT		1.8	2.5	2.0	2.3	1.7	1.1	-0.4	0.7								11.7
Solbec	SBP		1.7	2.2	1.4	1.4	1.6											8.3
Starpharma	SPL		5.8	5.8	7.5	3.4	5.4	4.0	3.6	6.5	9.8	9.8	9.8	13.6	17.8	17.0	10.2	129.9
Viralytics	VLA						3.0	3.2	3.6	3.0	3.6	3.9	5.5	4.5	7.5	11.4	11.7	60.9
Virax	VHL		3.8	2.8	4.3	4.3	1.2	1.2	0.9	0.8								19.3
Total			54	126	203	213	256	245	116	66	262	214	214	215	229	229	210	2,851

Entry Year

Exit Year

Not operating

PVG due to acquisitions and in-licensing ($ millions)																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Acrux	ACR																	
Actinogen	ACW												31					31
Alchemia	ACL																	
Amplia	ATX																	
Antisense	ANP																	
Arana	AAH				73													73
Avexa	AVX					121												121
Benitec	BLT																	
Biodiem	BDM																	
Bionomics	BNO			7							26							33
Biota	BTA																	
Biotron	BIT																	
Bone Medical	BNE																	
Cellmid	CDY																	
Chemgenex	CXS		9															9
Clinuvel	CUV																	
Cytopia	CYT																	
Immuron	IMC							14										14
Immutep	IMM																	
Imugene	IMU											11			14			25
Invion	IVX															123		123
Kazia	KZA										22							22
Living Cell	LCT																	
Mesoblast	MSB																	
Metabolic	MBP																	
Neuren	NEU																	

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Patrys	PAB							6										6
Peplin	PEP																	
Pharmaxis	PXS																	
Phosphagenics	POH																	
Phylogica	PYC																	
Prana	PBT																	
Progen	PGL																	
Qrxpharma	QRX																	
Regeneus	RGS																	
Select Vaccines	SLT																	
Solbec	SBP																	
Starpharma	SPL																	
Viralytics	VLA																	
Virax	VHL																	
Total PV Growth			9	7	73	121		20			48	11	31		14	123		457

Entry Year

Exit Year

Not operating

PVG after adjustment for acquisitions ($ millions)																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	PVG
Acrux	ACR				36.9	127.9	-121.4	207.7	153.6	88.0	-32.6	-42.0	-223.8	-151.1	-50.9	-38.4	7.7	-38.2
Actinogen	ACW							1.5	3.0	-0.8	-0.5	-1.6	-20.7	12.8	2.0	-0.7	15.5	10.5
Alchemia	ACL			51.2	-22.7	25.0	-92.4	65.0	11.0	-12.8	46.2	39.8	-100.1	-42.0	-19.7	0.1	1.2	-50.2
Amplia	ATX												-6.7	1.4	120.7	-143.7	5.4	-22.9
Antisense	ANP		4.0	-20.4	3.0	3.9	12.9	2.8	-25.2	14.2	-3.1	2.6	-3.0	-7.7	-5.6	0.8	9.2	-11.5
Arana	AAH		29.0	-77.8	-20.2	-144.6	-17.8	74.0										-157.4
Avexa	AVX				74.3	-51.8	-148.3	78.4	-79.8	5.5	-9.1	-7.1	12.3	-5.5				-131.1
Benitec	BLT		-25.0	-28.8	-10.7	19.1	-15.3	2.4	-1.2	-1.0	-0.9	11.2	39.7	-16.2	-47.3	20.8	13.3	-39.9
Biodiem	BDM			7.3	-6.3	-0.2	-7.6	8.3	-0.8	-3.1	-1.7	1.2						-2.9
Bionomics	BNO		0.3	-3.8	17.4	38.5	-5.7	28.4	-6.8	94.3	-110.8	177.4	-50.2	-45.6	-36.6	32.6	-100.5	28.8
Biota	BTA		14.6	179.6	-19.4	8.8	-174.7	307.7	-273.4	14.2	-21.9							35.4
Biotron	BIT		-4.1	0.8	2.9	0.5	-6.4	0.5	-1.0	5.1	3.9	-3.8	8.8	-5.1	-5.7	-5.5	64.4	55.3
Bone Medical	BNE				1.7	18.2	-4.7	-3.6	-12.6	-3.3	-0.3	0.2						-4.5
Cellmid	CDY					-0.6	-1.1	2.6	4.2	-5.8	2.0	14.3	-3.7	8.6	1.4	-8.2	4.5	18.2
Chemgenex	CXS		-1.0	31.1	-4.4	103.6	-18.9	67.5	-105.0	96.6								169.5
Clinuvel	CUV		47.8	-55.6	52.7	20.9	-82.9	23.5	-28.0	-8.6	11.6	-1.6	80.6	-9.7	188.6	36.4	470.2	745.9
Cytopia	CYT		5.2	4.9	-9.2	-3.7	-24.3	0.4										-26.6
Immuron	IMC		20.3	-7.2	-10.3	-13.6	-4.2	-4.9	8.3	-6.3	-13.2	3.0	4.8	15.1	0.7	-7.7	15.4	0.0
Immutep	IMM		-8.0	-1.2	-3.6	-2.4	-3.9	65.0	18.4	64.8	-13.0	-89.1	-13.5	60.5	-37.4	-9.8	51.4	78.1
Imugene	IMU		8.8	-13.0	1.0	5.1	-18.0	5.2	-3.5	-8.3	1.7	-7.9	5.8	3.2	-2.9	13.2	30.4	20.8
Invion	IVX									20.5	-24.4	24.0	-5.5	-21.5	-6.9	-118.4	178.4	46.2
Kazia	KZA		-81.5	9.2	-206.2	-111.1	-59.7	-39.8	-35.9	9.9	-27.7	27.1	-6.6	0.5	-14.9	-3.9	13.7	-527.0
Living Cell	LCT				3.6	32.2	-26.2	30.3	-16.0	-26.8	-1.3	12.2	-6.0	-5.4	21.2	-1.4	-16.6	-0.1
Mesoblast	MSB				50.0	80.7	-41.8	21.8	630.3	1,133.5	-375.2	45.3	-351.4	-509.5	-352.9	228.7	172.8	732.1
Metabolic	MBP		76.2	-175.8	50.8	-178.4	-6.8	3.2										-230.9
Neuren	NEU				-0.9	-5.9	-21.8	-2.2	-4.3	20.9	9.8	111.5	-10.6	10.0	-60.2	131.7	-86.3	91.6

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	PVG
Patrys	PAB						-44.5	10.4	0.5	-6.7	4.2	9.9	-15.4	-4.2	-0.8	11.9	21.6	-13.1
Peplin	PEP		-15.5	21.2	54.2	26.2	-98.8	101.9										89.3
Pharmaxis	PXS			234.9	122.1	264.8	-443.1	199.1	66.1	-266.5	73.1	-314.2	22.1	32.9	17.6	13.1	17.8	39.8
Phosphagenics	POH			82.5	64.3	-51.6	-106.6	13.0	23.8	83.3	-30.7	-22.6	-1.6	-97.3	20.1	-3.6	-7.4	-34.4
Phylogica	PYC				25.2	0.4	-21.8	9.7	-3.6	3.3	-8.8	-1.6	4.2	10.0	6.8	51.0	-11.8	63.0
Prana	PBT		-13.1	-28.9	32.7	25.2	7.3	-28.2	-14.6	8.2	33.3	137.3	-128.7	-41.3	-23.1	-1.2	-3.9	-38.9
Progen	PGL		115.6	-60.3	97.1	-92.7	-129.9	21.3	17.1	-6.0	6.6	5.5	-1.4	-1.4				-28.5
Qrxpharma	QRX						-62.0	62.6	57.5	83.1	-108.7	14.7	-104.9					-57.8
Regeneus	RGS												-31.3	-11.1	13.2	-10.3	16.7	-22.7
Select Vaccines	SLT		0.8	-6.0	-4.0	1.1	-2.4	0.3	2.7	0.3								-7.2
Solbec	SBP		3.8	-9.3	-5.2	-2.0	-5.2											-17.9
Starpharma	SPL		26.7	-16.3	12.0	-11.3	-18.9	72.6	32.0	142.7	54.6	-107.4	-61.5	40.7	-4.8	188.1	65.1	414.3
Viralytics	VLA						-6.0	-0.9	2.2	16.6	-8.4	3.5	6.7	71.3	98.7	-66.6	300.2	417.4
Virax	VHL		13.1	-13.2	2.0	-3.6	-6.3	4.4	-2.9	-1.1								-7.7
Total PV Growth			218	105	381	128	-1,829	1,412	416	1,548	-545	42	-962	-708	-179	309	1,248	1,585

Entry Year

Exit Year

Not operating

VCR by year ($ millions)																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Acrux	ACR				28.7	120.2	-124.1	201.9	201.8	154.1	-35.1	-35.6	-187.4	-140.6	-34.4	-33.0	2.4	118.9
Actinogen	ACW							0.9	2.3	-1.6	-1.4	-1.7	-21.1	9.1	-3.1	-1.8	7.6	-10.8
Alchemia	ACL			44.2	-34.5	10.8	-100.9	57.9	5.3	-24.3	34.4	26.5	-101.7	-48.2	-17.4	0.2	0.9	-147.0
Amplia	ATX												-8.3	-2.6	116.0	-149.9	1.8	-42.9
Antisense	ANP		1.8	-26.0	-1.0	1.2	9.5	-0.4	-26.5	12.3	-5.5	-0.2	-6.1	-6.4	-7.6	-2.2	6.9	-50.2
Arana	AAH		64.6	-50.4	-17.3	-141.5	-11.7	79.2										-77.1
Avexa	AVX				65.4	-67.5	-177.6	37.5	-96.6	0.4	-11.4	-9.8	10.6	-7.5				-256.4
Benitec	BLT		-33.8	-42.0	-19.1	17.1	-18.5	0.2	-3.5	-4.3	-4.1	8.5	30.4	-25.9	-67.5	12.5	3.5	-146.6
Biodiem	BDM			3.2	-9.1	-3.8	-11.9	6.8	-4.0	-5.6	-2.9	-0.8						-28.2
Bionomics	BNO		-2.7	-7.1	13.6	32.2	-12.3	23.4	-13.9	85.4	-114.8	167.3	-63.1	-40.7	-52.0	31.2	-121.0	-74.4
Biota	BTA		8.6	166.6	-27.1	29.8	-169.9	340.2	-226.8	-19.8	-37.4							64.2
Biotron	BIT		-6.8	-0.9	1.1	-3.1	-8.1	-1.4	-2.9	3.1	1.6	-6.9	5.9	-7.9	-8.8	-8.3	62.6	19.3
Bone Medical	BNE				-1.3	15.4	-7.1	-5.2	-13.4	-4.0	-1.5	-0.9						-18.0
Cellmid	CDY					-3.5	-2.7	1.5	3.0	-8.1	0.2	12.8	-6.0	5.5	-1.1	-12.2	-0.0	-10.5
Chemgenex	CXS		-3.3	24.4	-12.9	91.7	-34.9	43.3	-109.7	80.0								78.7
Clinuvel	CUV		41.8	-64.9	41.3	12.7	-90.1	12.5	-39.8	-18.0	1.6	-8.5	75.8	-14.3	183.6	46.4	481.9	661.9
Cytopia	CYT		1.7	-2.8	-14.3	-11.3	-31.6	-6.6										-65.0
Immuron	IMC		19.1	-9.0	-13.1	-16.6	-6.3	-7.0	6.1	-8.3	-15.6	0.9	2.1	12.1	-4.2	-14.7	11.8	-42.8
Immutep	IMM		-13.6	-6.0	-8.6	-5.8	-5.4	63.1	12.0	51.9	-32.1	-105.1	-27.8	52.7	-48.7	-18.3	43.6	-48.1
Imugene	IMU		7.2	-14.7	-0.9	3.4	-19.2	6.1	-5.2	-7.2	0.7	-9.2	4.7	1.1	-6.0	10.5	25.9	-2.6
Invion	IVX									7.1	-35.0	20.5	-9.9	-31.6	-10.8	-118.6	179.1	0.8
Kazia	KZA		-92.1	-3.7	-220.6	-125.8	-79.8	-60.4	-52.5	1.2	-35.0	18.3	-12.3	-5.3	-26.9	-14.6	7.6	-701.7
Living Cell	LCT				-3.0	26.6	-31.8	24.6	-21.9	-32.6	-3.8	13.6	-6.1	-9.0	18.0	-4.8	-20.1	-50.1
Mesoblast	MSB				46.2	71.6	-48.0	12.6	620.7	1,241.8	-438.0	-8.8	-433.3	-631.3	-430.1	106.8	71.7	181.9
Metabolic	MBP		67.3	-186.5	40.7	-191.9	-12.1	-0.3										-282.7
Neuren	NEU				-9.4	-16.6	-33.5	-6.9	-5.8	18.6	7.1	106.4	-17.9	1.6	-76.7	123.8	-91.5	-0.7

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Patrys	PAB						-52.0	3.1	-6.5	-11.8	0.5	7.3	-20.5	-8.3	-2.3	10.7	19.5	-60.4
Peplin	PEP		-19.5	13.7	42.4	3.1	-125.1	73.6										-11.7
Pharmaxis	PXS			225.6	108.3	244.1	-462.0	172.6	26.4	-303.8	35.9	-349.6	-6.0	54.7	5.6	-2.2	30.0	-220.3
Phosphagenics	POH			78.9	58.2	-61.0	-116.0	6.0	16.0	73.9	-42.8	-31.0	-8.1	-108.0	13.9	-9.5	-12.8	-142.3
Phylogica	PYC				22.4	-2.7	-26.8	5.8	-7.2	0.4	-13.0	-3.9	1.0	7.5	3.6	49.1	-18.5	17.7
Prana	PBT		-18.4	-40.4	21.0	16.0	-2.1	-35.1	-19.3	3.6	26.4	129.4	-142.2	-52.2	-30.5	-7.0	-10.2	-160.9
Progen	PGL		110.3	-65.6	90.6	-102.5	-145.6	5.5	4.2	-10.7	1.2	2.9	-3.9	-3.9				-117.3
Qrxpharma	QRX						-76.1	45.6	32.1	60.9	-120.4	2.9	-117.1					-172.1
Regeneus	RGS												-37.5	-17.0	10.9	-6.7	12.5	-37.8
Select Vaccines	SLT		-1.0	-8.4	-5.9	-1.3	-4.1	-0.8	3.1	-0.4								-18.9
Solbec	SBP		2.1	-11.5	-6.6	-3.4	-6.8											-26.2
Starpharma	SPL		20.8	-22.1	4.5	-14.7	-24.2	68.5	28.3	136.3	44.9	-117.2	-71.3	27.1	-22.6	171.1	54.9	284.4
Viralytics	VLA						-9.0	-4.1	-1.4	13.6	-11.9	-0.4	1.2	66.8	91.1	-78.0	288.5	356.5
Virax	VHL		9.3	-16.1	-2.3	-7.9	-7.5	3.2	-3.9	-1.9								-27.0
Total Value Creation			163	-21	177	-85	-2,085	1,167	301	1,482	-807	-172	-1,176	-922	-408	80	1,039	-1,266

Entry Year

Exit Year

Not operating

Value of dividends paid for years ending June 30 ($ millions)																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Acrux	ACR									99.0	0.6	13.4	33.3	13.3	10.0			169.6
Actinogen	ACW																	
Alchemia*	ACL												30.2					30.2
Amplia	ATX																	
Antisense	ANP																	
Arana	AAH			18.3														18.3
Avexa	AVX																	
Benitec	BLT																	
Biodiem	BDM																	
Bionomics	BNO																	
Biota	BTA							19.7										19.7
Biotron	BIT																	
Bone Medical	BNE																	
Cellmid	CDY																	
Chemgenex	CXS																	
Clinuvel	CUV																9.6	9.6
Cytopia	CYT																	
Immuron	IMC																	
Immutep	IMM																	
Imugene	IMU																	
Invion	IVX																	
Kazia	KZA																	
Living Cell	LCT																	
Mesoblast	MSB																	
Metabolic	MBP																	
Neuren	NEU																	

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Patrys	PAB																	
Peplin	PEP																	
Pharmaxis	PXS																	
Phosphagenics	POH																	
Phylogica	PYC																	
Prana	PBT																	
Progen	PGL																	
Qrxpharma	QRX																	
Regeneus	RGS																	
Select Vaccines	SLT																	
Solbec	SBP																	
Starpharma	SPL																	
Viralytics	VLA																	
Virax	VHL																	
Total Dividends				18.3				19.7		99.0	0.6	13.4	63.5	13.3	10.0		9.6	247.4

Entry Year

Exit Year

Not operating

Dividends

* Dividends include a capital return for Alchemia in 2014.

SP ($): VWA share price for July-December each year, adjusted for consolidations																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	SP Growth
Acrux	ACR			0.63	0.77	1.44	0.77	1.94	3.10	3.42	3.21	2.91	1.59	0.66	0.40	0.19	0.21	-67.4%
Actinogen	ACW						0.14	0.10	0.14	0.10	0.06	0.02	0.04	0.06	0.05	0.05	0.05	-63.5%
Alchemia	ACL		0.78	1.15	0.72	0.73	0.18	0.54	0.56	0.39	0.49	0.54	0.23	0.08	0.01	0.01	0.01	-98.4%
Amplia	ATX											0.20	0.21	0.18	0.69	0.04	0.03	-85.6%
Antisense	ANP	0.16	0.12	0.05	0.04	0.04	0.06	0.06	0.01	0.02	0.02	0.02	0.01	0.01	0.004	0.003	0.004	-97.6%
Arana	AAH	1.47	1.80	1.34	1.65	1.15	1.07	1.40										-5.2%
Avexa	AVX			0.24	0.51	0.58	0.13	0.16	0.04	0.04	0.02	0.01	0.02	0.01				-96.5%
Benitec	BLT	1.24	0.61	0.16	0.05	0.11	0.05	0.05	0.03	0.02	0.01	0.02	0.03	0.02	0.00	0.01	0.01	-99.4%
Biodiem	BDM		0.65	0.74	0.32	0.23	0.11	0.18	0.14	0.09	0.05	0.05						-92.7%
Bionomics	BNO	0.34	0.28	0.17	0.20	0.37	0.29	0.32	0.30	0.56	0.31	0.71	0.55	0.46	0.38	0.44	0.19	-43.6%
Biota	BTA	0.58	0.60	1.61	1.37	1.48	0.53	2.44	0.97	0.84	0.62							6.8%
Biotron	BIT	0.35	0.23	0.18	0.24	0.21	0.12	0.11	0.10	0.12	0.12	0.09	0.11	0.08	0.05	0.03	0.14	-61.1%
Bone Medical	BNE			0.33	0.28	0.36	0.26	0.19	0.05	0.01	0.00	0.00						-99.6%
Cellmid	CDY				0.23	0.12	0.06	0.03	0.04	0.02	0.02	0.04	0.03	0.03	0.03	0.03	0.02	-92.5%
Chemgenex	CXS	0.59	0.55	0.62	0.53	1.04	0.69	0.83	0.44	0.70								18.0%
Clinuvel	CUV	0.63	0.94	0.40	0.54	0.54	0.24	0.30	0.23	0.15	0.17	0.15	0.33	0.28	0.67	0.76	1.77	180.5%
Cytopia	CYT	0.79	0.66	0.74	0.70	0.57	0.18	0.10										-86.9%
Immuron	IMC	0.28	0.47	0.38	0.26	0.11	0.06	0.06	0.08	0.06	0.01	0.01	0.01	0.01	0.01	0.00	0.01	-97.2%
Immutep	IMM	0.36	0.15	0.11	0.06	0.03	0.01	0.13	0.12	0.19	0.14	0.06	0.04	0.05	0.04	0.03	0.04	-89.1%
Imugene	IMU	0.26	0.30	0.18	0.18	0.20	0.06	0.10	0.07	0.02	0.01	0.01	0.01	0.01	0.01	0.02	0.02	-91.8%
Invion	IVX								0.21	0.22	0.05	0.09	0.07	0.01	0.00	0.01	0.03	-83.4%
Kazia	KZA	5.77	5.17	5.13	2.85	1.77	1.07	0.66	0.13	0.14	0.10	0.21	0.11	0.16	0.09	0.05	0.04	-99.2%
Living Cell	LCT			0.22	0.21	0.35	0.16	0.24	0.16	0.06	0.05	0.09	0.07	0.05	0.08	0.07	0.04	-79.5%
Mesoblast	MSB			1.00	1.47	1.59	1.12	1.15	3.90	7.73	6.08	5.96	4.42	2.36	1.24	1.41	1.66	65.6%
Metabolic	MBP	1.11	1.39	0.57	0.71	0.07	0.03	0.03										-97.2%
Neuren	NEU			0.57	0.41	0.27	0.05	0.03	0.02	0.02	0.04	0.11	0.10	0.10	0.05	0.14	0.07	-87.6%

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	SP Growth
Patrys	PAB					0.55	0.14	0.13	0.10	0.06	0.04	0.05	0.02	0.01	0.01	0.02	0.04	-93.2%
Peplin	PEP	0.85	0.58	0.58	0.76	0.87	0.39	0.91										7.1%
Pharmaxis	PXS		0.75	2.27	2.80	4.02	1.70	2.49	2.53	1.09	1.21	0.13	0.11	0.27	0.28	0.26	0.30	-60.4%
Phosphagenics	POH		0.30	0.25	0.37	0.26	0.08	0.08	0.11	0.18	0.14	0.11	0.09	0.02	0.03	0.02	0.01	-96.7%
Phylogica	PYC			0.19	0.41	0.25	0.08	0.10	0.06	0.06	0.03	0.02	0.02	0.01	0.02	0.04	0.03	-83.0%
Prana	PBT	0.70	0.53	0.20	0.36	0.40	0.40	0.20	0.13	0.16	0.23	0.54	0.23	0.13	0.08	0.06	0.04	-94.0%
Progen	PGL	1.53	4.72	2.82	4.80	3.26	0.70	0.60	0.32	0.17	0.26	0.21	0.21	0.18				-88.2%
Qrxpharma	QRX					1.54	0.31	0.87	1.07	1.39	0.74	0.74	0.03					-100.0%
Regeneus	RGS											0.46	0.21	0.11	0.16	0.13	0.19	-58.1%
Select Vaccines	SLT	0.65	0.47	0.17	0.03	0.02	0.01	0.01	0.00	0.00								-100.0%
Solbec	SBP	0.14	0.16	0.10	0.05	0.04	0.01											-90.0%
Starpharma	SPL	0.56	0.80	0.54	0.52	0.38	0.26	0.56	0.69	1.19	1.35	0.94	0.65	0.74	0.69	1.24	1.38	147.4%
Viralytics	VLA					0.08	0.05	0.04	0.03	0.07	0.04	0.03	0.03	0.07	0.10	0.07	0.17	114.5%
Virax	VHL	0.27	0.47	0.20	0.17	0.10	0.04	0.06	0.03	0.02								-94.1%

Entry Year

Exit Year

Not operating

Share prices are calculated as the VWA (volume-weighted average) of the end-of-month MV for the six months Jul-Dec each year, divided by the VWA of the end-of-month SI (shares on issue) for Jul-Dec of the same year.

IRR per firm (%), based on SP and DIVPS (dividend per share) $																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	IRR
Acrux	ACR			-0.63						0.59	0.00	0.08	0.20	0.08	0.06		0.21	8.5%
Actinogen	ACW						-0.14										0.05	-9.6%
Alchemia	ACL		-0.78										0.09				0.01	-17.1%
Amplia	ATX											-0.20					0.03	-32.1%
Antisense	ANP	-0.16															0.004	-22.0%
Arana	AAH	-1.47		0.11				1.40										0.4%
Avexa	AVX			-0.24										0.01				-28.6%
Benitec	BLT	-1.24															0.01	-28.7%
Biodiem	BDM		-0.65									0.05						-25.2%
Bionomics	BNO	-0.34															0.19	-3.7%
Biota	BTA	-0.58						0.11			0.62							2.8%
Biotron	BIT	-0.35															0.14	-6.1%
Bone Medical	BNE			-0.33								0.00						-50.5%
Cellmid	CDY				-0.23												0.02	-19.4%
Chemgenex	CXS	-0.59								0.70								2.1%
Clinuvel	CUV	-0.63															1.79	7.2%
Cytopia	CYT	-0.79						0.10										-28.8%
Immuron	IMC	-0.28															0.01	-21.3%
Immutep	IMM	-0.36															0.04	-13.7%
Imugene	IMU	-0.26															0.02	-15.3%
Invion	IVX								-0.21								0.03	-20.1%
Kazia	KZA	-5.77															0.04	-27.7%
Living Cell	LCT			-0.22													0.04	-11.5%
Mesoblast	MSB			-1.00													1.66	4.0%
Metabolic	MBP	-1.11						0.03										-44.9%
Neuren	NEU			-0.57													0.07	-14.8%

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	IRR
Patrys	PAB					-0.55											0.04	-21.7%
Peplin	PEP	-0.85						0.91										1.1%
Pharmaxis	PXS		-0.75														0.30	-6.4%
Phosphagenics	POH		-0.30														0.01	-21.7%
Phylogica	PYC			-0.19													0.03	-12.7%
Prana	PBT	-0.70															0.04	-17.1%
Progen	PGL	-1.53												0.18				-16.3%
Qrxpharma	QRX					-1.54							0.03					-43.0%
Regeneus	RGS											-0.46					0.19	-16.0%
Select Vaccines	SLT	-0.65								0.00								-45.7%
Solbec	SBP	-0.14					0.01											-36.9%
Starpharma	SPL	-0.56															1.38	6.2%
Viralytics	VLA					-0.08											0.17	7.2%
Virax	VHL	-0.27								0.02								-29.8%

Entry Year

Exit Year

Not operating

DIVPS

Note: Negative figures indicate the SP ($) in the baseline year and are represented as a negative cash flow; positive figures represent positive dividend flows per share or the final price per share obtained in the terminal year.

Clinuvel dividend per share of $0.02 for 2018 included in 2018 figure of $1.79

Portfolio cash flows and IRR ($ millions)																		
Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	IRR
Acrux	ACR			-1,000						937	6	127	315	126	95		326	8.5%
Actinogen	ACW						-1,000										365	-9.6%
Alchemia	ACL		-1,000										120				16	-17.1%
Amplia	ATX											-1,000					144	-32.1%
Antisense	ANP	-1,000															24	-22.0%
Arana	AAH	-1,000		78				948										0.4%
Avexa	AVX			-1,000										35				-28.6%
Benitec	BLT	-1,000															6	-28.7%
Biodiem	BDM		-1,000									73						-25.2%
Bionomics	BNO	-1,000															564	-3.7%
Biota	BTA	-1,000						193			1,068							2.8%
Biotron	BIT	-1,000															389	-6.1%
Bone Medical	BNE			-1,000								4						-50.5%
Cellmid	CDY				-1,000												75	-19.4%
Chemgenex	CXS	-1,000								1,180								2.1%
Clinuvel	CUV	-1,000															2,837	7.2%
Cytopia	CYT	-1,000						131										-28.8%
Immuron	IMC	-1,000															28	-21.3%
Immutep	IMM	-1,000															109	-13.7%
Imugene	IMU	-1,000															82	-15.3%
Invion	IVX								-1,000								166	-20.1%
Kazia	KZA	-1,000															8	-27.7%
Living Cell	LCT			-1,000													205	-11.5%
Mesoblast	MSB			-1,000													1,656	4.0%
Metabolic	MBP	-1,000						28										-44.9%
Neuren	NEU			-1,000													124	-14.8%

Company Name	ASX Code	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	IRR
Patrys	PAB					-1,000											68	-21.7%
Peplin	PEP	-1,000						1,071										1.1%
Pharmaxis	PXS		-1,000														396	-6.4%
Phosphagenics	POH		-1,000														33	-21.7%
Phylogica	PYC			-1,000													170	-12.7%
Prana	PBT	-1,000															60	-17.1%
Progen	PGL	-1,000												118				-16.3%
Qrxpharma	QRX					-1,000							19					-43.0%
Regeneus	RGS											-1,000					419	-16.0%
Select Vaccines	SLT	-1,000								8								-45.7%
Solbec	SBP	-1,000					100											-36.9%
Starpharma	SPL	-1,000															2,474	6.2%
Viralytics	VLA					-1,000											2,145	7.2%
Virax	VHL	-1,000								59								-29.8%
New investments		-21,000	-4,000	-7,000	-1,000	-3,000	-1,000		-1,000			-2,000						-$40,000
Dividends				78				193		937	6	127	435	126	95		32	$2,029
Sale proceeds							100	2,177		1,246	1,068	77	19	153			12,856	$17,695
NCF		-21,000	-4,000	-6,922	-1,000	-3,000	-900	2,370	-1,000	2,183	1,073	-1,797	455	279	95		12,888	-$20,276
IRR		-6.2%													Portfolio liquidated value			$19,724

Entry Year

Exit Year

Not operating

Dividends

Note: Negative figures indicate the cash investment in the baseline year; positive figures represent dividend flows or the liquidation value of the shares in the terminal year.

Clinuvel dividend for 2018 included in 2018 cash flow