Further Evolution in the Pharmaceutical Sector:

*Changes in the Division of Labour and the Markets for Technology*

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Humanities

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Nicola T. Wall

Manchester Business School
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Abstract

The University of Manchester

Nicola Teresa Wall

Doctor of Philosophy

Further Evolution in the Pharmaceutical Industry: Changes in the Division of Labour and Markets for Technology

February 25, 2011

The pharmaceutical sector has undergone many changes, particularly in the past several decades. The purpose of this research was to ascertain the existence of further changes to the division of labour and changes in the markets for technology within the sector. This research was also undertaken to understand the specific issues that may be impacting the division of labour and the changes in the markets for technology including the role of finance and the role of a surplus of unexploited knowledge. The division of labour between large and small new firms was initially more pronounced as the fully integrated firms continued to develop, manufacture and market drugs while ‘classical biotechnology’ firms pursued an exploratory business model of supplying knowledge and early stage drug candidates to these fully integrated companies (McKelvey, 2008). However, firms are changing in this sector and changes may be evident that have not been discussed in the literature to date. A new type of firm is evident within this sector, the No Research Development Only (NRDO) firm, as well as changes in the existing firms. This has impacted markets for technology as changes are also apparent in the way in which firms exchange products and knowledge.

A combined quantitative and qualitative study was used to answer the research questions. A random sample of 100 EU and US companies that own and develop drug products was generated. Descriptive statistics were gathered to form a database of information and case studies were compiled to provide in-depth data related to a sample of eight firms. The newly identified NRDO firms do not possess internal capabilities to discover their own products; surprising given the historically research intensive nature of the types of small firms that operate in this sector. There also appears to be changes in the markets for technology as large firms are selling drug candidates to these hitherto research-intensive discovery and development (DD) firms who are willing to in-license these drug candidates to bolster pipelines and financial valuations. Markets for knowledge in this sector have undoubtedly evolved and a more complex set of arrangements are evident. The roles of finance and a surplus of unexploited knowledge have played an important part in these changes as the sustained level of exploration in the sector has resulted in a greater number of exploitation opportunities. Overall there is evidence to support further evolution in the sector.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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For Brigid

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Brigid, I dedicate my PhD to you. The best thing that ever happened to me, I love you so much. May we now embark on a journey that includes way more time together, longer story time and longer tickle time too without mom having to say… Sorry! I have to go upstairs to write!

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The participation of a number of executives in the industry who generously gave their time and their insight was a key factor in accomplishing this PhD. Their candour and willingness to enter into a discussion provided much needed knowledge and information that informed the generation of key arguments in this thesis. I heartily wish to thank all of them for their involvement and wish them all every success in the future.

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Lizzy, Sanj, thanks! To all of my peers here at Manchester: Chao-Chen, Hsing-Fen, Abdullah, Kadir, John and Sally to name but a few. It was a pleasure knowing all of you and I wish you all the very best in your futures. Watch out world! To Irina for being such a huge help and a great friend always. Thank you so much for coming up trumps at the last minute and rescuing a poor old SOP writer from the depths of Word-induced despair. Roll on June!

Goga, last but not least. Hvala vam toliko za sve. You were a lifesaver and came just when we really needed you. Who knew it would work so well? Come back now in March, ya hear?

Nicola
### Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AEI</td>
<td>Alpha Emitting Isotope</td>
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<td>BMS</td>
<td>Bristol Myers Squibb</td>
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<td>CEO</td>
<td>Chief Executive Officer</td>
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<td>CSO</td>
<td>Corporate Spin Out</td>
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<td>DD</td>
<td>Discovery and Development firm</td>
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<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<td>EU</td>
<td>European Union</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
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<td>HTS</td>
<td>High Throughput Screening</td>
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<td>IP</td>
<td>Intellectual Property</td>
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<td>IPO</td>
<td>Initial Public Offering</td>
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<td>MAb</td>
<td>Monoclonal Antibody</td>
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<td>NCE</td>
<td>New Chemical Entity</td>
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<td>NRDO</td>
<td>No Research Development Only firm</td>
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<td>PSO</td>
<td>Public Spin Out</td>
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<td>R&amp;D</td>
<td>Research and Development</td>
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<td>SEC</td>
<td>Securities and Exchange Commission</td>
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<td>SIC</td>
<td>Standard Industrial Classification</td>
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<td>UK</td>
<td>United Kingdom</td>
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<td>US</td>
<td>United States</td>
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<td>VC</td>
<td>Venture Capital</td>
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Chapter 1. Introduction

1.1. Overview

Eminent philosophers have told us that the only constant is change. Understanding changes and why they occur is a central theme of this research. This thesis identifies a new type of firm in the pharmaceutical sector illustrating changes in the division of labour and markets for technology. It sets out to update the current understanding of the division of labour and the way in which firms are trading products and knowledge by examining two key influences: The role of finance and the role of a surplus of unexploited knowledge.

1.2. Background to the Research

The developments in the pharmaceutical sector that have taken place since the introduction of aspirin in the 19th century have profoundly impacted the lives of many people with a range of illnesses. New drugs\(^1\) have improved quality of life and longevity for many people. Pharmaceutical innovation has increased life expectancy and lifetime income and represents a substantial contribution to economic growth (Lichtenberg, 2006). Maintaining a current understanding of how such a dynamic and important sector functions and the way in which it functions is key to making sure that the quest for better and cheaper drugs continues.

A great deal of change has taken place both within and outside of the sector particularly over the last 50 years. The growth of knowledge related to biotechnology (including molecular biology, biochemistry, immunology, virology and cell biology) chemistry and information technology, combined with the development of research tools, created many opportunities for small firms to enter the sector (Henderson et al, 1999; McKelvey and Orsenigo, 2001). Many of these new firms (Classical Biotechnology Firms) were formed to develop new ideas and scientific advances from public institutions

\(^1\) For the purposes of this research, a drug includes any product, small molecule or biologic intended for human therapeutic use but not diagnostic use.
(including universities and government laboratories) with the overall aim of discovering new and effective drugs. These developments in the knowledge bases also changed the way in which incumbent firms operated as these firms had to internalise new capabilities related to the new developments (Gambardella, 1995; Galambos and Sturchio, 1998). The growth in knowledge and the focus on drug discovery has ultimately resulted in the growth of the number of opportunities in terms of potential new drugs and a surplus of unexploited knowledge.

However, drug development requires concentration on those processes that can ensure successful commercialisation as a result of clinical trials and regulatory adherence. It also requires funding. Projections of financial requirements for drug discovery and development indicate that a firm can spend up to $1.7 Billion in related costs (PHrMA, 2007; www.Tufts.com). These costs have created serious problems for all firms who need to fund drug discovery and development. Big firms who have traditionally operated as the bastions of the sector with historically deep pockets, as far as funding is concerned, are increasingly facing financial pressures to make that funding stretch further. This year Pfizer\(^2\) announced cuts to its R&D budget of over $1.5 Billion and announced that they were exiting a number of therapeutic areas including internal medicine and urology (www.fiercebiotech.com; www.pfizer.com). Pfizer is not alone following moves by other companies including AstraZeneca, Roche, Bayer, Abbot and Sanofi Aventis who have laid off over 37,00 staff between them last year\(^3\) (www.fiercebiotech.com).

These problems, however, are related to one key issue: the new developments have not necessarily increased the success rate of new drug introduction (Hopkins et al, 2007). The changes that are now visible in the sector have actually created opportunities for a new type of firm that has emerged and has been visible for some time. This research has identified a new economic agent that has focused on drug development and provides

\(^3\) http://www.fiercepharma.com/special-reports/top-10-layoffs-2010
empirical support for this claim. This thesis argues that the emergence of this new type of firm is a response to a surplus of unexploited knowledge and the financial pressures that have become apparent in the sector. The thesis further argues that other firms in the sector, the traditional ‘classical biotechnology firm’ and the incumbent large firms, have also changed the way in which they operate in response to these two key factors.

1.3. Theoretical Framework

There is much prior research on the fundamental changes in the organisation of the pharmaceutical sector throughout its history that illustrates the dynamic nature of the sector. The notion that industrial change was an evolutionary process was key to a better overall understanding of industrial dynamics. Nelson and Winter proposed that firms adapt and change in response to their environment and with varying levels of success also dependent on the individual firm’s goals (Nelson and Winter, 1982). An associated body of literature on the firm level with respect to exploration and exploitation activities has also provided a critical context for this research. A balance of exploration and exploitation is key for the firm’s continued survival, however, exploitation activities will tend to dominate over exploration activities because the returns on investment are more visible and immediate (Levinthal and March, 1993; Rothaermel, 2001). The balance of exploration and exploitation will tend to change over the firm’s lifespan and the lifespan of a sector (Levinthal and March, 1993; Gilsing and Nooteboom, 2006).

The key changes that occurred in the pharmaceutical sector (impacting the organisation of the sector) include: the internal creation of research and development organisations within the large firms during the early part of the 20th century, increased funding of research at a government level during the mid 20th century (particularly in the US), key developments related to biotechnology and the corresponding development of the small classical biotechnology firm in the latter part of the century (Kenney, 1986; Gambardella, 1995; Malerba and Orsenigo, 1996; Galambos and Sturchio, 1998; Henderson et al, 1999; McKelvey and Orsenigo, 2001). This range of
disciplines related to discoveries in biotechnology created many opportunities for new classical biotechnology firms (McKelvey, 2008) to conduct research in this sector. A division of labour emerged as small firms conducted research and were primarily exploratory focused while the large firms focused on commercialisation and provided the exploitation capabilities for small firms (in addition to their own exploratory capabilities). For the new small firms, the relationships with large incumbent firms were a key part of the successful division of labour as these small firms provided potential new drugs to large firms who then provided the resources for commercialisation. Developments of prolific networks of firms and institutions emerged (Powell et al, 1996) as well as markets for technology (Arora et al, 2001).

Consequently scientific advances were (are) viewed as the lifeblood of success for small firms and a great deal of emphasis has been placed on research related to drug discovery activities. These small firms have taken on a ‘new importance’ in the sector’s innovative capability (Galambos, 2006). The developments in biotechnology have created many opportunities for new firm formation (combined with developments in chemistry and information technology). However, scientific advances alone are meaningless in terms of impact on lives and on society. Scientific advances must be translated into safe and effective drugs for use and this requires financial capital. The financial literature provides an important context and overall, illustrates that without adequate means of funding, small firms in particular will not be able to fund research or related exploratory activities (Oakey, 2003; Hyytinen and Toivanen, 2005; Tylecote and Ramirez, 2006). As recent evidence suggests the success rates of drug development (when measured using numbers of new drugs approved) have not matched expectations of financial markets (Pisano, 2006; McKelvey, 2008), the current organisation of the sector will have to undergo change.

1.4. Research Questions

This thesis is about change in the pharmaceutical sector and how the firms who provide the vital drugs that are so necessary to the well being and survival of most of us, are changing and/or adapting to the pressures
inherent in the search for new efficacious drugs. Understanding more about
the nature of this industry is key to ensuring that our knowledge is up to date
and relevant and that this knowledge can be used to inform important
debates and policy. The key premise of this thesis is that the sector is
undergoing important changes in how its firms are structured and how they
are interacting with one another. Changes in the nature of firms were visible
to the author while working in the industry from 2000 onwards. Exposure to a
range of firms through various work related projects as well as the local
network in the Philadelphia and New Jersey area (and the wider network
spanning to New York, Connecticut, Massachusetts and California) kindled a
number of questions with respect to the type of firms operating in the industry
and their key business drivers. Trade literature also pointed to changes in
small drug development firms with respect to their core business. The
anecdotal evidence in the trade literature together with personal experience
suggested that some firms were not necessarily research oriented as was
commonly understood.

This research has therefore set out to prove the existence of a new type of
firm and understand where it has come from. The first research question is
therefore as follows:

1. What changes have occurred in the division of labour in the
pharmaceutical sector?

Ongoing advances in both biotechnology and small molecule drug discovery
have increased the stock of available knowledge related to drug discovery
but the costs of drug discovery and development have continued to rise.
However, success in terms of new drugs approved has not risen in
conjunction with the expectations related to this new knowledge. The nature
of the impact of finance was visible in the firms that the author was exposed
to through the local and wider network and this also fostered key questions
about what this meant in terms of the decision making within the firm. The
key role of finance in terms of firms’ innovation strategies was also reflected
somewhat in the trade literature and reinforced the notion that there were
important questions to be answered. It was also apparent that some firms
were obtaining drug candidates for development from outside the firm, some of which were in advanced states of development. This seemed somewhat unusual for small firms but also seemed to be related to the financial considerations.

Therefore, this research then set out to understand both the role of finance and surplus of available knowledge in this division of labour based on personal experience, the literature review and anecdotal sector evidence. The following questions were posed on the specific role of financial considerations and a surplus of available knowledge related to drug candidates for development:

2. What was the role of finance in the new division of labour?

3. What was the role of a surplus of knowledge in the new division of labour?

Given that a new type of firm was visible in the sector and its focus was not on research, this also implied that changes to other firms may have been taking place and consequently changes in the markets for technology. Again, personal experience and evidence from the trade literature suggested that the flow of products and knowledge between the various firms in the sector may not be as straight forward as previously thought. Historically, these relationships were thought of as a flow of products from small firms to large firms with large firms providing expertise in clinical development but the flow of products and knowledge may be more complex with large firms transferring products to small firms and indeed the presence of a new type of firm. This was considered another very important area for testing empirically and the final question was as follows:

4. What was the nature of changes in the markets for technology?

It is hoped that by addressing these questions, this research will make an important contribution to knowledge on the extent and nature of the changes occurring in this sector.
1.5. **Research Approach**

The research questions above necessitated two complementary approaches to ensure that they were adequately addressed. Testing the changes in the division of labour meant identifying and classifying a new type of firm called the ‘No Research Development Only’ (NRDO) firm. This also meant distinguishing the traditional classical biotechnology firm and ensuring that the difference between the two was clear, hence the term Discovery and Development (DD) firm was used. This required a quantitative approach to ascertain the extent of the existence of a new type of firm. Understanding why changes had occurred in the division of labour and markets for technology consequently required a qualitative approach.

1.5.1. **Quantitative Analysis - Database and Descriptive Statistics**

The research question related to the division of labour was focused on a specific cohort of firms because it was believed that the division of labour that had taken place was specific to small firms and more importantly, those that develop drugs for human use. This required the compilation of a sample of firms that were small drug development firms (each firm had to own at least one product in development). A sample of 100 firms was compiled into a database to provide data for identification of descriptive statistics that would indicate the presence of a new type of firm and thus a division of labour. Specific information was collected on each firm to determine if it was a NRDO firm or a DD firm. The number of NRDO firms and DD firms was ascertained from the sample based on the information gathered in the database.

1.5.2. **Qualitative Approach - Case Studies**

There are many questions that can be answered by data collection activities and a quantitative approach but a series of important questions were related to why changes had occurred and a multiple case study approach was deemed most appropriate. Eight firms were selected and in depth company profiles were put together as well as interviews with chosen firms to answer the important ‘why’ question to ascertain specific knowledge required to answer research questions 2, 3 and 4.
1.6. Contribution to Knowledge

This is a story of change. This research has set out to update our understanding of changes in the pharmaceutical sector. A new type of firm has been identified, changes to existing firms have been identified and changing patterns of interaction within markets for technology between all the firms in the sector have been identified. This research has highlighted the importance of finance and a surplus of unexploited knowledge both of which have a critical impact on the development of firms and thus changes in the division of labour and the markets for technology. Overall, there are consequences for the level of innovation and experimentation (defined as exploration and exploitation) in the sector that warrant important future research.

1.7. Structure of the Thesis

This thesis is divided into eight chapters and a brief description of chapters 2 - 8 follows:

**Chapter 2: Understanding the Division of Labour and Changing Firms in the Pharmaceutical Sector.** This chapter reviews the literature on the pharmaceutical sector, its history and the developments that have occurred related to changes in the knowledge base, the new classical biotechnology firm and the markets for technology. It also discusses how the sector has evolved and the role of knowledge and finance in that evolution.

**Chapter 3: Identification of Further Changes in the Pharmaceutical Sector.** This chapter examines the evidence and presents arguments for changes in the sector including the division of labour (with the identification of a new type of firm - the No Research Development Only firm) and the markets for technology.

**Chapter 4: Methodological Approach.** This chapter discusses the research questions and presents the research approach. The appropriate methodological literature is reviewed and discussed and the approach to answering the research questions is detailed.
Chapter 5: *Evidence for the Changing Division of Labour and Markets for Technology*. This chapter presents the findings from the quantitative analysis that was conducted. It discusses the database that was formed and the results of the data analysis. The evidence for a new type of firm is put forward.

Chapter 6: *Case Studies*. Case studies were compiled on four NRDO firms and four DD firms. This chapter presents the highlights from the case studies and discusses the key issues that emerged from the study of the eight firms.

Chapter 7: *Understanding and Explaining the New Division of Labour and Changes in the Markets for Technology*. This chapter reviews all of the findings from the data gathered in the database and from the case studies and the case is presented for a changed division of labour in the pharmaceutical sector related to finance and a surplus of unexploited knowledge. Evidence for changes in the markets for technology is also presented and discussed.

Chapter 8: *Conclusions of the Research*. This is the final chapter and summarises the key findings from the research and outlines the overall contribution to knowledge. There is evidence for a changed division of labour with the identification of the NRDO firm and evidence for more complex markets for technology. Areas for future research are presented.
Chapter 2. Understanding the Division of Labour and Changing Firms in the Pharmaceutical Sector

2.1. Introduction

The dynamics of an industry and the way in which firms evolve, adapt and survive or die poses many interesting questions for researchers. The organisation of firms and firm boundaries will change continuously throughout the evolution of an industry (Malerba and Orsenigo, 1996) and this is particularly evident within the pharmaceutical sector\(^4\) with respect to those firms that discover and develop new drugs. Discoveries in biotechnology, particularly related to molecular biology, represented important advances in the way in which companies in the pharmaceutical sector looked at how to create and develop new drugs. The entry of the new ‘Classical Biotechnology Firms’ (McKelvey, 2008) into the pharmaceutical sector represented a fundamental change in the division of labour with respect to the discovery and development of new drugs.

These firms were the initial conduits of the new knowledge from public sector institutions to the commercial sector where this knowledge was then developed and sold. The supply of new knowledge from these institutions was a fundamental part of the reason for the existence of the new small ‘classical biotechnology’ firms whose primary business was the ‘exploration’ of knowledge, tools and techniques related to the new discoveries in biotechnology. This process was later facilitated by regulatory changes, particularly in the US, (the Bayh-Dole Act) allowing intellectual property to be traded between public institutions and private firms\(^5\).

The entry of new firms into the sector was also greatly impacted by the role of financial providers and their willingness to fund these new firms. These new small firms needed to finance their businesses and understanding the

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\(^4\) As captured particularly succinctly by Mazzucato and Dosi, ‘which we take nowadays to include both pharmaceutical and biotechnology firms’ (Dosi and Mazzucato 2007).

\(^5\) it should be noted that Genentech was created before this.
extent to which their businesses were the manifestation of the availability and source of finance is discussed as a fundamental enabler of the division of labour in this sector. This link specifically between the division of labour and the role of finance has not been researched in any great depth in the literature to date. The entire spectrum of drug development is a capital intensive process that has become steadily more expensive. The financial needs of those companies that pursue the development of drugs for human use are substantially different and are in marked contrast to any firm who has self funded (using personal finance) or obtained debt finance (Grieve-Smith and Fleck, 1988). Firms have had to look externally for finance because of substantial resource requirements and the time it takes to generate a product that can be sold. Estimates at the end of the 1990s put the cost of drug development at around $802 million (DiMasi et al, 2003) but current estimates are in excess of $1 billion and include potential costs of developing so called ‘biopharmaceuticals’ (DiMasi, 2007). However, more recent arguments on the poor performance of small firms in this sector have indicated that changing financial considerations and pressures may well be forcing firms in a different direction and thus fundamentally altering the division of labour once again.

The markets for technology that have emerged in this sector have been the source of much discussion and analysis (viewed by some as markets and others as networks with varying degrees of overlap, agreement and disagreement). The role of markets for technology in this sector is integral to the division of labour. There is considerable variety in the nature of how these transactions take place but they have been critical to the survival of both types of firm in the sector: the new small firm and the incumbent large firm. This discussion summarises why and how markets for technology emerged and characterises the current understanding of the flows of knowledge between the various main players in the sector.

The contention of this thesis is that a new chapter is unfolding in the pharmaceutical sector – a new division of labour associated with changes in the availability of knowledge and increasing financial pressures. This is also
accompanied by further changes in the markets for technology which are becoming more complex than has been previously recognised. The literature review therefore also covers previous conceptual and empirical studies that are subsequently used to build an analytical framework to investigate these propositions. The focus of this chapter is to discuss how and why firms have evolved in the business of making drugs and how the interplay of knowledge, finance and markets has impacted that evolution and thus the division of labour.

The chapter is structured as follows: the first Section, 2.2 describes the overarching literature on the dynamics of industrial evolution to provide a theoretical foundation for the research and also discusses the role of finance within firm development and growth on a macro level. Section 2.3 then provides an overview of the pharmaceutical sector. This section is divided into six main areas. The first three sections 2.3.1 to 2.3.3 deal with a historical overview of the sector by epoch. The developments in biotechnology and the subsequent impact on the sector as a whole are then discussed in the latter three sections 2.3.4 – 2.3.6 addressing the division of labour that was characterised by the classical biotechnology firm with a discussion of the emergence of this small firm and its major characteristics. This section also deals with the role of finance during this period and its relationship to the division of labour. The discussion then moves onto the role of networks and markets for technology a critical feature of the third epoch. Section 2.4 deals with how both the small firm and the large firm went through a series of changes to their activities and thus their business models and introduces the notion of exploration and exploitation as a lens with which to view how and why firms may change the scope of their activities.

2.2. **Industrial Evolution and Firm Growth**

2.2.1. **Structural Transformation of Industries**

The fact that industries grow and change (and within them firms are the engines of this change) should be no surprise to anyone in the second decade of the 21st century. The essence of this is captured by Malerba and Orsenigo who note that, ‘*Industrial evolution is characterized by intense*
change at any relevant time scale. New firms enter a sector, some exit, some firms grow, others decline. In addition, economic entities expand or contract their boundaries and undergo organizational change’ (Malerba and Orsenigo, 1996).

It must be recognised that our understanding of how and why that change takes place must constantly be updated and the way in which industries grow and change remains a constant push for research into how this transformation takes place. This is also because of the need for dynamic and responsive policy and economic and education systems that can nurture growth (Nelson and Winter, 1982). Much research has already been conducted within the realm of industrial change. According to Metcalfe, ‘it should not be necessary to belabour the evidence in favour of the ongoing structural transformation of economies as they develop and grow, the support for this most important of stylized facts is conclusive’ (Metcalfe, 2002).

That being said, this section very briefly revisits some of the major contributions in this area because they undoubtedly anchor this research to a body of critical knowledge that has been built up over the last century. There is probably no better place to start than with Schumpeter whose work recognised the inherent importance of technological change and innovation to the economy and the role of the entrepreneur in the development process of ‘carrying out new combinations’ (Nelson and Winter, 1982). His Mark I and Mark II theories alternately viewed the role of large and small firms as varying in their importance to economic growth. Notably Schumpeter revised his stance on the role of small firms in his Mark II theories from recognising them as important engines of economic growth to also acknowledging that large firms had a critical role to play in technological change and economic growth (Nelson and Winter, 1982). Schumpeter succinctly identified the varying contributions of large and small firms in sector change. The former was noted for its ability to reap advantages from large scale use of an innovation and the latter for its ability to carry out ‘new combinations’ (Nelson and Winter, 1982).
Nelson and Winter’s contribution to the theory of economic growth and sector evolution is another key part of the primary foundation to any contemporary study on industrial dynamics and change precisely because the theories inherent in this work were advanced to take account of the evolutionary nature of industrial change. That is, firms grow and change/adapt in response to their environment (Nelson and Winter, 1982). In changing situations, ‘...firms do different things... some of these turn out to be more successful than others. The least satisfactory of the responses may tend to be eliminated; the better of the responses tend to be used more wisely’ (Nelson and Winter, 1982).

This was critical in terms of the ability to explain varying outcomes of success for different firms in a range of situations. It is important for this research because it creates the starting point: that firms are responsive entities and will change in order to make sure that they can continue their business in their current environment. And yet according to Malerba and Orsenigo, a full understanding of the dynamics and evolution of industries is ‘far from accomplished’ (Malerba and Orsenigo, 1996). While some dimensions of sector dynamics have been examined in depth and structural dynamics have been explored by the sector life cycle model, not much is known about the structural evolution of industries (Malerba and Orsenigo, 1996). Malerba’s later contribution to the debate within the sectoral systems approach was key. He proposed that a ‘sectoral’ view provided a ‘multidimensional, integrated and dynamic view of a given sector’ (Malerba, 2002). The sectoral view took into account products and ‘the set of agents carrying out market and non-market interactions for the creation, production and sale of those products’ (Malerba, 2002). The interactions of various agents (individuals and organisations) are shaped by institutions and thus a sectoral system will undergo change through a process of coevolution of its various constituent parts. Essentially this tells us that industrial change is an all encompassing process that is shaped by a range of agents involved in many different ways. For this research it sets out an important framework with respect to understanding and explaining issues such as a division of labour and the markets for technology. It provides a base that acknowledges
the role of such factors as knowledge and finance in the evolutionary
process.

The role of knowledge in the process of industrial change is key. New
knowledge is unevenly distributed and will inevitably open up further
opportunities for innovation and investment; in essence economic growth is
predominantly due to the growth of practical knowledge. Knowledge driven
systems are unpredictable and necessarily evolutionary in their nature
(Metcalfe, 2002). This is particularly relevant for the pharmaceutical sector
and is discussed in further detail in the following section. The pharmaceutical
sector is an excellent example of how new knowledge can impact and
transform a sector and provides an important basis for this study. The major
changes that took place in this sector over its lifespan (but particularly in the
third epoch) provide an important foundation for discussing further changes.

2.2.2. Finance and Firm Growth

The role of finance in terms of its impact on the ability of a firm to emerge
and grow must be included in any discussion that relates to changes to firms,
industrial dynamics and evolutionary change. It becomes particularly relevant
in any discussion involving the pharmaceutical sector because of the very
high costs associated with product development (DiMasi et al, 1991; 2003;
2007). The entire spectrum of drug development is a capital intensive
process that has become steadily more expensive, particularly in the third
epoch (Grabowski and Vernon, 1994; Pisano, 2006). Therefore, this section
is intended to provide a high level overview of the key points related to
finance and firm growth in the innovation and finance literature to ground this
discussion in an overall context that clearly relates finance (including sources
of finance) to a firm’s strategy and indeed its existence and growth.

According to Denis, small firms and new businesses in general have become
an increasingly important part of economic development, particularly in the
US (Denis, 2004). Audretsch notes that new firm creation is important for
employment growth (Audretsch, 2002). Overall, the rate of new firm
incorporation has increased with this trend continuing throughout the 1990s
(Denis, 2004). The process of nurturing small firm formation and growth has been acknowledged in the context of its importance relative to the creation of new innovative sectors and therefore the role of government has expanded in the last few decades as many governments have instituted programmes to provide funding to new small firms (Moore and Garnsey, 1993; Lerner, 1999; Oakey, 2003). There has also been an increase in the amount of capital allocated to the private equity market with the most dramatic increase in funds allocated to venture capital increasing from $3.1 billion in 1992 to a high of $87.3 billion in 2000 (Denis, 2004). These numbers suggest that growing numbers of new firms correspond to growing capital markets.

The question of finance is central to the existence of all firms (but particularly new small firms) as they need to raise, use and reproduce capital in order to discover, develop and market products (Tylecote and Ramirez, 2006). While financial issues impact all firms, this has particular relevance for the smaller, human therapeutics firm or the (drug) discovery and development (DD) firm. Overall, one of the most important issues facing small firms is their ability to access capital (Denis, 2004). Historically, small firms have always faced funding issues (Moore and Garnsey, 1993; Oakey, 2003) where the problems of information asymmetry and sophistication of technology have traditionally impacted a firm’s ability to obtain funding. Small firm growth is constrained by lack of finance, particularly where technological sophistication is a factor (Westhead and Storey, 1997). Finance is required to conduct research and development at the pre-product stage and at this early stage, there are no guarantees that there is a viable market, let alone a viable product (Westhead and Storey, 1997).

In terms of access to capital for new small firms, studies such as that by Moore and Garnsey illustrated the difficulties that small innovative firms face.

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6 A private equity security (investment) is exempt from registration with the Securities and Exchange Commission by virtue of its being issued in transactions “not involving any public offering” and it includes all forms of investment such as venture capital and angel investments in a range of transactions. ([http://www.federalreserve.gov/pubs/staffstudies/168/default.htm](http://www.federalreserve.gov/pubs/staffstudies/168/default.htm))

7 Venture capital is a specific type of private equity
when financing their business. Uncertainty around the commercial prospects of new products as well as uncertainty around managerial competence explains why firms face difficulties raising capital (Moore and Garnsey, 1993). The study noted that an ‘information gap’ (which has also been labelled ‘information asymmetry’) between seekers and providers of capital also exacerbates the difficulties of financing new small firms. Available financing for small firms was also found to be deficient at the time (related to the 1980s in the UK). Westhead and Storey found that continual financial constraints on firms impeded firm growth, particularly when compared with less technologically sophisticated firms confirming prior findings by Oakey in 1984 (Oakey, 1984; Westhead and Storey, 1997). Therefore, if firm growth is impeded by a lack of finance, the converse must also be true that firm growth and change is therefore impacted by those financial sources that support and fund their growth. This is discussed further in Section 2.3.5.

2.3. Pharmaceutical Sector Overview

2.3.1. The Nature of Firms and Product Development 1850 - 1945

The history of the pharmaceutical sector can be broadly divided into three epochs, the first two of which are prior to the developments in modern biotechnology. The first epoch, which has been broadly related to the period between 1850-1945, was one where firms were concerned with making drugs related to chemicals (McKelvey and Orsenigo, 2001; Walsh, 2004) and a gradual integration of microbial biochemistry based on the acceptance of the germ theory of disease (Galambos and Sturchio, 1998). Many of the early companies leveraged competencies in organic chemistry to manufacture drugs. The approach to drug discovery was based on a tradition of the medical use of plants known also as the Extractive Paradigm (Walsh, 2004).

It was during the mid to late 19th century that major changes took place and firms were formed that supplied drug related products in the form of alkaloids (plant extracts) which were usually supplied to pharmacists for final preparation. The initial business model was for large firms to supply the intermediate products; the preparation of the drug using those products was
up to the pharmacist effectively illustrating a division of labour. It was dependent on the ability of pharmacists to prepare the drugs prior to sale to the customer. However, there were two major types of pharmaceutical firm during this first epoch. The first type were large chemical producing companies with specialised pharmaceutical divisions that diversified from their core business to produce pharmaceuticals. This included German chemical giants such as Ciba, Bayer, Hoechst, IG Farben and Sandoz as many of the first drugs were dyes and dye intermediates (Walsh, 2004). These firms that diversified were mainly German and Swiss chemical firms that capitalised on their scientific and technical competencies in organic chemistry as well as chemical synthesis and medicinal chemistry (Orsenigo, 1989; Walsh, 2004; Mazzucato and Dosi, 2006). According to Walsh, the first site of specialist mass production for pharmaceuticals was opened in 1813 in Germany (Walsh, 2004).

The second type of firm was formed specifically to produce pharmaceuticals predominantly in the UK and the US. These specialised ‘imitator’ companies included Pfizer, Wyeth, Eli Lilly and Warner Lambert that emerged to engage in the marketing and sale of pharmaceutical products. They also pursued linkages with universities for chemistry. These companies started out as manufacturing pharmacies and evolved into the fully integrated pharmaceutical companies that came to prominence in the 1930s and 1940s (Galambos and Sturchio, 1996).

During the first epoch of the development of the pharmaceutical sector the dominant business model was the large pharmaceutical firm and consequently the major source of funding was revenues from their product sales. It is generally understood that up until the discovery of Sulfonamide in the 1930s, very little formal research was conducted by these firms (McKelvey and Orsenigo, 2001). Some of these firms were publicly traded and listed on various international stock exchanges and so were able to utilise revenues from issues of stock for the conduct of their business.
2.3.2. **The Nature of Firms and Product Development 1945 – 1980**

The second epoch characterised as the random screening period, is generally considered to run from 1945 to the early 1980s. The Second World War created enormous changes in the pharmaceutical sector and stimulated greater demand for drugs and ultimately precipitated a large increase in research and production efforts of US companies as the government sponsored the accumulation of vast search capabilities (Mazzucato and Dosi, 2006). The Second World War also precipitated critical changes in the levels of government funding of research and greater amounts of research activity took place in publicly funded institutes. Governments ultimately became more active funders of research, particularly in the USA (McKelvey and Orsenigo, 2001).

The commercialisation of penicillin proved to be a profitable enterprise and firms began to organise large R&D units within their organisations. After the success of the discoveries related to antibiotic manufacturing and the realisation of the extent of the potential pharmaceutical market demand, firms’ business models were adapted to focus on research in drug discovery and the ability to randomly screen vast numbers of synthesised chemicals. But in terms of product development, the emphasis during this period was on naturally derived as well as chemical products which were randomly screened in test tube experiments and in laboratory animals for therapeutic activity. Companies were ‘mastering drug development by design, applying the molecular insights provided by microbial biochemistry and enzyme inhibition’ across a broad front (Galambos and Sturchio, 1998). However, this search process was inefficient and estimates put the rate of success at around one compound in five thousand (McKelvey and Orsenigo, 2001).

The large and vertically integrated firm led the sector into the age of medicinal chemistry (Galambos and Sturchio, 1998). Thus, companies funded capabilities in analytic and medicinal chemistry to design new compounds as firms realised that drug discovery and development could be a highly profitable enterprise given the target rich environment (McKelvey and Orsenigo, 2001). By the time significant advances in biotechnology were
being realised, the pipelines of large vertically integrated firms contained promising new drug candidates. The method of random screening worked well enough to generate several important new drugs creating these ‘blockbuster’ products that were extremely successful. This meant that firms were dependent on the revenues from these products, but as large markets were apparent, firms experienced high rates of growth and were able to internally fund their discovery and development activities.

However, during this epoch key changes in the regulatory environment also impacted the financial requirements of drug development. The regulatory requirements demanded by the Food and Drug Administration (FDA) in the USA (Kefauver-Harris Drug Amendments of 1962) and the Medicine Act in the UK in 1971 placed a burden of proof on firms to prove the efficacy and safety of a drug based on adequate and controlled trials (McKelvey and Orsenigo, 2001) and this dramatically increased the costs associated with new product development in this sector. This increased the resources necessary to obtain new drug approval (and thus increased drug development costs overall) as well as prolonging the time it took to develop a new drug (McKelvey and Orsenigo, 2001).

**Summary**

The history presented thus far of the pharmaceutical sector illustrates how the sector was dominated by the presence of large firms and the importance of the chemistry knowledge base. By understanding the historical development of the sector it is possible to contrast this to the following epoch and demonstrate the significant structural change that took place related to the emergence of new types of knowledge.
2.3.3. The Third Epoch of the Pharmaceutical Sector - Modern Biotechnology, the Division of Labour and Changing Markets for Technology

2.3.3.1. Sector Boundaries and Knowledge Bases

The third epoch of the development of the pharmaceutical sector is fundamentally characterised by the key discoveries related to biotechnology\(^8\) (and developments in information and communication technologies). The identification of the double helix by Watson and Crick in 1953 ultimately triggered a new epoch of technological and industrial change for a range of industries driven by biotechnology based discoveries. The development of new knowledge bases in modern biotechnology was then given another boost in 1973 with Cohen and Boyer’s recombinant DNA technique essentially providing the means for genetic engineering. This technique ultimately made it possible to alter the genetic code of an organism and manipulate protein production (Mowery and Rosenberg, 1998). For the pharmaceutical sector, these discoveries heralded the increased understanding of biological systems and the mechanism of action of many drugs.

There were now two distinct paradigms in drug discovery, but one did not displace the other. Biotechnology added new approaches to the toolkits of the drug innovators (Walsh, 2004) and radically changed both the prospects and the processes of drug discovery (McKelvey and Orsenigo, 2001). It provided a methodological basis for creating potential new pharmaceutical products including creation of targets for screening and evaluating potential drug products (Zucker and Darby, 1997). Changes in the underlying knowledge bases of the pharmaceutical sector occurred thanks to discoveries related to biotechnology and these knowledge bases are fundamental to the pharmaceutical sector and have profoundly impacted the organisation of the sector. Critically, a new breed of small firms emerged

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\(^8\) Authors such as Powell have noted that Biotechnology is not a sector but rather a set of tools and techniques (Powell 1996).
that were able to capitalise on the opportunities that this new knowledge created.

2.3.4. A New Division of Labour – Classical Biotechnology Firms

The most striking institution to come out of the developments in biotechnology was the small start up firm founded by entrepreneurs and university professors and funded by venture capital (Kenney, 1986). McKelvey has labelled this general model as the ‘classical biotechnology firm’ (McKelvey, 2008). However, it should be noted that this does not necessarily indicate a homogenous class of firms rather, it identifies firms with important similar characteristics overall. These were firms engaged in exploratory activities utilising new technologies (the balance between exploration and exploitation is discussed further in Section 2.4). The definition of exploration utilised here is ‘the pursuit of new knowledge of things that might come to be known’ (Levinthal and March, 1993). This characterised the division of labour. This is illustrated in Figure 1.

This diagram depicts the various stages of drug discovery and development in order to clearly demonstrate the key activities undertaken by this new agent, the classical biotechnology firm. These firms were formed primarily to develop new knowledge and technology associated with the early stages of drug discovery. This focus on these early stage exploratory activities illustrates clearly the division of labour where most new small firms focused their activities on the upstream areas of research in drug discovery (Kenney, 1986; Orsenigo, 1989; Gambardella, 1995; Powell et al, 1996; Henderson et al, 1999; McKelvey and Orsenigo, 2001). Some firms integrated further downstream as illustrated by the presence of firms to the right of the solid line in the diagram but it should be noted that these firms also continued to conduct research and discovery.
Figure 1. The Classical Biotechnology Firm and the Division of Labour
Based on a review of the associated literature, there were several attributes that many of these firms have in common and so three important dimensions of the classical biotechnology business model can be identified: 1. Source of knowledge and technology; usually an academic institution, 2. Source of funding; usually venture capital and large firms and 3. Collaboration; many of these firms entered into agreements with other firms and institutions (Kenney, 1986; Orsenigo, 1989; Henderson et al, 1999; McKelvey and Orsenigo, 2001; Pisano, 2006). The resulting classical biotechnology business model is indicative of many firms who have been founded since the 1970s. Genentech is a good example and indeed the first example of the classical biotechnology business model where the academic founders together with venture capital backing commercialised their university based scientific discoveries in biotechnology (McKelvey 1996) through research agreements with other firms (in this case Eli Lilly).

2.3.4.1. Source of Knowledge and Technology

Importantly, these firms formed during this epoch of the development of the pharmaceutical sector have been characterised as university spin-offs. Many firms were typically founded as a spin-off from publicly funded research in molecular biology following important discoveries that were made in an academic setting\(^9\) (Kenney, 1986; Henderson et al, 1999; McKelvey and Orsenigo, 2001). Academic scientific discoveries and technological inventions were then developed within the boundaries of these entrepreneurial firms. These were firms founded by new innovators who were not locked into the old established procedures and research perspectives (Walsh et al, 1995). This new knowledge originated in the universities and publicly funded government laboratories and as such these firms were formed as a result of collaboration between scientists (usually those responsible for the various discoveries being commercialised) and professional managers who brought business acumen to the venture.

\(^9\) Genentech, the first so-called classical biotechnology company, was formed by Herbert Boyer (involved in the development of recombinant DNA) with Robert Swanson (a venture capitalist).
However, the role of intellectual property rights (IPR) and changes in the rights of universities with respect to their IPR in particular (especially in the US), played a key role in the ability of universities to commercialise knowledge and thus the prolific genesis of new firms. The Bayh-Dole Act in 1980 allowed universities to retain the rights to inventions that were derived from federally funded research and a further change in 1984 expanded university rights further in terms of their ability to assign property rights to other parties e.g. spin out firms (Henderson et al, 1999). The increased direct involvement of universities and their scientists in commercial activities played a key role in enabling the new division of labour as universities became directly involved in entrepreneurial activities.

2.3.4.2. **Source of Funding**

Genentech was the first biotechnology firm founded in 1976 using a business model that included venture capital backing (McKelvey, 1996). Genentech’s example was closely followed by a large number of firms, particularly after their successful Initial Public Offering (IPO) in 1980 which opened up public markets to these types of firms (Ryan et al, 1995; Pisano, 2006). As the potential for a successful IPO became apparent, more funding for classical biotechnology firms was available from venture capital sources. However, established companies formed an equally important source of funding (Arora et al, 2001). Established companies needed to acquire and develop this new knowledge so they entered into a range of different types of agreements with the new small firms and provided funding in exchange for research and development contracts.

2.3.4.3. **Collaboration**

The growth of knowledge from the discoveries made in biotechnology created a need for incumbent firms to acquire and develop expertise in this new knowledge. Conversely, many new small firms who were involved in exploratory research and trying to make drugs were not able to become fully integrated because of the cost, scale and expertise required. Consequently, a market for knowledge and products emerged in the pharmaceutical sector. Many of these companies who were specialised suppliers of high technology
intermediate products entered into agreements with incumbent large firms (Powell et al, 1996; Henderson et al, 1999; McKelvey and Orsenigo, 2001; Arora et al, 2001; Pisano, 2006). The sheer number of these agreements resulted in a vast network of firms that also included many other agents including financial providers, universities and other intermediary firms (Powell et al, 1996; Powell, 1998; Arora et al, 2001). Markets for technology were an important part of this network (Arora et al, 2001). This is widely recognised as a key distinguishing factor of the third epoch and this discussion is revisited in greater detail in Section 2.3.5.

2.3.5. Finance and Drug Development During the Third Epoch

The substantial financial requirements prohibited many firms from becoming fully integrated and in essence, the division of labour is closely related to the financial difficulties faced by these classical biotechnology firms. Financial considerations are exceptionally important to firms in this sector because of the long product development life cycle and the associated regulatory requirements that are involved in terms of clinical testing as well as quality assurance. These regulatory requirements have impacted the time that it takes to develop and test a new drug product and therefore have impacted the cost of drug discovery and development (Grabowski and Vernon, 1994; McKelvey and Orsenigo, 2001; Pisano, 2006). Current estimates illustrate that it may take an average of 10 years to develop a product (DiMasi et al, 2003). According to Arora et al 'it soon became clear that the high costs and high failure rates of product development and commercialisation in pharmaceuticals were a serious barrier to the vast majority of biotech start-ups' (Arora et al, 2001). As a result, many small firms specialised in the earlier research stages (Orsenigo, 1989; Gambardella, 1995; Henderson et al, 1999; McKelvey and Orsenigo, 2001; Pisano, 2006). The following discussion is intended to understand more about the cost pressures involved in this sector and the providers of finance that in essence enabled the growth of the small classical biotechnology firm during the third epoch.
2.3.5.1. **Financial Requirements for Drug Development**

The drug discovery and development continuum diagram above (Figure 1) illustrates that the path of drug discovery and development can take up to 18 years (Pisano, 2006). The table below has been compiled by the author to capture four important aspects related to the financing of this sector that have not previously been assembled in this way: 1. Overall exploration/exploitation phases; 2. Specific key phases of the drug research and development (R&D) lifecycle within the overall exploration/exploitation phases; 3. the estimated costs for the various phases (where provided) and 4. The primary sources of funding. This was compiled based on a review of the available evidence from the range of key sources on the sector (noted below).

**Figure 2. Costs of Drug Development and Proposed Sources of Finance During the Phases of Drug Development**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Regulatory Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Out of Pocket Costs</td>
<td></td>
<td></td>
<td>$15.5m</td>
<td>$23.5m</td>
<td>$86.3m</td>
<td></td>
</tr>
<tr>
<td>Total Capitalised Costs - Preclinical and Clinical Period</td>
<td>$335m</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Source of Capital</td>
<td>Personal Finance</td>
<td>Business Angels</td>
<td>Government Seed Venture</td>
<td>Corporate Venture</td>
<td>Venture Growth Public Equity</td>
<td>Corporate Venture</td>
</tr>
</tbody>
</table>

**SOURCE:** Compiled by the Author based on DiMasi et al, 2003
NOTE 1. The Discovery phase includes the phases of: Target Identification, Target Validation, Lead Identification, Lead Optimisation.

NOTE 2. The proposed sources of capital by phase of drug development have been compiled by the author based on input from a range of sources (Kenney, 1986; Orsenigo, 1989; McKelvey and Orsenigo, 2001; Pisano, 2006; Hall and Wood, 2008) in an effort to gather together all of the current information on the financial life cycle of the drug development firm which was not explicitly available in the literature.

DiMasi et al analysed the research and development costs of a random selection of new drugs, utilising data obtained from 10 pharmaceutical firms (DiMasi et al, 2003). Their findings represent the most in-depth analysis to date and the best currently available estimates of the total costs for the clinical drug development period. The combined costs are estimated at $802 million. The table illustrates the required financial resources separated into the two major periods: drug discovery (exploratory phase) and drug development (exploitation phase). This allows a comparison of costs as they relate to these two major phases. The data shows that the discovery phase of drug development represents 42% of the total estimated costs while the development phase represents 58% of costs. From the perspective of the small firm, this means that developing a drug all the way to regulatory approval would, at a minimum, double the cost involved.

The difference between out of pocket costs and capitalised costs as presented in the table, however, is significant. It must be noted that capitalised costs are based on the data obtained from relatively large firms and include significant resources and funding needs associated with the running of a large firm. These costs include such things as the process of capital depreciation over time (DiMasi et al, 2003). The actual out of pocket costs are therefore significantly lower at roughly $125 million which is almost a quarter of the capitalised costs but still a substantial sum. If the same ratio was applied to the discovery phase out of pocket costs (about 27% of capitalised costs), these costs would still be around $90 million.
Undoubtedly, this still represents a large sum of money for a small firm to raise and represents one of the key reasons why the division of labour in the sector meant that small firms only focused primarily on the exploration/discovery end of the continuum. It was too expensive to be fully integrated. It also illustrates another key point: financial requirements were critical to the growth and survival of the firm and thus those who covered these costs ultimately facilitated the division of labour and the emergence of successive waves of small firms. External sources of finance were critical enablers of the division of labour by enabling the entry and growth of firms in this sector. Venture capital, the public stock market and large firms are the most widely cited sources of finance for new small firms in this sector (Kenney, 1986; Orsenigo, 1989; McKelvey, 1996; Henderson et al, 1999; McKelvey and Orsenigo, 2001; Walsh, 2004; Pisano, 2006; McKelvey et al, 2006; Lazonick and Tulum, 2010). Mc Kelvey and Orsenigo noted that ‘There is little question that venture capital played a key role in facilitating the creation of New Biotechnology Firms and of a market for technology in the USA’ (McKelvey and Orsenigo, 2001). They also add that ‘Larger established corporations provided a potentially even more important source of capital’ (McKelvey and Orsenigo, 2001).

2.3.5.2. Sources of Funding for the Classical Biotechnology Firm During the Third Epoch – Venture Capital, The Stock Market and Large Firms

Given the nature of the difficulties facing new small firms in obtaining finance, it therefore begs the question of who then provides these valuable sources of finance when they can be obtained. As most firms are typically not profitable in the beginning and lack tangible assets in many cases, debt financing is not an option (Denis, 2004). Primary sources of outside equity financing include: venture capital/angel investors and corporate investors. However, for those small new firms entering the pharmaceutical sector, the role of funding from established incumbent companies, public stock markets as well as venture capital have formed the most substantial sources of funding (Lazonick and Tulum, 2010). The role of large incumbent firms as funders of small new firms in the sector was (and is still) considerable (Gambardella, 1995; Arora et al, 2001, McKelvey and Orsenigo, 2001; Pisano 2006). Most recent figures
suggest that over $17.2 billion was spent by large incumbent firms on corporate partnering (of which R&D alliances are an important form) (Lazonick and Tulum, 2010). From 1978 – 2004, venture capital investments in the ‘biotech’ sector totalled over $38billion (Pisano, 2006). According to Pisano public equity markets accounted for $168 billion of IPOs (as well as secondary stock issues by US biotechnology companies) between 1978 and 2004 (Pisano, 2006). Two-thirds of these funds were raised after 1993 and most of the money flowing into the sector was during the speculative boom of 1999-2000 (Lazonick and Tulum, 2010). These sums of money suggest that the role of financial providers in shaping the sector is therefore significant.

Genentech’s business model was based on venture capital backing that meant that the firm eventually went public (listed on the stock market). Genentech’s example was closely followed by a large number of firms, particularly after its successful Initial Public Offering (IPO) in 1980 which essentially opened up public markets to classical biotechnology firms (Robbins-Roth, 2000; Pisano, 2006). Genentech’s alliance with Eli Lilly provided another valuable source of funding and was also influential in its IPO success. The story of Genentech essentially illustrates the three major sources of funding that were most notable for the new small firm. As the potential for a successful IPO became apparent, more funding for these new small firms was available from venture capital sources and the public stock markets (Pisano, 2006). Thus the development of small new companies in the early stages of the third epoch of the pharmaceutical sector was very closely associated with the availability and willingness of venture capitalists, large firms and the stock market to provide a source of finance to these new small firms. Financial deregulation encouraged the development of venture capital markets and in particular, the ability of pension funds to invest in venture capital (Jeng and Wells, 2000; Walsh, 2004). The Bayh-Dole Act of 1980 (that encouraged patenting of the output of publicly funded university research) was also another important development that played a part in the financial relationships that became widespread between small start-up companies and venture capital firms because intellectual property (from universities) ownership was a critical part of being able to value a company.
However, an additional consideration (particularly for firms in this sector that require so much in terms of finance) is how these sources of funding can impact the activities of small firms and the balance of exploration and exploitation\textsuperscript{10} within the firm. The division of labour discussed earlier indicates that many small classical biotechnology firms in this sector are primarily exploratory firms and therefore the sources of finance that have supported these firms have also supported this level of exploratory activity in the sector overall. This is fundamental to this discussion because the basis for this research concerns the factors impacting the division of labour in this sector. The information on sources of finance is briefly reviewed to ascertain how sources of finance can have a direct impact on firm activities.

**Venture Capital**

As noted above, venture capital represents a key source of funding for the pharmaceutical sector. Venture capital can be defined as independent professionally managed dedicated pools of capital that focus on equity\textsuperscript{11} or equity linked investments in privately held high growth companies (Gompers and Lerner, 2001). The venture capitalist is understood to provide intensive oversight of firms in their portfolio (Lerner, 1995). Venture capital funding may be staged and thus linked to key milestones as venture capitalists seek to gather information and monitor the progress of firms. Further commitment of capital is only made contingent upon the achievement of these milestones (Owen-Smith et al, 2002) and this staging of investments is used as a tool for keeping the management team of the firm focused on key milestones critical to the firm’s successful development. They will also maintain the option to abandon projects (Gompers, 1995). It appears that venture capital firms are in a strong position to direct the operation of the firm based on the evidence. The potential for control over the level of exploration and exploitation within a firm is considerable.

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\textsuperscript{10} Exploration is defined as ‘experimentation with new alternatives’ while exploitation is defined as the ‘refinement and extension of existing competencies’ (March 1991).

\textsuperscript{11} Equity defined as ownership.
This influence increases with syndication. Venture capital investments in firms may also be made as part of a syndicate whereby a group of venture capitalists will make a joint investment in a firm. Consequently, another venture capitalist company’s willingness to invest may be an important factor in the final decision made by the lead venture investor (Lerner, 1995). This also means that if one investor decides not to invest, others may in turn also decide not to invest and so the nature of syndication also implies a wider impact on the entire sector because of the links between venture capital firms (Lerner, 1995). There is considerable potential for a widespread influence that would impact large numbers of firms and this has implications for a sector such as pharmaceuticals where so much venture capital is invested.

**Large Firms**

Most large pharmaceutical firms were (and still are) publicly traded and have historically had access to public stock markets to fund drug development. But the creation of NASDAQ and changes to stock market listing rules in various European countries created important opportunities for new and small firms to access capital through stock markets (Bertoni and Randone, 2004; McNamara and Baden-Fuller, 2007). But critically, Genentech’s successful IPO initially demonstrated that it was possible to raise money from public stock markets even without product sales revenues and that it also might be possible for these new firms to consider vertical integration (Henderson et al, 1999; McKelvey and Orsenigo, 2001; Pisano, 2006).

Established incumbent companies formed an important source of funding for new small firms in the sector which included equity and non-equity based investment. They needed to acquire and develop this new knowledge so they entered into a range of different types of agreements with small firms and provided funding in exchange for knowledge and products (Gambardella, 1995; Galambos and Sturchio, 1998, Henderson et al, 1999; McKelvey and Orsenigo, 2001). Historically, funding of research external to the large firm operating in the pharmaceutical sector was through agreements with universities or government funded institutions (Walsh, 2004). But large firms
essentially realised that they could exchange financial support and a range of capabilities in clinical research, regulatory affairs, manufacturing and marketing for the smaller firm’s technical expertise and/or patents (Galambos and Sturchio, 1998). As many new small firms represented a source of new product ideas it is understood that they offered the corporate sponsor a window on emerging technologies as well as a way to create new revenue streams.

**Public Stock Markets**

Public stock (equity) markets offer a way in which firms can raise enough capital to adequately fund the scope of their operations and this is the main motivating factor for firms that choose to go public (Arkebaur, 1991). As noted above, the costs involved in funding drug development, manufacturing and clinical testing operations are huge and venture capital and alliance revenues are not usually adequate particularly for those firms wishing to pursue vertical integration (Pisano, 2006). However, an additional benefit resulting from being a publicly traded firm is that the management of the company can issue subsequent shares at a later date to generate more funds. While this is subject to a range of particular rules and regulations, the potential to do this still represents a powerful way in which to generate subsequent funding.

Therefore, access to the large amounts of capital available through public stock market funding mechanisms was (and still is) an important funding opportunity for firms. A number of firms went public (issued shares on the stock market) to obtain significant amounts of funding for their business and their predominantly exploratory activities. But it was the creation of new small firm focused stock markets and thus the willingness of shareholders in both the US and the EU to invest in these promising new firms that was influential in the access to public stock market funding. A range of successful IPOs meant that investment in these new small companies who were predominantly exploratory in nature promised lucrative financial returns on investment for investors.
2.3.6. Coordinating the New Division of Labour

While some collaboration has been evident from the very earliest stages of the development of the pharmaceutical sector (sector/university collaboration between Hoechst and Cassella and the Erhlich institute in Frankfurt in the late 1800s) the greatest change in the extent and nature of collaborative relationships took place during the third epoch of the pharmaceutical sector. This ‘network’ of relationships became a critical feature of the sector (Arora and Gambardella, 1990; Powell et al, 1996; Powell, 1998). The discoveries in biotechnology impacted the development of complex organisational solutions between the academic community, established companies and classical biotechnology firms (Powell et al, 1996; Malerba and Orsenigo, 1996). This also meant that a market for technology emerged as firms entered into a range of agreements and transactions for trading technology, products and knowledge. The discussion below reviews the general nature of these relationships and the markets for technology in order to illustrate their importance and relevance, particularly to the division of labour discussion.

2.3.6.1. The Development of Networks

The literature concurs on one very important general point: that there has been a considerable increase in corporate partnering in various forms (Hergert and Morris, 1988; Hagedoorn and Schakenraad, 1990; 1995, Powell et al, 1996; Arora et al, 2001). Firms are working with external organisations to produce and exchange knowledge and products. According to Powell et al firms ‘execute nearly every step in the production process from discovery to distribution through some form of external collaboration’ (Powell et al, 1996). This corporate partnering has been characterised broadly as a ‘network’ of interorganisational collaboration by these authors (and others since) in order to capture the nature and extent of the variety of ways in which firms work together. The network is a term thought to best describe the interconnectedness between firms and other organisations that is all encompassing. The idea of a network covers the many ways that firms come together to work on various aspects of their knowledge and production processes including: R&D partnerships, equity joint ventures, technology exchange agreements, licensing and sub-contracting.
The network view also holds that ‘the complex reality of rapidly developing fields in which knowledge is both sophisticated and widely dispersed transcends the simple calculation of a make or buy decision’ (Powell et al, 1996). Collaboration in high-tech industries involves more than just formal contractual exchange and although these served a range of needs the key point is that these various forms of relationships were about more than contracts. Contracts were merely one of the many vehicles used by firms to exchange knowledge, services and products. For the pharmaceutical sector, this is particularly relevant because the nature of new and complex knowledge created the need for a wide variety of forms of collaboration between firms.

2.3.6.2. Markets for Technology

A related discussion has since focused on a more specific topic: the nature and working of ‘markets for technology’ (also called ‘markets for knowledge’) – namely markets for intermediate technological inputs12 (Arora et al, 2001). It is important to define technology in order to define intermediate technological inputs. The definition for technology as described by Arora et al is that technology can take the form of ‘intellectual property or intangibles, be embodied in a product or take the form of technical services’ (Arora et al, 2001). These intermediate technological inputs are the essence of what is being exchanged by large and small firms in the pharmaceutical sector. Drug candidates that have not yet been approved are a perfect example of an intermediate technological input.

These authors noted at the outset that the use of the term ‘market’ had to be utilised in a very broad sense because ‘strictly speaking, market transactions are arms-length, anonymous and typically involve an exchange of a good for money’ but the key issue is that ‘many if not most transactions for technology would fail one or other of these criteria’ (Arora et al, 2001). These authors discuss the nature of the way in which knowledge and technology are

12 There is a clear line between the market for the thing itself and the market for the technology used to create it (Arora et al, 2001).
exchanged in the pharmaceutical sector and conclude that ‘alliances are still a major factor in the sector and these are the form through which exchange takes place in this market for technology’ (Arora et al, 2001). They conclude that markets for technology are not easily defined but the value of this discussion for this sector is that it focuses on how and why firms can trade drug candidates which are intermediate technological inputs.

But the way in which these technologies are exchanged must also be understood which is how discussions on markets may provide more detail than discussions related to networks. Licensing is one of the many forms of technology exchange taking place within markets for technology in the sector and some authors have paid particular attention to its role in the sector because it is viewed as an important mechanism of exchange. According to Luukkonen, the drug discovery and development business is all about developing and out-licensing product innovations (Luukkonen, 2005). McKelvey also notes that business models of firms depend on obtaining and selling licenses in order to invest in research with long time horizons (McKelvey, 2008). Kollmer and Dowling define licensing as an important means of exploiting technological innovation within a firm that does not have the resources or assets to exploit their developments internally (Kollmer and Dowling, 2004). However, Powell et al reflect that licensing rarely occurs without prior contact between the two parties to explore the viability of the project. For this research, the network and market perspectives are complementary ways in which to view how firms in this sector work together to exchange and share technology on a continuum that involves a vast array of relationships. Having established some ways in which to view these relationships, the discussion can now turn to the nature of the relationships and why they were established.

2.3.6.3. The Development of Networks – New Knowledge Produced by Classical Biotechnology Firms

The classical biotechnology firm was a key agent in the exploratory research realm of the sector and embodied much of the new knowledge that was generated. Classical biotechnology firms concentrated on the development and transfer of these new technologies through various interactions
The classical biotechnology firms were faced with a much different problem to the incumbent firm which in turn led them to offer products and knowledge for sale. They lacked the resources to be able to manufacture, develop, distribute, market and support their own products. They needed financial assistance and clinical development expertise which they obtained from fully integrated companies. Many of the small firms who were involved in research and development to make drugs were not able to become fully integrated because of the cost, scale of resources and expertise required, as noted earlier. As a result, many of these companies became specialised suppliers of high technology intermediate products and entered into a wide range of agreements with large firms to exchange new products and knowledge for financial support as well as clinical development and regulatory expertise (Arora et al, 2001; McKelvey and Orsenigo, 2001; Pisano, 2006).

2.3.6.4. Acquisition of New Knowledge by Incumbent Firms

These new developments in the various fields related to molecular biology were not immediately integrated into the R&D departments of the majority of large incumbent firms. This was the first twentieth century transition in this sector where the initial stages of applied research and commercial development did not take place in the incumbent firms (Galambos and Sturchio, 1998). During the 1970s, at the same time the developments in biotechnology were taking place, large incumbent firms were more concerned with ‘mastering drug development by design’ building upon the knowledge gained from microbial biochemistry and enzyme inhibition in the 1950s and 1960s (Galambos and Sturchio, 1998). This approach was producing important new therapies for the large firms and was their primary consideration.

In addition, these large firms were making substantial investments in microbial biochemistry and enzyme inhibition illustrating that their focus was elsewhere at the time. As noted by Galambos and Sturchio ‘the former investments remained too promising; the latter investments [in
biotechnology] still too questionable to justify so sudden a change in research strategy’ (Galambos and Sturchio, 1998). The new developments were thus primarily the realm of the new small firm. Arguably this slow transition by the large incumbent firms created an important opportunity for small firms who were able to fashion themselves as research boutiques and therefore upstream providers of the new knowledge, tools and products (Galambos and Sturchio, 1998). In addition, Powell noted that large pharmaceutical companies lacked the kind of internal research environment that fosters innovation and that this was one of the primary drivers of why large companies sought relationships with smaller companies and paid for R&D (Powell, 1996).

The types of technological changes resulting from discoveries related to biotechnology meant that fully integrated pharmaceutical firms had to expand their knowledge bases and keep abreast of scientific developments (Gambardella, 1995; Galambos and Sturchio, 1998). The established large firms channelled their investments in biotechnology research to these new, smaller firms through a range of agreements forming a ‘network’ of collaborative endeavours and contracts. Ultimately, the incumbent firms had to incorporate the knowledge, tools and products associated with developments in biotechnology and this was done through many various agreements that were established between themselves and the new players in their market: the small classical biotechnology firm. Collaboration was key and these large fully integrated firms sustained their business model as competencies were gained through external relationships.

2.3.6.5. Characterising the Key Relationships in the Pharmaceutical Sector in the Third Epoch Market

The nature of the development of knowledge and technology in the sector meant that classical biotechnology firms were able to trade technology\textsuperscript{13} at various early stages of development because there was a corresponding

\textsuperscript{13} Defined utilising the Arora et al (2001) discussion that distinguishes ‘technology’ as an intermediate input.
need to acquire this technology on the part of large incumbent firms. The flows of technology can be thus illustrated in Figure 33.

The diagram shows the way in which knowledge flowed between the major types of organisation in this sector. The arrows are uni-directional to reflect the evidence the flows of technology specifically. The diagram thus represents what is currently understood in terms of the markets for technology in the pharmaceutical sector. It also reflects the division of labour. The universities and government laboratories are positioned at the top to reflect their important position as knowledge generators during this epoch. There is a better defined arrow that connects these institutions to the classical biotechnology firms to reflect the flows of knowledge. There is a less well defined arrow that connects these institutions to large pharmaceutical firms to reflect a smaller flow of technology and knowledge than that between public institutions and small classical biotechnology firms (as discussed). The most well defined arrow connects the classical biotech firm to large pharmaceutical firms to reflect a more substantial flow of technology and knowledge between these two major types of firm in the sector.

Figure 3. Markets for Technology – Historical Representation of Flows of Technology and Knowledge
2.4. **Understanding the Evolving Landscape of the Third Epoch of the Pharmaceutical Sector**

2.4.1. **Heterogeneity of Classical Biotechnology Firms – Analytical Debates**

The classical biotechnology model described above is a broad characterisation of the business model of many different firms that have emerged in the last 35 years. However, discoveries in modern biotechnology had consequences for a number of industries. As a result of the proliferation of research trajectories and techniques, a wide range of opportunities opened up for the creation of new firms who set about commercialising the discoveries that were being made at academic institutions (Orsenigo et al, 2001). Brink et al’s ‘Axis of product based sectors’ captures the diversity of the sectors impacted by biotechnology (Brink et al, 2006) including: Pharmaceuticals, Agriculture, Chemistry, Forestry, Pulp, Paper, Environment, Instruments and Equipment, Food and Medical Technology. Essentially, these discoveries created a market for new technology and opportunities for the formation of a large number of firms in a range of industries (Quéré, 2006).

Some recent studies on biotechnology firms have contributed to a deeper understanding of the heterogeneity of those firms within the classical biotechnology business model across the range of sectors impacted by biotechnology. Mangematin et al studied biotechnology firms across all application segments and looked closely at the pattern of development of and determined that there was a key difference in the business models of firms based on the desired growth and the subsequent size of the innovation project. This study differentiated biotechnology firms based on their innovation projects concluding that there are two major types of biotechnology firms: Those that are less research intensive and target smaller markets and those that are research intensive firms that target bigger markets with a broader reach (Mangematin et al, 2003). The former Type A firms experience steady growth and are usually less risky in comparison to the latter Type B firms who have greater ambitions to become large firms. Luukkonen’s study of biotechnology firms also examined all biotechnology
application sectors and firm organisation, but this study concluded that the forms of organisation of a firm will in fact vary by application sector in biotechnology and that there is more variability among biotechnology firms than the two business models as proposed by Mangematin et al (Luukkonen, 2005). She notes that this variability relates to the degree of forward integration, backward networking or forward networking (Luukkonen, 2005).

This study determined that when the application area of the biotechnology firm was part of a stringent regulatory system, the form of organisation tended to be a ‘network firm.’ This ‘network firm’ was less vertically integrated, obtaining resources through collaborations with other firms. These firms were involved in drug development.

While the overall characteristics of biotechnology companies’ business models are generally agreed, there is a considerable debate between various authors concerning ways in which further dimensions of variability in business models can be characterised, illustrated in part by the discussions above. Classifications such as those by Pisano, Orsenigo et al and Quere also represent differences in the characterisations of the business models of these classical biotechnology firms based on the knowledge base of these companies and when they were formed (Orsenigo et al, 1998; Pisano, 2006; Quere, 2006). All of these studies represent differences in the way that various authors have tried to make additional classifications of biotechnology companies.

Overall, the findings of these studies also create an awareness of the difficulties of looking at biotechnology companies and business models across the range of application segments of biotechnology. These studies also illustrate that the range of application segments of biotechnology have impacted the variety of business models of firms as they highlight the diversity of business models that are apparent and undoubtedly result from the different industries that these firms ultimately operate within. Reviewing a cohort of biotechnology firms therefore presents difficulties when trying to identify the specific issues that impact firms within one sector. While different industries have been affected by developments in biotechnology, reviewing
one single cohort of biotechnology firms makes it difficult to ascertain direct influences on changes to firms. This is best achieved by singling out these firms that specifically operate in one sector. The pharmaceutical sector has been profoundly impacted by biotechnology with firms utilising the technologies and knowledge to discover and develop drugs and so it is the pharmaceutical sector that represents the focal point of this research.

2.4.2. Waves of Entry of New Classical Biotechnology Firms

The classical biotechnology firm has been a useful description that encompasses a set of important features that many small firms have in common in this sector. However, while this overall general description is useful, it is necessary to explore the heterogeneity of firms within this classical biotechnology group and to understand what has influenced this heterogeneity. The purpose of this section is to review the literature that looks in more detail at firm differences.

Different waves of new entrants into the sector have been described based on various technologies and knowledge bases and consequently, differences in business models are apparent (Orsenigo, 1998; Pisano, 2006). The first wave of new entrants during the period of 1976-1985 focused on the new technologies of recombinant DNA and Monoclonal Antibodies (Pisano, 2006). Orsenigo et al’s distinction is slightly different. They distinguish between generations of firms formed between 1973-1980, 1981-1986 and then from 1986 onwards based on increasing specialisation of firms with each new generation becoming more narrowly specialised (Orsenigo et al, 1998). Importantly, they note that the life sciences in general have evolved by deepening more specific research hypotheses and consequently, new generations of classical biotechnology firms have tended to focus on more specific domains within each research paradigm (Orsenigo et al, 1998).

According to Pisano, during the initial stages of the development of biotechnology, some firms wanted to be ‘all things to all markets’ (Pisano, 2006). These firms were ‘research boutiques’ with great ambition, expecting to compete with large established firms (Quéré, 2006). Companies such as Amgen, Cetus and Biogen formed during this first period utilised a broad
range of techniques related to genetic engineering to produce a range of products for the agrochemical, biofuel and human therapeutic markets (Pisano, 2006). Some of these companies pursued specialised niche markets, for example, diagnostics based on hybridoma technology. They developed products that could be sold in the marketplace as soon as possible, concentrating on the most immediate applications of genetic engineering and on products that did not require large scale production processes or substantial marketing efforts (Malerba and Orsenigo, 1996). Some of these firms were able to access capital from public equity markets which allowed them to pursue a strategy of becoming more fully integrated drug development firms (Pisano, 2006). Some of the earliest firms, Genentech and Amgen, for example, initially started off as contract research companies but changing financial fortunes enabled them to pursue a fully integrated strategy.

During the mid to late 1980’s, a second wave of new entrants to the sector took place and the focus of a number of these companies was on disease and new methodologies around structure based drug design and small molecule drugs (1985-1990). The difficulties associated with the development of drug products (especially those based on proteins) became more apparent as well as difficulties related to funding issues for these firms. Consequently the second wave of entrants¹⁴ did not necessarily aspire to become fully integrated companies and focused efforts on research and collaborative strategies based on technologies that included gene therapy, cell therapy, tissue engineering, and antisense (Pisano, 2006). As further research was conducted on biological systems and disease, it was evident that there was a way to leverage these technologies to understand the role of both small molecules as well as larger molecules traditionally associated with the new biotechnologies. During the second wave of new entry and into the third wave, from the 1990s onwards, many firms specialized in early research.

¹⁴ Notably, this period was characterised by firms who were more willing to examine and review the role of small molecules.
The third wave of new entrants during the 1990s resulting from the developments in Genomics and the mapping of the human genome created a new wave of ‘investor enthusiasm’ and platform technology based business models were adopted by many firms (Pisano, 2006). This business model focused on inputs into the drug discovery process including tools, data and disease targets. The expectation was that firms founded using these new technologies would provide important information that would speed up the drug development processes and so public stock markets were responsive to these types of business models. The trend became one where many firms opted not to become fully integrated and pursued a model where they provided drug discovery research services to other firms and entered into research agreements that also provided much needed capital financing (Saviotti, 1998; Rothman and Kraft, 2006).

The discussion above has highlighted some of the differences in the types of business models adopted by new firms that were formed during the last 35 years. For these smaller firms, much of the change was related to the type of knowledge upon which the firm was founded. But some firms did move down the integration continuum pursuing further development and production of products internalising either the activities or the management of these activities. As some of the larger fully integrated firms desired products to be in more advanced stages of development, this in turn created opportunity (or pressure) for firms to develop products further downstream (Pisano, 1991). Large pharmaceutical companies were investing substantially in collaborations with these firms and the productivity of these agreements was not as always as expected. Consequently, larger firms began to demand products to be in later stages of development and this created pressure on some of these firms to integrate further downstream to produce products with greater evidence of efficacy (Pisano, 2006). This also meant that the small classical biotechnology firm realised a greater pay-off for products that were further developed (Luukkonen, 2005) and this acted as an incentive for companies to pursue clinical development of products.
Recent studies of genomics companies have revealed further changes in their business models akin to moving down the integration continuum. While this business model initially focused on platform technologies and the provision of licenses or subscriptions fees as a method of revenue generation, this model was to have short lived commercial viability (Rothman and Kraft, 2006). The increased availability of DNA sequencing technologies made possible by the development of open access and free public genomic data reduced these services/products to commodities and furthermore, these technologies were integrated into large pharmaceutical companies effectively reducing the market considerably (Rothman and Kraft 2006; McMeekin and Harvey 2007). A study of a US genomics company cohort revealed that over half of the sample had established internal drug development programmes, thereby moving downstream into drug development and manufacturing activities. Thus the business model of these companies evolved to cope with the market pressures that were effectively eliminating the viability of their business model.

2.4.3. Changes to Existing Firms - Evolving Fully Integrated Large Firms

The developments in biotechnology in the last 30 years have created pressures on the fully integrated incumbent firms to adapt their business models in order to take advantage of the new discoveries. Many fully integrated companies gradually strengthened their in-house research capabilities in biotechnologies during the 1980s and the 1990s (Malerba and Orsenigo, 1996). A case study on one large pharmaceutical firm highlighted the tasks involved in transforming technological identity and the business model in response to the developments in biotechnology. This was one of the top five pharmaceutical companies with proven abilities in science based drug discovery, management of clinical testing and regulatory affairs as well as marketing (Zucker and Darby, 1997). A new head of research was recruited and led the conscious effort of transformation of how the firm conducted drug discovery. The new head of research introduced the organisation of focused groups of scientists (within the drug discovery unit) on various biotechnologies as a method of implementing biotechnological
based drug discovery. Over a period of three to four years, the use of biotechnologies such as cloned human targets, were introduced and many experienced scientists in the field of biotechnology were hired to diffuse new methods within the firm. The firm’s strategy was to develop excellent in-house research that would also enable the firm to make more informed decisions with respect to selective relationships with new small classical biotechnology firms. This firm devoted the resources necessary and hired the right personnel to transform its research technologies to include cutting edge, leading technologies of the biotechnology period.

During the 1980s and the 1990s some firms modified their business models in the hope that integrating pharmaceutical and agro-biotechnology divisions would create synergies that could be built on the basis of the new biotechnology discoveries (Chataway et al, 2004). But by the late 1990s/early 2000s, most companies had again split their pharmaceutical and agro-chemical divisions. The negative public reaction and difficult policy environment in Europe created potential conflicts of interest between agricultural and health based sectors. The result was a change in business model of these large firms and a series of mergers and de-mergers among companies with agro-chemical and seed divisions who were eventually split off from pharmaceutical divisions (Chataway et al, 2004).

Even though academic based biological sciences created a series of new technological breakthroughs, productivity in the sector declined in the late 1990s because more drugs were coming off exclusivity protection than were being replaced by new drugs (Higgins and Rodriguez, 2006). The internal productivity issues meant that those firms who had not yet integrated biotechnology based drug discovery and design capabilities had to review the sources of innovation and determine how best to integrate these new capabilities into their existing business model. The integration of these capabilities has complemented rather than supplanted medicinal chemistry and random screening to discover new and effective drugs (Walsh, 2004).

However, the continued survival of these firms has also been contingent on one or more of both of two main strategies including: 1. Mergers and
Acquisitions and 2. Various forms of joint development of products and processes. Mergers and consolidation among incumbent firms has produced behemoths such as Sanofi Aventis, Novartis, and Pfizer in an effort to overcome the negative effects of declining productivity. Many fully integrated companies experiencing a decline in their research pipelines have tried to reverse this trend through acquisitions of small firms to acquire competencies in new technologies (Higgins and Rodriguez, 2006). One notable example is Roche who acquired a controlling interest in Genentech. Eli Lilly, Merck and Pfizer have also made some substantial investments through acquisition of firms to enhance their in-house biotechnology-related research and development competencies. Finally, as noted earlier, collaborative efforts with a range of partners have been an important strategy for firms to bolster their in house R&D production. While the core business model of the vertically integrated firm has arguably remained the same (firms continue to discover, develop, register, market and support the sale of their products) the business model for these firms has evolved from the sole reliance on in-house capabilities providing all technology to one where external sources of technology are sourced to complement in-house efforts.

2.4.4. Changes to Firms – The Exploration/Exploitation Balance

Throughout this chapter, there has been consistent reference to the notion of exploration and exploitation in firms. The reason for this is related to the importance of the division of labour in the sector and to begin the discussion on how that may be evolving by utilising the exploration/exploitation framework. The exploration/exploitation literature discusses the notion that firms incorporate two basic sets of activities into their business (exploration and exploitation) at any point in time and that this ‘balance’ will change. March notes that ‘A central concern of studies of adaptive processes is the relation between the exploration of new possibilities and the exploitation of old certainties’ (March, 1991). The study of adaptive processes is a particularly relevant theme for this research and thus the exploration/exploitation discussion provides a framework that can be used to characterise the nature of firms in the sector and consequently to understand changes to those firms. Exploration can be defined as the search for new
ways of doing things and the search for new opportunities. It can be defined using such terms as discovery, experimentation and risk taking (March, 1991). Exploitation on the other hand is the development of things that are known/existing opportunities and can be defined using terms such as refinement, efficiency, selection and implementation (March, 1991). The exploration/exploitation distinction is a particularly helpful way of distinguishing how firms differ in the core nature of their activities. The diagram below uses the drug development continuum to helps to understand the key differences in the nature of tasks that firms undertake in this sector and how the division of labour can be understood clearly using the exploration/exploitation framework.

The discussions throughout this chapter have highlighted that firms in this sector display particular characteristics in terms of their operational focus on the exploration/exploitation continuum. The classical biotechnology firms have been discussed in terms of their exploratory focus while the large incumbent firms are portrayed as having the characteristics of both exploratory and exploitation related activities although undoubtedly the emphasis is placed on the latter.
Figure 4. Exploration and Exploitation as it Relates to the Drug Development Continuum
However, the particular focus of a firm on one set of activities over another can lead to problems. March notes that ‘Adaptive systems that engage in exploration to the exclusion of exploitation are likely to find that they suffer the costs of experimentation without gaining many of its benefits. They exhibit too many undeveloped new ideas and too little distinctive competence. Conversely, systems that engage in exploitation to the exclusion of exploration are likely to find themselves trapped in suboptimal stable equilibria’ (March, 1991). As a result, maintaining an appropriate balance between exploration and exploitation is a primary factor in system survival and prosperity (March, 1991). There is evidence to suggest that firms will change the balance of exploration and exploitation in their activities because ultimately, the external environment will change around the firm as demonstrated by the changes in this sector. This is evidenced by the case study presented here on Celltech. This case study is presented because the firm chose to concentrate its resources on exploratory driven activities in changing the balance of its activities (McNamara and Baden-Fuller, 1999). While this reflects the orientation of many classical biotechnology firms in the sector, it is interesting to note that this is in contrast to what is typically expected from firms who are moving towards a more mature phase in their lifecycle.

2.4.4.1. The Case of Celltech

The case of Celltech presents an interesting story of how a biotech firm was able to change the balance of exploration and exploitation within the firm to its advantage but by focusing on exploration rather than exploitation. McNamara and Baden-Fuller illustrated that the issues that the firm faced throughout its life cycle were dealt with through a change in the balance of exploration and exploitation related activities (McNamara and Baden-Fuller, 1999). In its earliest days, the firm Celltech started off with two businesses: in house R&D of novel therapeutics (drugs) and contract manufacturing and research in Biologics in which it had developed a leading edge capability centred on recombinant DNA and hybridoma technologies: The former representing the firm’s exploratory activities and the latter representing its exploitation related capabilities. The contract research and production
business was the major source of revenue for the firm and covered in-house R&D expenditures which initially only amounted to roughly 25% of turnover by 1987 but had risen to 50% of turnover by 1990. During this period, the majority of employees were based in the Biologics division.

In 1990 the firm was split into two divisions and the expenditure on in-house R&D increased dramatically as the new CEO believed that the future of the firm lay in development of drugs because of the enormous revenue potential (McNamara and Baden-Fuller, 1999). During this two year period, the firm developed capabilities in activities related to drug discovery through to regulatory clinical trials. The company used collaborations to continue its drug development business model during the next four years and equal amounts of resources were devoted to both its drug development and contract manufacturing business. Then in 1996 a decision was made to sell the biologics contract manufacturing business and concentrate all resources on drug discovery and development. Revenues from contract manufacturing had been steadily declining and with an internal financial crisis, the pressure was on to devise a new strategic direction for the firm. Investments to develop a strong drug discovery and development business were made and the company acquired new scientific, technical and management capabilities to create an effective drug discovery and development organisation. The capital value of the company rose substantially over the following eight years and Celltech was taken over in 2004 by UCB. UCB paid over £1.5 Billion for the company reflecting that the change in business model turned out to be a profitable one especially for a company that was only 21 years old. For firms during this period, the focus on exploration activities was key.

2.4.4.2. The Cycle of Discovery

The evidence from the literature suggests that in fact exploitation of current knowledge tends to dominate over exploration of new knowledge, over time (March 1991, Levinthal and March, 1993). The reasoning behind this can be understood as follows; ‘exploitation generates clearer, earlier and closer feedback than exploration. It corrects itself sooner and yields more positive results in the near term. As a result, the primary challenge to sustaining an
optimal mix of exploration and exploitation is the tendency of rapid learners and successful organisations to reduce the resources allocated to exploration’ (Levinthal and March, 1993).

According to Levinthal and March, the gains to be made from exploitation are more readily visible and easily obtainable. However, more recent studies describe a more dynamic process of the movement between exploration and exploitation and then back to exploration and the reasons why this occurs. Nooteboom proposed a ‘cycle of discovery’ and described how exploration and exploitation are ‘mutually related and build on each other’ (Nooteboom, 2000; Gilsing and Nooteboom, 2006). Exploitation starts when ‘variety of content is reduced or consolidated into a dominant design’ resulting in reduced uncertainty, increased demand and new producers (Abernathy and Utterback, 1978; Bettis and Prahalad, 1994; Gilsing and Nooteboom, 2006). Eventually there is an increase in specialisation and novelty is ‘consolidated’ in dominant designs and overall, knowledge becomes more codified enabling more rapid diffusion as firms progress through the ‘generalisation’ phase into exploitation (Gilsing and Nooteboom, 2006). In order for firms to progress to exploration once again, they must work to open up a new variety of contexts of application. Minor adjustments are made to products (and processes are also adjusted for efficiency) and firms then progress through a process of ‘differentiation’ which then leads to the reciprocation phase. This reciprocation phase involves a greater degree of configuration of ‘experiments conducted with novel elements with hybrids of new and established elements’ based on new or existing insights gained from the prior processes and leads back to the exploration phase (Gilsing and Nooteboom 2006).

Celltech divested its contract manufacturing business in response to declining revenues from that business and so its business model was reconfigured to take advantage of a market that still promised opportunity; that of the drug discovery and development business. There were both internal and external pressures on the company to change its business model and much of the evidence from this case study points to the influence
of various sorts of financial pressures on the company. The cycle of
discovery study illustrates an interesting model that helps to understand how
as well as why firms can move along the exploration/exploitation continuum.
This is important for the purposes of this research as this evidence (and that
from the Celltech case above) reinforces the idea that firms will continue to
adapt to their market circumstances and this is reflected in both changes to
the models of new start up firms and changes to the business models of
existing firms.

2.4.4.3. **The Future Sustainability of the Exploration Focused Firm**

The evidence presented in this chapter illustrates the exploratory focus of the
classical biotechnology firm which has been in existence for over 30 years.
The evidence also suggests that different waves of new entrants have
experimented with new types of knowledge as well as organisational
arrangements which have included some incorporation of exploitation related
activities in their business model. However, the arguments put forward by
March and later by Levinthal and March clearly define a risk in the singular
focus of firms on one approach versus another i.e., exploration focused
versus exploitation focused hence the explicit need for a balance of activities
is cited (March, 1991; Levinthal and March, 1993). The classical
biotechnology firms have almost exclusively focused on exploratory activities
but the evidence suggests that this is not sustainable. Evidence presented in
the following chapter suggests that changes are already taking place and
that the exploratory focus might not be sustainable for the sector. The
evidence above suggests that the logical next step for the sector is to
progress to an exploitation phase.

2.5. **Conclusions**

The previous sections of this chapter have presented an overview of a
dynamic sector that has witnessed many changes to both industrial structure
and internal structure of firms. Biotechnology discoveries profoundly changed
the pharmaceutical sector. This new knowledge created new opportunities
for firm creation and a division of labour emerged as a result which also
created opportunity and pressure for firm adaptation. The discussions on
business models and the changes already observed within the pharmaceutical sector would suggest that firms’ business models will change over time and potentially the division of labour will also change. The evidence above suggests that this is usually in response to changing knowledge. These trends in the evolution of business models of all firms also illustrate that firms have to adapt to various sector conditions around changing technologies and resource availability.

Given the dynamic nature of the sector, it would seem necessary to ensure that an up to date understanding of the potential changes to firms and the division of labour is undertaken and that this includes an understanding of the key influences on these changes. Changing business models and changes to the division of labour are crucial to the ongoing commercial viability of the sector and an economic inevitability (Nelson and Winter, 1982). As Pisano notes in the closing chapter of his review of the need for changing business models in the sector, ‘Scientific revolutions like biotechnology are only partly about science. Inextricably linked to the science are experiments in institutional arrangements, organisational forms, business models and management practices’ (Pisano, 2006). The co-evolution of science, technology and institutions can only be understood in precisely that way – as a co-evolution whereby changes in all of these areas profoundly impact each other (Nelson, 2005). The goals of this research are to further understand and validate the potential existence of new experiments in institutional arrangements, business models and management practices in the pharmaceutical sector. The following chapter presents the key arguments that will form the research questions for this research on the evolving pharmaceutical sector.
Chapter 3. Identification of Further Changes in the Pharmaceutical Sector

3.1. Introduction

The aim of this chapter is to develop an analytical framework for studying more recent changes in the pharmaceutical sector to fully understand the claims that are being made (based on the literature reviewed) that form the basis of this research and subsequently, the research questions. The previous chapter discussed four key issues: the changing nature of firms and thus the division of labour in the sector, the changing nature of the sector’s knowledge base and thus the role of knowledge in the division of labour in this sector, the role of finance in the changes in the division of labour and the role of markets for technology that enabled the changing division of labour. The pharmaceutical sector over the last decades of the twentieth century has been impacted by developments in biotechnology and other disciplines. In particular, the prior chapter discussed the changing nature of the large and small firms that are the key players in this sector reflecting that this is a truly dynamic sector that responds to changes in the knowledge base. This discussion also reflected that new knowledge has had a profound impact on the sector dynamics. It also examined the role of finance in this sector because of the unique product development pathways and timelines that create enormous financial pressures on firms. And finally, a discussion of the literature on the markets for technology was also included because of the critical importance of these markets for the division of labour in this sector.

However, the purpose of this chapter is to propose that there have been further changes in the division of labour and that the sector has continued to evolve due to changes in knowledge and financial considerations. The growing importance and complexity of markets for technology is also proposed. The characteristics of how the sector has evolved have yet to be analysed and documented in the literature. This chapter proposes that there are significant gaps in the literature with respect to these four issues and proposes that there are new associations to be made based on existing evidence in the literatures as presented, to try to answer some questions that
have arisen from a review of the literature in conjunction with a review of the trade literature. The following four sections discuss these claims in greater detail.

3.2. **Changing Division of Labour**

The following section discusses the proposed ways in which the division of labour has changed. There is evidence to suggest that a new type of firm has emerged that does not focus on the same part of the drug development continuum than was previously understood. The section also discusses how this is not only the entry of new types of small firms but the adaptation of existing firms.

3.2.1. **A New Type of Firm**

The previous chapter of this thesis has presented an overview of a dynamic sector that has witnessed many changes to both the overall industrial structure and the internal structure of firms. Biotechnology discoveries significantly impacted the pharmaceutical sector and thus the development of drugs for human therapeutic use. This integration of knowledge into the pharmaceutical sector created new opportunities for firm creation and also created both opportunity and pressure for firm adaptation. The discussions on business models in the sector would suggest that firms’ business models will change over time and usually in response to various pressures/opportunities.

There is evidence to suggest that regulatory and financial pressures particularly impact the current industrial climate in this sector and so existing and new firms must experiment with different types of business models (McKelvey, 2008). Some authors have speculated on the potential types of business model that may emerge in the future. McKelvey notes that various types of business models will likely emerge between the two dominant models of the large firm and the small classical biotechnology firm and differentiates these based on a continuum that changes focus based on whether or not the firm is competing on technology or on market/customers. She also speculates that financial issues related to the availability of venture
capital will make it increasingly difficult to obtain finance and consequently the classical biotechnology business model will likely become less popular as a mode of start-up firm (McKelvey, 2008).

Pisano has also described potential changes that are needed to both the vertically integrated (large firm) and classical biotechnology business models and advocates changes to the classical biotechnology business model in order for these types of firms to realise their commercial and economic potential (Pisano, 2006). He points out that only a tiny fraction of these types of firms have actually become profitable enterprises (Pisano, 2006). Pisano also notes that some classical biotechnology firms have moved from ‘the frontier to less risky ventures’ with firms ‘retreating’ from the radical and risky end of the R&D spectrum (Pisano, 2006) but this was not further discussed, described nor analysed. So while there has been some speculation on potential changes to business models, there has been no definitive discussion in the academic literature on the potential business model that has possibly already emerged, that of the No Research Development Only (NRDO) firm.

Conversely, there is evidence in the trade literature to suggest that more recent changes have already occurred to the business models of firms that were discussed in the previous chapter. It appears that some companies are opting for a business model that seeks to focus on products that are in the later stages of clinical development. Lahteenmaki and Baker reviewed the biotechnology sector in 2003 and noted that some companies ‘got rid’ of more speculative, early stage research programmes for ones closer to the market and abandoned early stage drug development programmes’ (Lahteenmaki and Baker, 2004). Hodgson described the investor popularity of ‘no-research, development only’ companies in 2004 and most importantly noted that these companies received the most equity in 2004. Hodgson also described business models of some firms that use innovative technology platforms but to re-engineer compounds that had already been in the clinic, adding that this model proved popular with investors also (Hodgson, 2006).
Lahteenmaki and Baker described variations of what they called a ‘Specialty Pharma’ business model. Some companies, from their inception, may be ‘Speciality Pharmaceutical Companies’ created to develop a product that was obtained from another company rather than a product that was the result of internal application of discovery technologies and development (Lahteenmaki and Baker, 2004). Then there are those companies that may have started out with a promising new and innovative technology platform but the technology was not successful in producing a drug candidate for clinical testing and they dispensed with scientists and scientific capabilities and opted to in-license drug products to pursue clinical development.

There may be a range of reasons for the emergence of these new firms and changes to existing firms. However, reasons for the emergence and existence of these new firms have not been well discussed in the literature with only summary observations on the role of finance and financial pressures. This evidence suggests that a new type of firm is emerging that is concentrating on downstream, exploitation focused activities. There is also the suggestion that this new type of firm may be emerging as a result of financial pressure. Academic literature certainly shows that new firms emerge to follow opportunities (as in Chapter 2) and sections 3.2 and 3.3 will follow up on this discussion as it relates to proposing the reasons for a new type of firm but the evidence from the trade literature points to a changing division of labour with new small firms shifting their focus away from research and exploration.

3.2.2. Changes in the Activities of Existing Firms – The Traditional Classical Biotechnology Firm

The evidence from the discussion on the evolving nature of the sector in the academic literature has indicated that changes to existing firms can also be expected. The question is how existing (classical biotechnology business model) firms may have changed. The traditional classical biotechnology business model is characterised as an exploratory based business that is concerned with highly scientific, early stage drug discovery and limited clinical development. These firms were always responsible for generating
their own new drugs internally. The following table illustrates the types of business models apparent in the drug development sector to date (discussed in Chapter two) together with their perceived core competencies/capabilities based on the literature reviewed:

<table>
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<tr>
<th>Business Model</th>
<th>Time Period</th>
<th>Generally Understood Capabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical Biotechnology Firms (Large Molecules and FIPCOs\textsuperscript{15}) – Focus on Genetic Engineering and Hybridoma Techniques</td>
<td>1\textsuperscript{st} Wave (1976 – 1985)</td>
<td>• Acquiring university/academic knowledge • Alliances • Out-licensing • Discovery Research - genetic engineering, hybridoma technology • Specialised Protein Production</td>
</tr>
<tr>
<td>Classical Biotechnology Firms – Focus on Gene Therapy, Cell Therapy, Tissue Engineering, Antisense</td>
<td>2\textsuperscript{nd} Wave (1986 – 1990)</td>
<td>• Acquiring university/academic knowledge • Alliances • Out-licensing • Discovery Research - Specific diseases, structure based drug design, small molecules</td>
</tr>
<tr>
<td>Classical Biotechnology Firms – Focus on Genomics, Platform Technologies</td>
<td>3\textsuperscript{rd} Wave (1991 - 2000s)</td>
<td>• Acquiring university/academic knowledge • Alliances • Development of platform tools and technologies • Out-licensing • Discovery Research - Genomics</td>
</tr>
<tr>
<td>Large Integrated Firms</td>
<td></td>
<td>• Clinical development • In-licensing • Marketing/Distribution • Regulatory Affairs</td>
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\textsuperscript{15} Definition from Pisano, 2006
The idea of ‘core competencies’ was expounded by Prahalad and Hamel in 1990 when they discussed the idea that it was a corporation’s ability to identify, realise and nurture core competencies and then capitalise on those specific competencies that fostered success (Prahalad and Hamel, 1990). The terms core competencies, competencies (in general) and capabilities are used interchangeably. A competence is essentially a skill or strength in a particular area (usually in production or a technology) that a company possesses that allows it to successfully pursue its strategy and goals. Core competencies should provide potential access to a wide variety of markets, make a significant contribution to the perceived customer benefits of the end product and be difficult to imitate (Prahalad and Hamel, 1990). Most importantly, the authors proposed that companies needed to understand their competencies and capabilities in order to then successfully capitalise on these capabilities.

Later literature has expanded on the notion of competencies and capabilities. Teece and Pisano noted that competences and capabilities are intriguing assets as they typically must be built because they cannot be bought (Teece and Pisano, 1994). Their discussion on ‘dynamic capabilities’ in particular expounded the view that firm competencies/capabilities must be responsive and adaptable if the firm is to survive in a rapidly changing environment. It is important for the context of this research to illustrate these perceived competencies and capabilities of the classical biotechnology firms as they are currently understood because it provides a foundation and a potential contrast to any changes that might become apparent from the research findings pertaining to a new type of firm (NRDO). For the classical biotechnology companies during the 1980s, 1990s and 2000s, these competencies included the ability to obtain technologies from academic settings, create an environment to foster research and discovery of new products and to work with large companies on development (alliances and

<table>
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<th>Business Model</th>
<th>Time Period</th>
<th>Generally Understood Capabilities</th>
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<tr>
<td></td>
<td></td>
<td>Research (Discovery)</td>
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out-licensing). However, it is possible that changes in the relative importance of these competencies/capabilities may be evident.

However, changes to traditional firms have been described in the trade literature in relation to how these firms’ conduct product discovery and development. Firms who pursue ‘internal scientific endeavours’ may also in-license products (Hodgson, 2004; McCook, 2005; Silverman, 2006). In other words, small firms who discover their own products may also still supplement their pipeline with external products from other companies despite their own internal capabilities. The key point is that these firms will buy in other firms’ products which have been discovered elsewhere. They are no longer solely reliant on internally generated drugs. While this well discussed ‘open innovation’ approach will not be new to many firms in different industries, it has not been discussed in terms of the small traditional classical biotechnology firm as an intermediate technology (drug candidates in this case) ‘purchaser’ in the pharmaceutical sector. This type of behaviour was always discussed and observed in terms of the large firm. But this evidence points to the fact that the roles may be changing and critically, that changes have occurred in the markets for technology, as discussed below.

However, it has been suggested in the trade literature that the existence of a new type of firm has invoked a positive response from financiers and thus provokes speculation that this firm has evolved partly in response to financial pressures. These will be financial pressures that are present in the system and these have been summarily mentioned by McKelvey and discussed more by Pisano however, discussion of a ‘no research development only’ firm model has not taken place (Pisano, 2006; McKelvey, 2008). The actual issues relating to the influence of finance are discussed more below but there may also be consequences for the traditional classical biotechnology firm who may have had to adapt their activities due to the same pressures. As a result, this suggests that an important change in the activities of traditional classical biotechnology companies may also be taking place but again, no definitive discussion nor systematic empirical evidence exists that
can deny or support this claim despite speculation present in the trade literature.

The proposed change in the division of labour is important to acknowledge and thus empirically prove. The small traditional classical biotechnology firm (as discussed in the previous chapter) has consistently been described as a research intensive organisation that discovers products and in some cases goes on to develop them. All small firms in the pharmaceutical drug development sector, usually under the banner of the classical biotechnology firm, have been ‘credited’ with being the lifeblood of discovery of new products. Conversely, the role of the large firm has always been acknowledged as the ‘buyer’ and developer of these products discovered by these small research intensive firms. These research activities conducted by small firms were considered of paramount importance to the dissemination and generation of new knowledge in the sector. What has been described here with respect to the NRDO firm turns things around. NRDO firms focus specifically on development and not discovery. The extent to which these firms exist is now a key question for the sector moving forward. The existence of a new firm as well as proving and understanding changes to existing firms has to be explained.

3.2.3. Summary

Overall, this evidence related to new firms as well as changes to traditional classical biotechnology firms illustrates a gap in the academic literature. These so called ‘no research development only’ (NRDO) companies appear not to have drug discovery capabilities of their own. The sector literature speculated that this approach may have emerged as a new business model (Silverman, 2006; McCook, 2005; Hodgson, 2004). This evidence also suggests important changes in the activities of existing firms, the traditional discovery and development (DD) firm. These important observations indicate a change in the division of labour in the sector that warrants empirical investigation due to an apparent gap in the current academic literature.
3.3. **Surplus of Unexploited Knowledge and Changes in the Division of Labour**

The evidence above with reference to explaining potential changes in the division of labour points to the influence of finance on these important changes that are taking place. However, there is a complementary aspect to this explanation that also represents a gap in the current literature and this is related to the current level or ‘surplus’ of unexploited knowledge in the sector. As just discussed, the firm’s need for finance and conversely the financier’s need for a return on investment is potentially influencing the changing division of labour in the form of a new type of firm focused on downstream exploitation activities. But these changes are predicated on one important aspect: The ability to obtain products from other firms that are in an advanced stage of development. Therefore, as in the case of the NRDO firm, there has to be products available that other firms are willing to sell to these firms in order for them to exist in the first place. As they have no research capabilities, they buy in drug candidates from other firms who have decided not to develop these particular drug candidates.

Surplus, by its very definition, implies that there is extra available, or excess of something. In this case, the point is that there are more drug candidates being generated by firms than they can develop and thus they are willing to sell this ‘surplus’ to other firms for development. But the origin of this surplus must be examined for the purposes of supporting this argument. A number of important and interlinking developments in biology, chemistry, process technologies and informatics resulted in the development of industrialised high-throughput screening (HTS) platforms (Nightingale, 2000). Together, these enabled generation and rapid screening of extensive chemical libraries against a greater number of new targets created by significant advancements in fields such as genomics and information technology (Hopkins et al, 2007). The new developments also created a more significant focus on quantity over quality (Hopkins et al, 2007; Pisano, 2006).

As a result, a larger number of potentially clinically active compounds have been identified. This is reflected in changes in the total number of patents
granted in the US\textsuperscript{16} over the period 1978–2002 (these are patents for therapeutically active compounds). Essentially, this can be used as an indicator of the number of compounds considered ‘attractive enough to warrant patent protection, but not necessarily viable enough to enter development’ (Hopkins et al 2007). During this period, the number of patents rose from less than 2,500 in 1978 to over 20,000 in 2003 representing an 800% increase in the number of patented compounds, however, the most significant increase has taken place over the last 10 years. This is the result of a significant increase in exploration that was a characteristic feature of both the second and particularly third epochs of the sector.

This evidence in Chapter Two discussed the move by pharmaceutical incumbents to acquire competencies in the new technologies (not just biotechnologies). These firms had the financial ability to assimilate these new developments in discovery technologies and therefore generate many new compounds (Gambardella, 1995). It is therefore feasible that many compounds may have been developed but not all were deemed worthy of further development through human clinical trials thus creating a surplus of unexploited knowledge in the form of drug candidates. Yet this has not been discussed in any detail by authors in this field. A direct reference in Mazzucato and Dosi provides a tenuous key link between this argument for a surplus of unexploited knowledge (and the follow on assumption that this knowledge is then sold) as they refer to the actual sale of these ‘surplus’ products by large firms (Mazzucato and Dosi, 2006). The question that then arises is why these products are being traded. It points to a ‘surplus’ of potentially useful knowledge that instinctively firms should hold on to and yet they are not.

This knowledge represents more opportunities than firms can or are willing to develop into viable drug candidates themselves and this has profound consequences for the sector as a whole. This represents an interesting line of inquiry simply because most discussions of knowledge in this sector are

\textsuperscript{16} This was in patent classes 424 and 514 for potentially therapeutically active compounds
about newly discovered knowledge that is bought by large firms but no real
discussion of the potential for surplus unexploited knowledge has taken
place. The question then becomes what do firms do with this knowledge.
Trade in products and knowledge in this sector is by no means a new
development, as discussed in Chapter Two. However, the products being
traded were usually newly discovered drug candidates generated by small
classical biotechnology firms. The products in question here that are being
bought by small firms are either being generated by other small firms or large
firms.

However, this also has consequences for the overall balance of exploration
and exploitation in the sector and suggests that a surplus of unexploited
knowledge may mean that the overall stock of knowledge from exploratory
activities may have reached a critical mass. The balance may be shifting
towards exploitation as firms try to maximise value from the vast stock of
knowledge that already exists which would also explain the changing division
of labour. The argument that the surplus of unexploited knowledge may
partly help to explain why a new division of labour has taken place becomes
more compelling when placed in the context of the financial argument. These
two explanations become interrelated. A division of labour may have arisen
because of the existence of excess knowledge/products in the system but
equally, pressure for better financial performance may have driven the trade
of these products. These associations and arguments have not been
previously made in the academic literature surrounding this sector and
represent a new line of inquiry that propels this research.

3.4. **The Role of Finance and Changes in the Division of Labour**

This research proposes that there is further evidence to suggest that new
firms may be emerging that are not focused on research and some firms may
be changing their business model and cutting back on the development of
early stage technologies (such as those that may be useful in discovering
new drugs). This is therefore a change in the currently understood division of
labour that has been extensively discussed and analysed. However, this
research seeks to go a step further and propose that this is closely related to financial issues and pressures from capital markets. While the literature has focused on the issue of overall firm survival and the need to finance, particularly for young firms, the particular focus here is linking the discussion on finance and capital markets to new types of firms and thus the changing division of labour. This implies that VC firms, the public stock markets and financing from large firms have a role to play in the changing division of labour which needs to be understood in greater detail. However, this research also proposes that the changes in the division of labour are a result of a surplus of unexploited knowledge and that the role of finance in conjunction with this are two important explanatory factors for the changes. It is not suggested that these two factors are the only reasons that may explain the changing division of labour but it is proposed that these two factors are interrelated and associated with a changing division of labour.

As noted in the previous chapter, it has been possible for smaller firms to concentrate on some parts of the drug development process. In this sense, the division of labour was around the discovery of products which was undertaken by new small firms (classical biotechnology firms) that entered the sector. However, this concentration on one part of the drug development continuum was also a reflection of the extensive financial requirements that the full research and development cycle of human therapeutic product development requires. Therefore, it could be argued that the division of labour that has already taken place has potentially been influenced by the limitations of the availability and willingness of capital to fund the entire development process. However, this explicit link has not been made in the academic literature.

Following on from this theory, this research proposes that there are fundamental links between the more recent developments in terms of the emergence of NRDO firms (and therefore the division of labour) and capital markets. This is based on a couple of observations. The first is that there is some evidence to suggest that the current business model that is evident (that of the classical biotechnology firm) is not sustainable in its current form
due to disappointing performance overall throughout the third epoch of the sector (Pisano, 2006; McKelvey, 2008). This disappointing performance ultimately challenges the financial models that had been hitherto dominant in the sector. It is therefore possible that there is now less demand for discovery stage assets and results and increasing demands for drugs that are more developed with better defined safety and efficacy profiles. In terms of the response of capital markets, the evidence has shown that the IPO market has decreased considerably for firms in this sector (Lerner et al, 2003) and this in turn compromises the exit strategy for VCs and thus their reason to invest.

The trade literature has already made reference to these links in an explicit manner and suggests that these sorts of changes to firms are warranted to ensure the flow of capital resources into the firm (Silverman, 2006; McCook, 2005). This literature makes it clear that the requirements for speedy product development and profitability can prove extremely difficult for companies in the drug development business and this may account for further changes in the division of labour – NRDO firms and existing firms buying in more advanced drug products. Ultimately, buying in products that have already passed through almost 7 years of discovery and pre-clinical testing reduces the time it will take to become closer to the market and thus potential sale of the product. This is the allure of this type of firm for investors. These firms should not take as long to develop products for sale or license thus providing a quicker return for investors.

While it has been acknowledged that finance is important for firm growth, there has been limited discussion of finance (and the resulting corporate governance) and how it may exert an influence on changes to firms and their core activities which would seem to be a large gap in the innovation literature. However, some key authors on this sector have made reference to the role of financial pressures facing firms and discussed changes to the core activities of firms. As noted earlier, Pisano has discussed the poor performance of smaller firms in this sector and has explicitly stated that the current business model of the traditional classical biotechnology firm is not
sustainable. The overall performance of small firms in the sector has not been ‘particularly healthy’ providing only ‘lacklustre rewards for investors’ (Pisano, 2006). McKelvey also noted that firms will be more diverse in response to serious problems of profitability as well as changing technologies, medical knowledge and demand. But she also notes that this is a combination of factors that together, will exert pressures on firms to adapt and change (McKelvey, 2008).

However, there is another discussion related to the ‘biotechnology revolution’ and the disappointing impact of advances made in the sector that may also provide an important context for this argument. Hopkins et al (among others including Nightingale and Martin, 2004 and Arundel and Mintzes, 2004) reviewed the ‘biotech revolution’ and concluded that the translation of advances in biosciences into new technology has been far more difficult, costly and time consuming than has been widely promoted (Hopkins et al, 2007). This in turn has impacted expectations of both governments and financiers who have been widely led to believe that the developments in biosciences would rapidly transform pharmaceutical innovation when in fact this has yet to occur (Hopkins et al, 2007). It may therefore form part of the explanation for the division of labour as it relates to finance. While this discussion has not been previously associated with any claims related to this new proposed division of labour, it does provide a potentially powerful argument in support of these claims.

It is therefore possible that this slow progress may have resulted in changes in some investors’ behaviour who may have already responded to the unfulfilled promises and ultimately slow performance and disappointing impact of the new technologies. Significant investments have already been made and 35 years later many of these have not resulted in the returns that were promised because the so called ‘revolution’ is in fact a slower incremental pattern of technological change and ‘creative accumulation’ (Hopkins et al, 2007). Investor response to this disappointing performance may now be manifested as a change in the investment model to fund firms that are following a different business model, i.e., the NRDO business model.
with no scientific/exploratory research taking place but instead the focus is on exploitation and product development.

When this view is taken in conjunction with the claims made with respect to the existence of the NRDO firm and why it may have emerged, the role of finance would seem to warrant greater attention as a potential explanatory factor for the new division of labour in this sector. As technology appears to be proceeding at a slower and continually unpredictable pace, more investors may now, more than ever, (35-40 years after the discoveries made in the 1970s) be wary of the potential success rate as well as the length of time required for classical biotechnology companies to become profitable through the discovery and development of their own products. In addition, the key discussions on how business models have changed in the trade literature as well as academic references to why they will need to change provides an important platform for this research. Together, these claims related to poor performance of firms and of the sector as a whole support the need to further examine the potentially more recent changes to the division of labour that have taken place and more specifically, why they have taken place. The pharmaceutical sector provides an excellent case study of how finance influences firms because of the financial requirements and difficulties associated with product development. This research therefore seeks to understand in greater detail the interaction of finance, a surplus of unexploited knowledge and changes to the division of labour.

3.5. Changes in the Markets for Technology

An excellent, succinct description of the markets for technology in the pharmaceutical sector has been provided by Arora et al who remark that ‘…we see a market for technology with a well defined division of innovative labour, involving DBFs (dedicated biotechnology firms) as technology suppliers and established pharmaceutical and chemical companies as buyers.’ (Arora et al 2001). This also implies a close association between all of the three issues discussed above: the division of labour, the surplus of unexploited knowledge and finance. However, given the evidence discussed above (the division of labour and a new type of firm as well as the surplus of
unexploited knowledge), part of the purpose for this research has to understand how the existing market relationships have actually become more complicated because the division of labour has changed and the exchange of products and knowledge. The previous chapter provided the detail around these markets for technology and how and why they had arisen. Most importantly the key flows/sale of information/products in the sector was modelled. However, the discussion in the previous three sections in this chapter has pointed out that there is evidence to suggest changes in the sector in the division of labour, changes in the level of unexploited knowledge and the importance of finance in these issues. One remaining factor will complete these argument and this is that markets for technology have changed and become more complex. It must be pointed out that changes in the markets for technology will impact the changing division of labour and enable the changing division of labour but it in turn will be impacted by the division of labour, knowledge and finance.

This research proposes that changes in the markets for technology lie in changes in the flows of technology/products and changes in the volume of these flows. The markets for technology must have become more complex than previously described if there is a changing division of labour and a surplus of unexploited knowledge. Therefore, a gap in knowledge of the sector exists that must be updated. Changes in the flows of knowledge will be connected to the role of the new NRDO firm, the changing role of the existing traditional classical biotechnology firm and the changing role of the large firm as discussed above. It has been proposed that the new NRDO firm is essentially a buyer of products. This represents a new ‘player’ in the markets that is not currently reflected (nor validated yet) but this research seeks to prove this changing complexity. The complexity lies in the fact that existing flows of technology still hold true but new flows of technology/products and new players must be added to the model. If there is a surplus of unexploited knowledge, as is proposed by this research, then this explains the changes in the flows of technology and products and illustrates a changing role of large firms as suppliers of these products.
Although much has been written about the transfer of knowledge from small biopharmaceutical firms to larger vertically integrated firms, this transfer of products and knowledge from large firms to small firms has not been as well discussed and is only dealt with on the surface in terms of the academic literature. According to Mazzucato and Dosi, larger fully integrated companies are now more than ever, making a thorough evaluation of their technology portfolio, and therefore considering licensing as a commercialisation strategy to generate additional revenue at almost no additional cost (Mazzucato and Dosi, 2006). This is supported by Kollmer and Dowling in their licensing study of US firms who found that fully integrated firms out-license non-core products due to a misfit with their overall strategy before the marketing and sales phase (Kollmer and Dowling, 2004) providing the intellectual assets to these firms. The extent of licensing activities that are occurring in the opposite direction (larger vertically integrated companies to smaller companies) is not discussed to any extent in the pharmaceutical sector literature and determining the extent of this activity creates an opportunity for further research. Licensing is an important knowledge and technology acquisition channel for a company, especially those who are fully integrated (Kollmer and Dowling, 2004) and has become a well-established strategy in which to achieve a transfer of knowledge. There are existing mechanisms set up by which relationships are managed with small firms so it is possible that large firms are utilising this experience or capability to sell their products.

3.6. The Need for Further Empirical Research

The previous four sections above have discussed key areas for further study that form the basis for this thesis. The model below, Figure 5, is a diagrammatic representation of the interplay of these arguments.
Part of the purpose of this research is to develop a novel analytical framework which combines insights from several bodies of knowledge (innovation literature, finance literature, trade literature) to help make sense of the changes occurring in the sector. This representation of the four areas as discussed is intended to show the associations between these various aspects of the research based on the evidence presented above. Each of the four areas can now be said to represent four key dimensions that are closely related and impact each other. Each dimension is impacted by and impacts upon the other illustrated by the presence of two way arrows between each dimension. These relationships are not unidirectional and the aim of this model is to clearly show that all four areas are interrelated. This research will aim to analyse these associations in greater detail. Given the dynamic nature of the sector, it would seem necessary to ensure that an up to date understanding of the changes to the sector is undertaken.
3.7. **Summary**

This research proposes four important claims:

1. A changing division of labour
   a. A new type of firm has emerged – the No Research Development Only (NRDO) firm
   b. Fundamental changes to the business models of existing firms have taken place

2. A surplus of unexploited knowledge exists in the sector and forms a key explanation for these changes and is explained by other changes

3. The interplay of finance on the changing division of labour is significant and forms part of the explanation for these changes

4. There have been significant changes to the markets for technology impacted by (and impacting upon) the changing division of labour, finance and the surplus of unexploited knowledge

The basis for these claims has been discussed above. As there is some evidence to suggest that a new firm exists, this has created an important academic research opportunity to examine the extent of the existence of this firm. It has been pointed out that serious problems exist with current business models in the sector where the returns to R&D investment have decreased (Pisano, 2006; McKelvey, 2008). The evidence presented in the prior chapter indicates that firms in the pharmaceutical sector of drug development have evolved and will continue to evolve. Changing business models are crucial to the ongoing commercial viability of the sector and an economic inevitability. Now there may be another emerging firm, the No Research Development Only Firm. This business model is one where companies have no exploratory research capabilities in house and may be buying drugs from other companies to develop them. This is in marked contrast to the typical classical biotechnology business model suggesting that large pharmaceutical companies are becoming providers of potential new products. But changes in the classical biotechnology business model may also be evident as these firms also may buy in products for development. These developments influence a whole new pattern of
technology/knowledge exchange and thus the markets for technology. Taken together, it is hoped that research on these factors will provide the evidence required to ensure a thorough understanding of changes that have occurred in the sector and why. The following chapter discusses how the research strategy will aim to achieve these goals.
Chapter 4. Methodological Approach

4.1. Introduction

Chapter 2 provided an overview of the pharmaceutical sector and discussed how the sector has evolved particularly focusing on the third epoch and the impact of biotechnology on the organisation of the sector. The division of labour that has taken place with respect to the role of classical biotechnology firms was analysed and an important discussion related to the role of finance, knowledge and markets for technology was also presented. Chapter 3 then presented the arguments for further changes in the sector with respect to the division of labour, the role of finance, a surplus of unexploited knowledge and markets for technology. Evidence was presented to provide a foundation for the claim that a new division of labour has taken place and that this is related to changes in the availability of knowledge as well as financial considerations. Evidence for changing markets for technology was also discussed. The purpose of this chapter is to present the research questions and the associated methodological approach that was used to address these questions to provide a context and background for the choice of research methods.

4.2. The Research Questions

There were several important goals of this research. The first of which was the identification of a new type of firm and a corresponding division of labour. The evidence presented in Chapters two and three suggest that there may be a new division of labour in the sector. The analysis of the emergence and development of the classical biotechnology firm indicated changes to firms and their activities throughout the last several decades. The literature on industrial dynamics and evolutionary economic theories also provide strong evidence that changes in the division of labour can be expected. In addition, anecdotal evidence from the trade literature has suggested that a new type of firm exists, the NRDO firm, with distinct differences in its scope of activities in comparison to the much discussed classical biotechnology firm. This firm
is focused on exploitation activities. The following key research question was identified as an important starting point for the research:

1. What changes have occurred in the division of labour in the pharmaceutical sector?

This question has been posed to understand whether or not there has been a change in the division of labour reflecting a change in the balance of exploration and exploitation in the sector. The trade literature also suggested more pervasive changes in the sector related to existing firms and so this question directs the research toward a number of specific questions that will be addressed including the following:

- Is there a new type of exploitation focused NRDO firm?
- What are their origins?
- What are the characteristics of this new type of firm?

Evidence presented in Chapter three noted that there were changes to the Discovery and Development (DD firms) firms traditionally involved in exploration based discovery and to a limited extent in exploitation based drug development. The anecdotal evidence suggested that DD firms were no longer solely relying on their own internal discovery efforts to populate their drug pipelines and sourcing drugs externally for development. Understanding the extent of this activity is also a primary goal of the research and so the following research questions are posed:

- Are DD firms also sourcing products externally for development?

These four questions illustrate the need for a quantitative approach to ascertain the answers to these questions on a scale large enough to impart meaning to the results.

The second part of the research goals was to ascertain (if a change was discovered) why these changes had occurred, hence a comparative case study methodology was the preferred methodology for this overall question of why changes have occurred. The literature presented in Chapter two and the evidence suggested in Chapter three pointed to a need to have a specific
focus on the role of a surplus of exploitation knowledge and capital markets both of which have played an important role in the prior division of labour. This framework was extended to understand the interaction of both of these factors on a new division of labour. The resulting overarching research questions are posed to understand the contextual situation that impacted the division of labour:

2. What was the role of finance in the new division of labour?

The role of finance and capital markets is questioned as part of this research because prior evidence from the literature and evidence from the trade literature suggest that this may have a significant role to play in the new division of labour.

3. What was the role of a surplus of unexploited knowledge in the new division of labour?

The role of new knowledge is clearly fundamental to the division of labour that has occurred in the sector to date as discussed in chapter two. However, it is not yet known what role a surplus of unexploited knowledge plays in the proposed new division of labour. This question is posed to ensure that the role of knowledge is adequately addressed in this research. The following questions will form part of the inquiry directed by questions 2 and 3:

For NRDO firms:

- Why was the firm formed as an NRDO organisation?
- How have these NRDO firms developed?
- Why is this new type of firm emerging? E.g., What is prompting the formation of these types of firms? Is it related to firm origin, opportunity, finance?
- What factors are influencing the development trajectory of the NRDO firms?

For DD firms:

- Why was the firm formed as a DD organisation?
How has it developed?
Why did out source products externally?
What factors are influencing the development trajectory?
Why are these changes in strategy taking place within DD firms? What is influencing these changes?

The role of the markets for technology have been discussed in Chapter two and the discussion in Chapter three has also illustrated that changes in the markets for technology can be expected. This research will examine these changes. The following question is proposed:

4. What is the nature of changes in the markets for technology?

The role of the different types of firms in the markets for technology will be examined to understand the nature of trade in intermediate technological inputs (Drug candidates) and knowledge and how that may have changed in response to the changing division of labour.

4.3. Research Approach – Mixed Methods: Quantitative and Qualitative Methodologies

Historically, distinctions have been made between these two broad descriptors (quantitative and qualitative) of the range methodological approaches that can be employed in social sciences research. This has generally been attributed to the proposition that each methodological type is associated with separate and unique paradigmatic perspectives that are not reconcilable (Reichardt and Cook, 1979). According to one observer, ‘the adherence to one paradigm as opposed to another predisposes one to view the world and the events within it in profoundly different ways’ (Rist, 1977). The broad distinctions can be described as follows: Quantitative methods have been described as ‘thin’, ‘narrow’ but ‘generalizable’ (McClintock and Greene, 1983). Examples of quantitative techniques include randomized and quasi-experiments, multivariate statistical analysis and sample surveys. The major benefits of quantitative research are generalisable results, reduction in bias etc. Formulated hypotheses can be tested through controlled experiments or statistical analysis. In this respect this methodological
approach lends itself well to the initial questions that this research seeks to answer which concerns the extent of a division of labour in the sector. According to Reichardt and Cook, quantitative methods have been developed most directly for the task of verifying or confirming theories (Reichardt and Cook, 1979).

Qualitative research, however, has been described as having a ‘long, distinguished and sometimes anguished history’ and many methods and approaches fall into this category (Denzin and Lincoln, 2003). However, while qualitative research may encompass a wide range of approaches it can be broadly described as follows: qualitative research is a situated activity that locates the observer in the world and consists of a set of interpretive practices that make the world visible. It involves the studied use and collection of a variety of empirical materials – case studies, personal experience, introspection, life story, interviews to name but a few (Denzin and Lincoln, 2003). It can yield data from which process theories (and richer explanations of how and why processes and outcomes occur) can be developed (Marcus and Robey, 1988). Qualitative strategies emphasise an interpretive approach that uses data to both pose and resolve research questions (Kaplan and Duchon, 1988). Once again, the benefits from the qualitative approach that seek to understand and explain research findings make it another suitable component of the research methodology.

The goals of this research have meant that different types of questions form the basis of inquiry. The questions that were asked fell into two categories as a result: Those that required a statistical approach to provide an acceptable set of answers and those that required a far more detailed and contextual analysis that were best answered through a qualitative approach. Ultimately, the nature of the questions has prompted the need for a dual approach that maximises the value inherent in both qualitative and quantitative methods. According to Jick, ‘there is a distinct tradition in the literature on social science research methods that advocates the use of multiple methods’ (Jick, 1979). Also known as ‘convergent validation’ or ‘triangulation’ (Campbell and Fiske, 1959; Webb 1966) the use of multiple
methods is believed to maximise the complementary nature of both approaches given the strengths and weaknesses inherent in single method designs (Jick, 1979). Jick also goes on to note that triangulation through mixed methods can allow the researcher to be more confident in his/her results (Jick, 1979).

The approach used therefore, was twofold: Descriptive Statistics and Multiple Case Studies. A random sample of companies in the pharmaceutical sector was compiled that facilitated the identification of NRDO firms. The creation of a database of firm descriptors was generated to enable this interpretation. A qualitative multiple case study review combined with interviews of a selection of firms from that database was used to determine a. why changes in the division of labour occurred as well as b. what there the changes in the markets for technology and c. to understand the role of capital markets and knowledge in those changes. An important foundation of this research has been the ability to characterise a random sample of firms and examine why changes have occurred in this sector (drug development) and to look at this sample as a representative cohort of the sector based on the quantitative sampling approach.

4.3.1. Quantitative Analysis – Determining the Existence of the NRDO Firm

As discussed above, the approach of random sampling was determined to be most appropriate to the research questions that addressed the prevalence of the NRDO firm. Desk based research to create a database of a random sample of 100 companies in the US and the UK that captured data related to the firm was created.

4.3.1.1. Data Collection - Cohort of Firms Selected

*Drug Development Firms With Ownership of Product(s)*

There are thousands of firms that are involved in the pharmaceutical sector and their businesses cover the full range of service provision and product development. Many companies call themselves biopharmaceutical firms or biotechnology firms and this covers a multitude of businesses and business
models. This sample is restricted in order to obtain a specific cohort as the focus is only on firms that owned and developed drug products for human therapeutic use, at the time of sampling. In other words companies that develop drugs/therapeutics that are placed inside the human body. The anecdotal evidence presented in Chapter three indicates that the division of labour that is taking place specifically concerns firms involved in developing drugs hence this research intends to focus on this cohort only.

*Discovery and Development (DD) and No Research Development Only (NRDO) Firms*

McNamara and Baden-Fuller have characterised the sector’s R&D process into six stages while authors such as Pisano have characterised them even further into nine stages to accurately reflect the four different stages within the exploratory research and five stages of exploitation development and approval stages (McNamara and Baden-Fuller, 1999; Pisano, 2006). The early stages of the process, patenting and preclinical trials can be understood primarily as the exploration phase of this R&D continuum (McNamara and Baden-Fuller 1999). Human clinical trials and the submission of the New Drug Application (NDA) represent the latter five stages of R&D and can be characterised as exploitation related activities.
Figure 6. The Drug Development Continuum

Phases of human therapeutic (drug) development

**Clinical Development**

- Preclinical Development
- Phase I Trials
- Phase II Trials
- Phase III Trials
- Regulatory Approval

**Exploratory Phase**
- Target Identification
- Target Validation
- Lead Identification
- Lead Optimization

**Exploitation Phase**
- Up to 6 years
- 1 year
- 1 year
- 1 year
- 1-2 years
- 2-4 years
- 1-2 years

Source: Pisano, 2006
Firms that are engaged specifically in drug development face a particularly unique product development, financial and regulatory environment. The development of drugs for therapeutic human use is heavily regulated and the development pathway is particularly specific and costly. The product approval process for human health drug products is contingent on the conduct of a series of animal, clinical and manufacturing tests that demonstrate product safety and efficacy and are unique in their requirements for companies in this sector. This dramatically influences the product development process for firms involved in this sector: it can take between 8-15 years to actually develop a product and bring it to market successfully. It is the strictness of the regulatory approval system that is a big factor influencing the strategic approach for firms in the human health drugs sector (Luukkenon, 2005; Pisano 2006) and an important reason for examining the firms that operate in this subsector as an exclusive cohort. Ultimately these firms face vastly different development times and costs than diagnostics firms, firms involved in developing platform technologies (that usually do not intend to develop therapeutic drugs) and service based firms that may provide other inputs to these human therapeutic product development firms. These firms do not face the same regulatory environment or challenges and there are many of these firms that are involved in the human therapeutics sector but cannot be analysed as part of this research because of these fundamental differences in their business. The focus of the research is on a division of labour that concerns drug development firms. In summary, for these reasons noted, all of the following types of firm have been excluded in this sample:

- Firms that provide services only:
  - Firms providing drug discovery based services only including firms that generate targets or biomarkers. This includes those firms that may be developing therapeutics but have only reached micro stage 4 and 5 (Lead optimization and preclinical).
  - Contract Research Organisations (CROs) – These firms perform services only and usually these firms do not own products.
- Diagnostics focused firms
- Firms that are primarily involved in providing what would be classed as inputs into the therapeutic development process such as reagents, machinery, etc.
• Large incumbent pharmaceutical firms\textsuperscript{17}

\textit{Note on Large Firms}

The sample cohort outlined above technically includes large pharmaceutical firms. However, this research is trying to understand the division of labour and changes to small firms that have evolved during the third epoch.

\textbf{4.3.1.2. Data Collection – Sampling and Sources}

\textit{Population of Drug Development Firms}

It was determined that a random sample of 100 US and EU drug development firms would be identified for further analysis. The idea of randomness in sampling specifically in statistics, however, has definite significance closely related to probability (Kendall and Babington Smith, 1938). A table of random sampling numbers was used to select 50 appropriate firms from each of the total sector lists generated for the US and the EU. The main benefit of simple random sampling is that it guarantees that the sample chosen is representative of the population. A random number table is a list of numbers. Numbers in the list are arranged so that each digit has no predictable relationship to the digits that preceded it or to the digits that followed it. In short, the digits are arranged randomly to allow the sampling of a population to also be random. This ensures that the statistical conclusions will be valid (\url{www.stattrek.com}). The random sampling table of figures was generated based on the overall size of the master list and the required number of firms (100) utilising a random number table generating website (\url{www.random.org}).

It was expected (based on the numbers below) that 100 firms would represent at least 20\% of the entire segment:

• In the 1999 Biotechnology Guide USA, 421 ‘Biopharmaceutical’ firms (all drug development human therapeutics firms) were identified (the latest available data).

\textsuperscript{17} IMS Health data on the top 20 pharmaceutical companies by drug sales was utilised to distinguish large firms and remove them from the sample. \url{www.imshealth.com}
• Kasch and Dowling estimated that there were 114 human therapeutics firms that were publicly listed on the US Securities and Exchange Commission online database EDGAR in 2005. Their search was based in the Standard Industrial Classification Codes of 2834 (Pharmaceutical Preparations) and 2836 (Biological Products, excluding Diagnostic Substances). However, this only represents those firms who are publicly listed.

By selecting 100 firms, it was also anticipated that a manageable range of firms could be selected and analysed from a qualitative perspective.

Identifying and Selecting Drug Development Firms

A range of information was gathered related to firm origin, products, finance and alliances (12 points of information in all – see Table 1 below) and descriptive statistics were identified and used to gather and organize information on the firms. While the technique of random sampling was used to select firms initially, a further review of each selected firm was necessary to ensure that the firms matched the criteria as discussed above in terms of their activities and to ensure that they were in fact drug development firms. This was done by first examining their overall company description available on their website (including a review of any description of their technology platform) and this was then verified in using the Thomson One or AMADEUS description. A review of their product pipeline and the stage of development of their drug products was then conducted to further ensure that they had drug products in development. Again, company websites together with analyst reports and descriptions found in databases such as the Thomson One and AMADEUS databases were also utilised to verify drug development activities.

These firms represent three different types of companies: those that are focused on small molecule drugs; those companies involved in the development of biopharmaceuticals (recombinant products, vaccines and monoclonal antibodies for example) and those companies that use both approaches. This meant that the sample had to be restricted to only these companies operating in this segment of the sector. There is no definitive list of these companies available and so it was necessary to pull together a
unique list (Meta sample) utilising a range of sources to ensure that the entire list of possible companies operating in the segment could be compiled. This was done utilising data from a range of sources for both regions to try to compile a complete meta list of firms operating in the segment of drug development. The main sources were organisations of firms (www.bio.org, www.fiercebiotech.com, www.PhRMA.org, www.biotechnology-europe.com) and lists provided by financial databases including Thomson One Banker and AMADEUS.

Sector membership lists were utilised in addition to the financial databases because it was determined that the standard industrial classification (SIC) code was not perfect and it was possible that it may not include all relevant firms (Guenther and Rosman, 1994). However, SIC codes were also utilised to obtain a list of companies from these financial database sources. SIC codes are commonly used in empirical research to identify a homogenous cohort of firms that includes certain firms and excludes others. In other words the classification produces groupings of companies with homogenous members (Guenther and Rosman, 1994). The main three digit code (sector group for drugs) is 283. This included the following four digit codes for drug development: 2834 (Pharmaceutical Preparations) and 2836 (Biological Products, excluding Diagnostic Substances).

Sources Utilised for Identification of Firms for the Sample

AMADEUS

This database is a comprehensive, pan-European database that contains financial information on over 11 million public and private companies in 41 European countries. It combines data from over 30 specialist regional information providers. Data available within AMADEUS includes including detailed financial reports, details on business activities and other information including subsidiaries, director and shareholding data. The list was created using SIC codes 2834 and 2836.
Sector Membership Lists

Lists of firms from two industry membership sources were also used to compile the meta sample of firms and these include the following: [www.biosector.org](http://www.biosector.org) and [www.fiercebiotech.com](http://www.fiercebiotech.com) which were two of the largest publicly available lists of companies. BIO is the world's largest biotechnology organization, providing services for more than 1,200 members worldwide. BIO members are involved in the research and development of innovative healthcare in addition to agricultural, industrial and environmental biotechnology technologies. Corporate members range from entrepreneurial companies developing a first product to Fortune 100 multinationals. These lists also include traditional pharmaceutical companies reflecting the integration of biotechnology into the pharmaceutical sector. These lists were considered the largest publicly available without any required subscription.

Thomson One Banker

The sample of firms was supplemented by creating a dataset of firms using the Thomson One Banker website. This database provides detailed financial analysis for over 65,000 UK/European and Internationally quoted companies. Data includes up to 10 years annual filings, archived annual reports and company filings, share price/estimates data and international deals. The list of firms from this source was selected based on the SIC codes 2834 and 2836.

4.3.1.3. **Data Gathering - Quantitative Research and Presentation**

These lists of firms were then put together for each region and the random sampling table was generated based on the list size. The random sampling tables were then used to select a firm from the list. However, a further process of verification then had to take place to ensure that the company was in fact a drug development organisation. This was done using a dual information review approach whereby verification was sought by looking at the company information provided by the financial database and the company website.
There were twelve data points (types of information) captured for each firm in the sample. Each of these data points were selected based on the available evidence in the literature that characterised small firms in the sector. Once a company had been selected for inclusion in the database, a process of information review then took place to capture the relevant information on the company (as listed below). The data and information collected also acted as a basis of comparison between any new type of firm identified and existing firms whose characteristics have been discussed and analysed. The following table summarises the way the data was captured and when appropriate, why the data point was selected:

<table>
<thead>
<tr>
<th>Data Points</th>
<th>Descriptions</th>
</tr>
</thead>
</table>
| 1. Technology platform (NRDO - Y/N)                                         | Used to capture the type of technology the firm is utilising in the discovery and development of its products. This was also used to verify the presence of exploratory activities (discovery) in which the firm is engaged.  
  ❖ Used to determine if the firm is an NRDO or DD firm                                                                                                                                   |
| 2. Age                                                                      | In order to determine if a new type of firm was emerging, the focus was ultimately on firms formed in the last 35 years. This variable is important to try and understand when new types of firm were formed and the length of time over which firms have been forming.                                                                                                                                                                                                                           |
| 3. Origin of firm – Corporate Spin Out (CSO) or Public Institution (University/GOV) spin out (PSO)                                                                                           | Captured to ascertain where the firm came from i.e., who formed it (public institution/academic spin out or corporate spinout), to try and understand the potential variety in the origins of firms.                                                                                                                                                                                                                                                                           |
| 4. Place on the drug development continuum (NRDO – Y/N)                     | To fully understand the range of activities that the firm is conducting by using the drug discovery - development continuum of activities. Again this helps to ascertain the nature of the firm and its core activities. So, if a firm is listed as Discovery – Phase II, this means that it presently conducts                                                                                                                                                                                                 |

Table 1. Categories and Descriptions of Data Collected on Firms
<table>
<thead>
<tr>
<th>Data Points</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Table 1. Categories and Descriptions of Data Collected on Firms</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Data Points</strong></td>
<td><strong>Descriptions</strong></td>
</tr>
<tr>
<td>activities in drug discovery and in Phase II. This also indicates how far the firm has progressed along the drug discovery – development continuum.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>❖ Used to determine if the firm is an NRDO or DD firm</td>
</tr>
<tr>
<td>5. <strong>Number of drug candidates - #</strong></td>
<td>This is the total number of drug candidates that the firm has indicated it has in preclinical development and clinical development. Products listed that are in any stage prior to pre-clinical development are not included.</td>
</tr>
<tr>
<td></td>
<td>i. Note: Products being tested for more than one indication are counted as one product.</td>
</tr>
<tr>
<td>6. <strong>Number of marketed products</strong></td>
<td>This is the total number of products that the firm has on the market. Helpful to ascertain the extent to which companies are engaging in activities at this end of the drug development continuum.</td>
</tr>
<tr>
<td>7. <strong>Current financial status – Public or Private</strong></td>
<td>To indicate if a firm was public or privately owned (stock market traded or not). Used to determine any further relationship between the firm type (NRDO/DD) and financial status.</td>
</tr>
<tr>
<td>8. <strong>Finance history</strong></td>
<td>To understand the firm’s funding history and variety of sources of funding:</td>
</tr>
<tr>
<td></td>
<td>❖ CV – Other firm took an equity stake in the firm</td>
</tr>
<tr>
<td></td>
<td>❖ De – Firm used debt financing</td>
</tr>
<tr>
<td></td>
<td>❖ Gr – includes government grants, other agencies such as Charities/Foundations and government contracts</td>
</tr>
<tr>
<td></td>
<td>❖ PF – Firm founders used personal finance</td>
</tr>
<tr>
<td></td>
<td>❖ VC – Venture Capital</td>
</tr>
<tr>
<td>9. <strong>Revenue Stream</strong></td>
<td>Captures the firm’s other income gained from revenue generating activities including:</td>
</tr>
<tr>
<td></td>
<td>❖ P – Product sales where the company retains the product rights</td>
</tr>
<tr>
<td></td>
<td>❖ L – Revenue from licenses granted including royalties from licenses</td>
</tr>
</tbody>
</table>
### Table 1. Categories and Descriptions of Data Collected on Firms

<table>
<thead>
<tr>
<th>Data Points</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>granted</td>
<td>R – Revenue for various research collaboration agreements.</td>
</tr>
</tbody>
</table>

**10. Did the firm in-license technology from non-university sources?**

Y/N

Given the focus on the division of labour and markets for technology and the anecdotal evidence presented in Chapter three, this activity was an important indicator to discern to what extent this activity was taking place.

**11. Does the firm have product development partnerships with other firms?**

Y/N

Partnerships and alliances are a significant aspect of innovation strategies of firms in this sector so it was deemed interesting to ascertain to what extent the new type of firm was also engaging in this sort of activity.

**Note:** partnerships for manufacturing or other enabling technologies are not counted.

**12. Did the company experience any major strategic changes?**

Y/N

This important point indicated if a company has experienced any of the following:

- Discovery Activities Discontinued
- Discovery Activities Added
- Development Activities Increased
- Significant lay-offs
- Buy out
- Merger
- Acquired other companies

Methodology – Analyze and review press releases and analyst reports to discern major strategic changes.

The range of data gathered has provided the basis for identifying and characterising the new type of NRDO firm and updating the characteristics of the existing DD firm. It was then possible to compare key differences and similarities between the two types of firms (who all share the common characteristic of having one or more products in clinical development which they own) from the data collected.
4.3.2. Qualitative Approach – Multiple Case Studies

As discussed, the research questions were also focused on understanding important contextual issues to help answer the central questions of why changes in the division of labour may have taken place as well as changes in the markets for technology. A different type of information and insight was required that was not obtainable from an analysis solely on the information in the database. In addition, the results from the database of information in turn prompted more research questions that could only be answered from conducting in-depth studies on a further cross section of these firms. Therefore, it was determined that a series of case studies was the best way in which to obtain in depth information about a subset of firms. In general, case studies are the preferred strategy when ‘how’ or ‘why’ questions are asked (Yin, 2003). In terms of the suitability of case studies over other methods such as surveys or histories, if the ‘how’ and ‘why’ questions (which are explanatory in nature, usually dealing with operational links that have to be traced over time) are being posed, case studies are an appropriate form of research (Yin, 2003). The form of the question (in this case ‘how and ‘why’) should drive the appropriate research strategy. In order to answer the particular research questions posed for this research, neither surveys nor simple stand-alone ‘histories’ were adequate in addressing the type of feedback and information required to try to answer these questions.

4.3.2.1. Case Study Selection

The evidence from the multiple case design approach is often considered to be more compelling and the overall study is usually regarded as being more robust than simply focusing on one case study (Herriott and Firestone, 1983). Selection of cases is an important aspect of building theory from case studies (Eisenhardt, 1989). Yin notes, ‘every case should serve a specific purpose within the overall scope of the inquiry’ and therefore the inclusion of a case within the design approach should follow a replication logic (Yin, 2003). Cases chosen can attempt to duplicate the findings of the initial cases or they can look to identify diversity. Overall, the ability to look at a number of companies in detail was considered of primary importance for the study and for conducting a multiple case study approach.
The selection of firms for inclusion in this research was systematic and deliberate and the table below summarises the companies chosen and the key criteria used in the decision making and selection process. The case study firms were selected based on criteria to ensure that there was variety in the firms and their experiences. Firstly, it was determined that an equal number of DD and NRDO firms would be selected. In terms of DD firms, that meant a choice of four companies out of 73 firms and for the NRDO firms, the choice was four companies out of a possible 27 firms. The next criterion pertained to the their location and therefore two US and two EU firms were required from the DD and NRDO firm lists. The next criterion was related to whether or not the firm had experienced any key changes in their business related to their focus on drug development or discovery. This is the ‘Adaptation’ criterion and was interesting in relation to both types of firms and so two DD firms and two NRDO firms that had undergone changes in their business model were selected. Firm age was also considered and where possible, firms of differing ages were selected. Once eight firms were selected, they were contacted to determine if they would be willing to participate in interviews. Out of the initial eight chosen, the following firms did not respond:

Table 2 Selected Case Study Firms - No response

<table>
<thead>
<tr>
<th>Case Study Firm</th>
<th>Age</th>
<th>Location</th>
<th>Type of Firm</th>
<th>Adaptation Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elusys</td>
<td>11</td>
<td>USA</td>
<td>DD</td>
<td>N</td>
</tr>
<tr>
<td>Minster</td>
<td>9</td>
<td>EU: UK</td>
<td>NRDO</td>
<td>N</td>
</tr>
<tr>
<td>Silence Therapeutics</td>
<td>15</td>
<td>EU: UK</td>
<td>DD</td>
<td>N</td>
</tr>
<tr>
<td>Biotie Therapies</td>
<td>15</td>
<td>EU: Finland</td>
<td>DD</td>
<td>N</td>
</tr>
</tbody>
</table>
The following sets of companies were thus identified and agreed to participate in the study:

**Table 3. NRDO Firms – Both Regions – No Changes to Firms**

<table>
<thead>
<tr>
<th>Case Study Firm</th>
<th>Age</th>
<th>Location</th>
<th>Type of Firm</th>
<th>Adaptation Y/N</th>
<th>Employees</th>
<th>Turnover</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinium Pharmaceuticals</td>
<td>17</td>
<td>USA</td>
<td>NRDO</td>
<td>N</td>
<td>N/A</td>
<td>N/A</td>
<td>3 Products Pre-clinical – Phase II</td>
</tr>
<tr>
<td>PanGenetics</td>
<td>5</td>
<td>EU: The Netherlands</td>
<td>NRDO</td>
<td>N</td>
<td>11</td>
<td>$51m Venture Finance received</td>
<td>4 Products Preclinical – Phase I</td>
</tr>
</tbody>
</table>

**Table 4. NRDO Firms – Both Regions – Changes to Firms**

<table>
<thead>
<tr>
<th>Case Study Firm</th>
<th>Age</th>
<th>Location</th>
<th>Type of Firm</th>
<th>Adaptation Y/N</th>
<th>Employees</th>
<th>Turnover</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViroPharma</td>
<td>15</td>
<td>USA</td>
<td>NRDO</td>
<td>Y</td>
<td>115</td>
<td>$135m (Income)</td>
<td>4 Products Phase I - Marketing</td>
</tr>
<tr>
<td>ProStrakan</td>
<td>15</td>
<td>EU: UK</td>
<td>NRDO</td>
<td>Y</td>
<td>259</td>
<td>£79m (Income)</td>
<td>10 Products Phase II - Marketing</td>
</tr>
</tbody>
</table>
### Table 5. DD Firms – Both Regions – Changes to Firms

<table>
<thead>
<tr>
<th>Case Study Firm</th>
<th>Age</th>
<th>Location</th>
<th>Type of Firm</th>
<th>Adaptation Y/N</th>
<th>Employees</th>
<th>Turnover</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacopeia</td>
<td>16</td>
<td>USA</td>
<td>DD</td>
<td>Y</td>
<td>169</td>
<td>$21.4m (Income)</td>
<td>13 products Discovery – Phase II</td>
</tr>
<tr>
<td>Pharming</td>
<td>22</td>
<td>EU: The Netherlands</td>
<td>DD</td>
<td>Y</td>
<td>81</td>
<td>€1.1m (Income)</td>
<td>4 Products – Discovery – Phase III</td>
</tr>
</tbody>
</table>

### Table 6. DD Firms – Both Regions – No Changes to Firms

<table>
<thead>
<tr>
<th>Case Study Firm</th>
<th>Age</th>
<th>Location</th>
<th>Type of Firm</th>
<th>Adaptation Y/N</th>
<th>Employees</th>
<th>Turnover</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cara</td>
<td>6</td>
<td>USA</td>
<td>DD</td>
<td>N</td>
<td>N/A</td>
<td>$28.7M Venture Finance</td>
<td>2 Products Discovery – Phase II</td>
</tr>
<tr>
<td>Actelion</td>
<td>13</td>
<td>EU: Switzerland</td>
<td>DD</td>
<td>N</td>
<td>2,493</td>
<td>€1.4B Income</td>
<td>12 Products Discovery - Marketing</td>
</tr>
</tbody>
</table>
4.3.2.2. **Data Collection**

Overall, the case study approach was utilised to gather, review, analyse, question and present a range of information obtained on eight firms. This was partly in order to understand the emergence of a new type of firm involved specifically in drug development and to understand changes to existing firms but also to look at how markets for technology were impacted. It was also important to examine firms that displayed a different focus on exploration and exploitation, some of which were stable but some of which were experiencing a process of change. This provided interesting diversity in the cases. This approach necessitated the use of several different sources of evidence without which an invaluable advantage of the multiple case study strategy will be lost (Yin, 2003). This included documentation, archival records, interviews and direct observation (which includes both primary and secondary data). The following sources were utilised in this process:

**Company Web Sites (Secondary Source)**

The exponential rise of the internet as a means of communication of important information about companies and the specifics of their business is indisputable. As a result, this was the first source of information reviewed. Many companies have several sections on their websites providing information in the following categories:

- Company Overview
- History and Origins
- Management Team
- Board of Directors
- R&D and Technology
- Pipeline and products
- Alliances and Partnerships
- Financial Information for Investors and Members of the Public
- Annual Reports and Other Publications
- News and Press Releases

A review of all of the available information in every category was undertaken to put together initial profiles on each of the companies which was expanded based on other available information that was gathered over time.
Trade Literature (Secondary Source)

As noted in the prior section on company websites, the rise in the availability of information from a range of sources via the internet has been exponential. This is particularly true in terms of the pharmaceutical industry where there is a proliferation of information available. This trade literature includes BioWorld, FierceBiotech, Nature Biotech, Pharmaceutical Executive, Pharmaceutical Technology, The Pink Sheet, Scripintelligence.com and various blogs including InVivo and Pharmalot. A range of business journals as well as various newspapers also report on the industry in particular, the Boston Globe, The Economist, the Financial Times, The New York Times, the Philadelphia Business Journal, the Philadelphia Inquirer, and the San Diego Union Tribune.

This literature provided some impetus for the initial thrust of this thesis as much as it provided some speculative insight into the companies, what they were doing and why. These sources and the information they offered provided some key insights into the reasons why companies were doing what they were doing and provided rich contextual background for the case studies and the interviews that followed. Speculation and information provided in the trade literature (but not always available in press releases or analyst reports) offered a way in which to initiate key discussions with some companies and verify information that was utilised from these sources. However, for the purposes of this research and indeed any research, it is necessary to distinguish between the types of information and literature reviewed. The distinction being made here is necessary because trade literature is not peer reviewed and in many cases nor is it a primary source hence the designation as a secondary source.

Thomson Research – Secondary Source

Thomson Research is a comprehensive data collection system that includes Investext®, Disclosure® and other industry leading databases. It offers a wide breadth of company research includes global filings, annual reports and market research studies. This was utilised to review analyst reports on each
of the companies and the appropriate/relevant information was then added to
the company profiles.


The SEC provides a free search system primarily for publicly listed
companies on the US stock exchange utilising the EDGAR database. The
laws and rules that govern the securities sector in the United States derive
from the concept that all investors, whether large institutions or private
individuals, should have access to certain basic facts about an investment
prior to buying and so long as they hold stock in that company. To achieve
this, the SEC requires public companies to disclose meaningful financial and
other information to the public. This provides a common pool of knowledge
for all investors to use to judge for themselves whether to buy, sell, or hold a
particular stock. This promotes the steady flow of timely, comprehensive, and
accurate information can people make sound investment decisions
(www.sec.gov). One of the most useful documents available to researchers
is the public company ‘10K’ document which is an annual requirement
whereby companies must publicise pertinent activities that have taken place.
All 10Ks were reviewed for the publicly listed companies in this study to
ensure that the relevant information was captured.

**Factiva – Secondary Source**

Factiva is a business information database covering about 10,000 business
and news publications, many in full text, including business magazines, trade
journals, newspapers, newswires, media programs and company stock
reports. This provides a valuable central source of articles on companies. A
search for each company was also conducted using this database to ensure
pertinent information about the company was captured.

**Google – Secondary Source**

With the advent of the 'read/write web' - Web 2.0 (Achterman, 2006),
applications such as the Google suite and Wikipedia have become the
standard service for information seekers and creators. Google indexes
billions of web pages so that users can search for the information they desire
through the use of keywords and operators. According to Google, they have increased both size and freshness in recent months indexing more quality content. Google is arguably the fastest and most effective search engine and is useful when used as an adjunct to other forms of research to ensure that any additional information that may be contained in other sources not noted above can be accessed. A search for each of the firms was conducted to ensure that any additional information relevant to the company and the profiles being created was captured.

4.3.2.3. **Semi Structured Interviews**

The success of this research is also rooted in understanding why changes are taking place with respect to small firm development and how these are influenced by other factors such as capital markets and the source of knowledge. Through analysing these firm development trajectories, these influences can be reviewed and the critical questions asked – is this the case and why? The need to have a longitudinal view of the company and its key milestones in terms of origin, business model, finance and product development strategy is necessary to support this goal. A valuable way in which to achieve these goals is through a related set of insights from its executives to capture the rationale behind why certain decisions were made and why events took place the way they did from the firm’s perspective. Miller and Glassner argue that ultimately, information about social worlds is achievable though in-depth interviewing and that it is possible to achieve authentic accounts (Miller and Glassner, 2004). Yin notes that ‘well informed respondents can provide important insights into a situation’ (Yin, 2003). The type of knowledge that was obtained from interviews as part of this approach would not have been obtainable from information gathered from secondary sources alone because what was required from the interview approach was insight.

While the case study approach allowed more information to be gathered with respect to various details, this approach was not just about gathering more detail. Insight into why firms made the decisions they did and what specifically prompted those decisions was a key output that was required
from this research and the only way to gain that type of insight was through case studies with interviews. In addition, it was necessary to gain access to the top executives who would be privy to the decision-making processes in effect at the firm and thus the influences on various decisions that were made. The following interviewees participated in the research:

Table 7. Participants in Company Interviews

<table>
<thead>
<tr>
<th>Company</th>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinium</td>
<td>Howard Wachtler†</td>
<td>CEO</td>
</tr>
<tr>
<td>Actelion</td>
<td>Walter Fischli</td>
<td>Former Founder and VP</td>
</tr>
<tr>
<td>Cara</td>
<td>Derek Chalmers</td>
<td>CEO</td>
</tr>
<tr>
<td>PanGenetics</td>
<td>Kevin Johnson</td>
<td>CEO and VC Partner</td>
</tr>
<tr>
<td>Pharming</td>
<td>Rienk Pypstra</td>
<td>VP R&amp;D</td>
</tr>
<tr>
<td>Pharmacopeia</td>
<td>David Kimball</td>
<td>VP R&amp;D</td>
</tr>
<tr>
<td>ProStrakan</td>
<td>Nigel Atherton</td>
<td>VP R&amp;D</td>
</tr>
<tr>
<td>ViroPharma</td>
<td>Tom Doyle</td>
<td>VP Strategy</td>
</tr>
</tbody>
</table>

4.3.2.4. Further Interview with GlaxoSmithKline (GSK)

The evidence from the database and the case studies indicated a very interesting issue with respect to the behaviour of large firms. The findings illustrated what appeared to be extensive out-licensing activities and spin out activities being undertaken by large firms who were exercising options to trade or spin out products in the form of drug candidates to small firms. It was decided to conduct an interview with a representative from a large firm to understand more about these findings. The individual selected was a director of the firm in drug discovery transactions. The remit of this group was not only to bring in products but to sell products also. The following key questions were asked at the interview:

1. Discuss the role of portfolio management at GSK
2. When did the company start out-licensing?
3. Why did the company start out-licensing?
4. Why is the firm cutting back on its work in certain therapeutic areas?
5. How does the firm decide between a spin out or out-licensing a particular drug?

4.4. **Evaluation of the Research Methodology**

The purpose of this research was to ascertain the emergence of a new firm (and thus a new division of labour), understand the reasons why this has happened as well as characterise the changes in markets for technology. The research approach was a mixed methods approach utilising quantitative methods to fulfil the first part of the research objectives and qualitative methods to fulfil the latter research objectives. However, the application of both of these methodologies involved a substantial amount of work. A great deal of data was collected on 100 firms and then further detailed research was conducted on the eight case study firms.

4.4.1. **Mixing Quantitative and Qualitative Research Methods**

The approach to constructing a database of information on firms was a classic attempt to address both the limitations of quantitative and qualitative research approaches. It involved the collection of over 1,500 pieces of data and information about firms. During this process a variety of sources were consulted as discussed. The use of a survey may have somewhat reduced the data collection required by the author however, the concerns were that the response rate would be poor and that the quality of information received back from firms would be substandard and incomplete. There was the added concern that information would have to be double checked, resulting in more work overall. While the process was extremely time consuming, it was a success providing a richly detailed picture of a range of firms operating in the sector.

The production of multiple case studies was also excessively time consuming and the constant concern that there was more information needed was always present. So much data on the firms was reviewed to try to create a complete picture in relation to the firm and its activities (in line with recommendations in the methodology literature) and again, some of this information was conflicting which then involved an iterative process of trying
to uncover which source was correct. This information gathering exercise was necessary prior to every interview in order to ensure that certain points of information could be verified and also to ensure that the various information provided by respondents could be corroborated as far as possible through the available data. While the use of multiple case studies is very valuable, the amount of effort required to duplicate the information gathered for more than one firm was extremely daunting.

4.4.2. Issues With Previous Research Samples – Focus on ‘Biotech’ Firms

The specific sectoral characteristics (high costs, length of development time and regulatory framework) make the study of the how these firms develop products in this sector particularly interesting (Bertoni et al, 2004; Mazzucato and Dosi, 2006; Pisano, 2006; McKelvey 2008). Yet much of the analysis and discussion concerning this sector has been conducted on a collective group of firms operating in a range of industries that together make up what has been traditionally been known as the biotechnology sector which is problematic. Biotechnology can no longer be described as a sector because it refers more to a set of technologies that profoundly affect a range of existing industries including the pharmaceutical sector (Powell et al, 1996; Gilsing and Nooteboom, 2006). Much of the literature does not single out this particular sector for analysis in its own right despite the important evidence as noted above, that would seem to point to the necessity of this type of cohort analysis. This research seeks to address this issue by focusing on companies in drug discovery and development.
Chapter 5. Evidence for the Changing Division of Labour and Markets for Technology

5.1. Introduction

An examination of the existence and prevalence of a new type of No Research Development Only (NRDO) firm in both the US and the EU and thus a new division of labour was a major driver for this research. A strategy was devised to distinguish firms based on the presence of exploratory (early stage research products prior to pre-clinical development in animals) activities and the presence of an identifiable technology platform. This was a way to distinguish firm activities based on their exploration/exploitation orientation. Two databases of firms were initially created, one database for each region. These databases were then combined when the same split of NRDO and DD firms was determined for each region. In order to be selected, a firm had to have at least one product in the clinical development stage and to have ownership of that product. Each database captured the same specific set of variables that have been analysed in this chapter related to firm origin, pipeline, finance, trade of products and alliances.

5.2. Evolution of the Sector – A New Type of Firm and a New Division of Labour

It was apparent that there was a key difference between the firms in the sample reinforcing anecdotal evidence from the trade literature: Not all firms had activities in discovery (evidenced by the fact that they had no potential products that were in these early stages) nor an exploratory technological platform pointing to the absence of product generating exploration activities. These key differences enabled the identification of a new type of firm and ultimately a new division of labour - The NRDO firm. This firm does not conduct any early stage exploratory/research/discovery activities to discover its own drug products. Previous studies related to drug development firms have primarily indicated two overall types of firms: Fully integrated large pharmaceutical firms and classical biotechnology firms (it should be noted that discovery only firms have historically been included in this overall category but not sampled in this study as discussed). This research,
however, introduces another specific type of firm: the No Research Development Only (NRDO) firm. The newly identified NRDO firms represent 27 % of the firms sampled which was unexpected. The sample can be divided as follows:

**Table 8. Summary of Major Types of Firms in the Sample**

<table>
<thead>
<tr>
<th>Type of Firm</th>
<th>Number of Firms</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US</td>
<td>EU</td>
</tr>
<tr>
<td>Discovery and Development</td>
<td>70% (35)</td>
<td>76% (38)</td>
</tr>
<tr>
<td>No Research Development Only</td>
<td>30% (15)</td>
<td>24% (12)</td>
</tr>
</tbody>
</table>

The NRDO firm and how its activities map onto the drug development cycle relative to the other major types of business models of firms is illustrated using the drug development continuum, in Figure 77.

NRDO firms do not have a business model based on a technological platform that would allow them to discover their own products or work on exploratory activities around early stage research related to discovering drugs. This was a surprising finding given that the literature on these companies and the development of this sector clearly discuses the research intensive nature of these small types of (hitherto classical biotechnology) firms. As noted above, one of the key differentiating facts in describing the small firms present in this sector and their business models is the presence of ‘discovery’ activities within the firm. These activities can be described as exploration-based activities (March, 1991; Levinthal and March, 1993; McNamara and Baden-Fuller, 1999; Gilsing and Nooteboom, 2006). They are generally resource intensive and will have a profound impact on the ability of the firm to develop products for its pipeline. This differentiating characteristic of the NRDO firms marks a key difference in the business models of these firms and a further notable change in the division of labour. However, it also follows that if these types of small firms are not generating products they are acquiring them from other firms. This indicates a change in the markets for technology.
Table 5. DD Firms – Both Regions – Changes to Firms

<table>
<thead>
<tr>
<th>Case Study Firm</th>
<th>Age</th>
<th>Location</th>
<th>Type of Firm</th>
<th>Adaptation Y/N</th>
<th>Employees</th>
<th>Turnover</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacopeia</td>
<td>16</td>
<td>USA</td>
<td>DD</td>
<td>Y</td>
<td>169</td>
<td>$21.4m (Income)</td>
<td>13 products – Discovery – Phase II</td>
</tr>
<tr>
<td>Pharming</td>
<td>22</td>
<td>EU: The Netherlands</td>
<td>DD</td>
<td>Y</td>
<td>81</td>
<td>€1.1m (Income)</td>
<td>4 Products – Discovery – Phase III</td>
</tr>
</tbody>
</table>

Table 6. DD Firms – Both Regions – No Changes to Firms

<table>
<thead>
<tr>
<th>Case Study Firm</th>
<th>Age</th>
<th>Location</th>
<th>Type of Firm</th>
<th>Adaptation Y/N</th>
<th>Employees</th>
<th>Turnover</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cara</td>
<td>6</td>
<td>USA</td>
<td>DD</td>
<td>N</td>
<td>N/A</td>
<td>$28.7M Venture Finance</td>
<td>2 Products – Discovery – Phase II</td>
</tr>
<tr>
<td>Actelion</td>
<td>13</td>
<td>EU: Switzerland</td>
<td>DD</td>
<td>N</td>
<td>2,493</td>
<td>€1.4B Income</td>
<td>12 Products – Discovery – Marketing</td>
</tr>
</tbody>
</table>
4.3.2.2. **Data Collection**

Overall, the case study approach was utilised to gather, review, analyse, question and present a range of information obtained on eight firms. This was partly in order to understand the emergence of a new type of firm involved specifically in drug development and to understand changes to existing firms but also to look at how markets for technology were impacted. It was also important to examine firms that displayed a different focus on exploration and exploitation, some of which were stable but some of which were experiencing a process of change. This provided interesting diversity in the cases. This approach necessitated the use of several different sources of evidence without which an invaluable advantage of the multiple case study strategy will be lost (Yin, 2003). This included documentation, archival records, interviews and direct observation (which includes both primary and secondary data). The following sources were utilised in this process:

**Company Web Sites (Secondary Source)**

The exponential rise of the internet as a means of communication of important information about companies and the specifics of their business is indisputable. As a result, this was the first source of information reviewed. Many companies have several sections on their websites providing information in the following categories:

- Company Overview
- History and Origins
- Management Team
- Board of Directors
- R&D and Technology
- Pipeline and products
- Alliances and Partnerships
- Financial Information for Investors and Members of the Public
- Annual Reports and Other Publications
- News and Press Releases

A review of all of the available information in every category was undertaken to put together initial profiles on each of the companies which was expanded based on other available information that was gathered over time.
Trade Literature (Secondary Source)

As noted in the prior section on company websites, the rise in the availability of information from a range of sources via the internet has been exponential. This is particularly true in terms of the pharmaceutical industry where there is a proliferation of information available. This trade literature includes BioWorld, FierceBiotech, Nature Biotech, Pharmaceutical Executive, Pharmaceutical Technology, The Pink Sheet, Scripintelligence.com and various blogs including InVivo and Pharmalot. A range of business journals as well as various newspapers also report on the industry in particular, the Boston Globe, The Economist, the Financial Times, The New York Times, the Philadelphia Business Journal, the Philadelphia Inquirer, and the San Diego Union Tribune.

This literature provided some impetus for the initial thrust of this thesis as much as it provided some speculative insight into the companies, what they were doing and why. These sources and the information they offered provided some key insights into the reasons why companies were doing what they were doing and provided rich contextual background for the case studies and the interviews that followed. Speculation and information provided in the trade literature (but not always available in press releases or analyst reports) offered a way in which to initiate key discussions with some companies and verify information that was utilised from these sources. However, for the purposes of this research and indeed any research, it is necessary to distinguish between the types of information and literature reviewed. The distinction being made here is necessary because trade literature is not peer reviewed and in many cases nor is it a primary source hence the designation as a secondary source.

Thomson Research – Secondary Source

Thomson Research is a comprehensive data collection system that includes Investext®, Disclosure® and other industry leading databases. It offers a wide breadth of company research includes global filings, annual reports and market research studies. This was utilised to review analyst reports on each
of the companies and the appropriate/relevant information was then added to the company profiles.


The SEC provides a free search system primarily for publicly listed companies on the US stock exchange utilising the EDGAR database. The laws and rules that govern the securities sector in the United States derive from the concept that all investors, whether large institutions or private individuals, should have access to certain basic facts about an investment prior to buying and so long as they hold stock in that company. To achieve this, the SEC requires public companies to disclose meaningful financial and other information to the public. This provides a common pool of knowledge for all investors to use to judge for themselves whether to buy, sell, or hold a particular stock. This promotes the steady flow of timely, comprehensive, and accurate information so people make sound investment decisions (www.sec.gov). One of the most useful documents available to researchers is the public company ‘10K’ document which is an annual requirement whereby companies must publicise pertinent activities that have taken place. All 10Ks were reviewed for the publicly listed companies in this study to ensure that the relevant information was captured.

**Factiva – Secondary Source**

Factiva is a business information database covering about 10,000 business and news publications, many in full text, including business magazines, trade journals, newspapers, newswires, media programs and company stock reports. This provides a valuable central source of articles on companies. A search for each company was also conducted using this database to ensure pertinent information about the company was captured.

**Google – Secondary Source**

With the advent of the 'read/write web' - Web 2.0 (Achterman, 2006), applications such as the Google suite and Wikipedia have become the standard service for information seekers and creators. Google indexes billions of web pages so that users can search for the information they desire.
through the use of keywords and operators. According to Google, they have increased both size and freshness in recent months indexing more quality content. Google is arguably the fastest and most effective search engine and is useful when used as an *adjunct* to other forms of research to ensure that any additional information that may be contained in other sources not noted above can be accessed. A search for each of the firms was conducted to ensure that any additional information relevant to the company and the profiles being created was captured.

### 4.3.2.3. Semi Structured Interviews

The success of this research is also rooted in understanding why changes are taking place with respect to small firm development and how these are influenced by other factors such as capital markets and the source of knowledge. Through analysing these firm development trajectories, these influences can be reviewed and the critical questions asked – is this the case and why? The need to have a longitudinal view of the company and its key milestones in terms of origin, business model, finance and product development strategy is necessary to support this goal. A valuable way in which to achieve these goals is through a related set of insights from its executives to capture the rationale behind why certain decisions were made and why events took place the way they did from the firm’s perspective. Miller and Glassner argue that ultimately, information about social worlds is achievable though in-depth interviewing and that it is possible to achieve authentic accounts (Miller and Glassner, 2004). Yin notes that ‘*well informed respondents can provide important insights into a situation* (Yin, 2003). The type of knowledge that was obtained from interviews as part of this approach would not have been obtainable from information gathered from secondary sources alone because what was required from the interview approach was insight.

While the case study approach allowed more information to be gathered with respect to various details, this approach was not just about gathering more detail. Insight into why firms made the decisions they did and what specifically prompted those decisions was a key output that was required
from this research and the only way to gain that type of insight was through case studies with interviews. In addition, it was necessary to gain access to the top executives who would be privy to the decision-making processes in effect at the firm and thus the influences on various decisions that were made. The following interviewees participated in the research:

Table 7. Participants in Company Interviews

<table>
<thead>
<tr>
<th>Company</th>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinium</td>
<td>Howard Wachtler</td>
<td>CEO</td>
</tr>
<tr>
<td>Actelion</td>
<td>Walter Fischli</td>
<td>Former Founder and VP</td>
</tr>
<tr>
<td>Cara</td>
<td>Derek Chalmers</td>
<td>CEO</td>
</tr>
<tr>
<td>PanGenetics</td>
<td>Kevin Johnson</td>
<td>CEO and VC Partner</td>
</tr>
<tr>
<td>Pharming</td>
<td>Rienk Pypstra</td>
<td>VP R&amp;D</td>
</tr>
<tr>
<td>Pharmacopeia</td>
<td>David Kimball</td>
<td>VP R&amp;D</td>
</tr>
<tr>
<td>ProStrakan</td>
<td>Nigel Atherton</td>
<td>VP R&amp;D</td>
</tr>
<tr>
<td>ViroPharma</td>
<td>Tom Doyle</td>
<td>VP Strategy</td>
</tr>
</tbody>
</table>

4.3.2.4. Further Interview with GlaxoSmithKline (GSK)

The evidence from the database and the case studies indicated a very interesting issue with respect to the behaviour of large firms. The findings illustrated what appeared to be extensive out-licensing activities and spin out activities being undertaken by large firms who were exercising options to trade or spin out products in the form of drug candidates to small firms. It was decided to conduct an interview with a representative from a large firm to understand more about these findings. The individual selected was a director of the firm in drug discovery transactions. The remit of this group was not only to bring in products but to sell products also. The following key questions were asked at the interview:

1. Discuss the role of portfolio management at GSK
2. When did the company start out-licensing?
3. Why did the company start out-licensing?
4. Why is the firm cutting back on its work in certain therapeutic areas?
5. How does the firm decide between a spin out or out-licensing a particular drug?

4.4. **Evaluation of the Research Methodology**

The purpose of this research was to ascertain the emergence of a new firm (and thus a new division of labour), understand the reasons why this has happened as well as characterise the changes in markets for technology. The research approach was a mixed methods approach utilising quantitative methods to fulfil the first part of the research objectives and qualitative methods to fulfil the latter research objectives. However, the application of both of these methodologies involved a substantial amount of work. A great deal of data was collected on 100 firms and then further detailed research was conducted on the eight case study firms.

4.4.1. **Mixing Quantitative and Qualitative Research Methods**

The approach to constructing a database of information on firms was a classic attempt to address both the limitations of quantitative and qualitative research approaches. It involved the collection of over 1,500 pieces of data and information about firms. During this process a variety of sources were consulted as discussed. The use of a survey may have somewhat reduced the data collection required by the author however, the concerns were that the response rate would be poor and that the quality of information received back from firms would be substandard and incomplete. There was the added concern that information would have to be double checked, resulting in more work overall. While the process was extremely time consuming, it was a success providing a richly detailed picture of a range of firms operating in the sector.

The production of multiple case studies was also excessively time consuming and the constant concern that there was more information needed was always present. So much data on the firms was reviewed to try to create a complete picture in relation to the firm and its activities (in line with recommendations in the methodology literature) and again, some of this information was conflicting which then involved an iterative process of trying
to uncover which source was correct. This information gathering exercise was necessary prior to every interview in order to ensure that certain points of information could be verified and also to ensure that the various information provided by respondents could be corroborated as far as possible through the available data. While the use of multiple case studies is very valuable, the amount of effort required to duplicate the information gathered for more than one firm was extremely daunting.

4.4.2. Issues With Previous Research Samples – Focus on ‘Biotech’ Firms

The specific sectoral characteristics (high costs, length of development time and regulatory framework) make the study of the how these firms develop products in this sector particularly interesting (Bertoni et al, 2004; Mazzucato and Dosi, 2006; Pisano, 2006; McKelvey 2008). Yet much of the analysis and discussion concerning this sector has been conducted on a collective group of firms operating in a range of industries that together make up what has been traditionally been known as the biotechnology sector which is problematic. Biotechnology can no longer be described as a sector because it refers more to a set of technologies that profoundly affect a range of existing industries including the pharmaceutical sector (Powell et al, 1996; Gilsing and Nooteboom, 2006). Much of the literature does not single out this particular sector for analysis in its own right despite the important evidence as noted above, that would seem to point to the necessity of this type of cohort analysis. This research seeks to address this issue by focusing on companies in drug discovery and development.
Chapter 5. Evidence for the Changing Division of Labour and Markets for Technology

5.1. Introduction

An examination of the existence and prevalence of a new type of No Research Development Only (NRDO) firm in both the US and the EU and thus a new division of labour was a major driver for this research. A strategy was devised to distinguish firms based on the presence of exploratory (early stage research products prior to pre-clinical development in animals) activities and the presence of an identifiable technology platform. This was a way to distinguish firm activities based on their exploration/exploitation orientation. Two databases of firms were initially created, one database for each region. These databases were then combined when the same split of NRDO and DD firms was determined for each region. In order to be selected, a firm had to have a least one product in the clinical development stage and to have ownership of that product. Each database captured the same specific set of variables that have been analysed in this chapter related to firm origin, pipeline, finance, trade of products and alliances.

5.2. Evolution of the Sector – A New Type of Firm and a New Division of Labour

It was apparent that there was a key difference between the firms in the sample reinforcing anecdotal evidence from the trade literature: Not all firms had activities in discovery (evidenced by the fact that they had no potential products that were in these early stages) nor an exploratory technological platform pointing to the absence of product generating exploration activities. These key differences enabled the identification of a new type of firm and ultimately a new division of labour - The NRDO firm. This firm does not conduct any early stage exploratory/research/discovery activities to discover its own drug products. Previous studies related to drug development firms have primarily indicated two overall types of firms: Fully integrated large pharmaceutical firms and classical biotechnology firms (it should be noted that discovery only firms have historically been included in this overall category but not sampled in this study as discussed). This research,
however, introduces another specific type of firm: the No Research Development Only (NRDO) firm. The newly identified NRDO firms represent 27% of the firms sampled which was unexpected. The sample can be divided as follows:

Table 8. Summary of Major Types of Firms in the Sample

<table>
<thead>
<tr>
<th>Type of Firm</th>
<th>Number of Firms</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US</td>
<td>EU</td>
</tr>
<tr>
<td>Discovery and Development</td>
<td>70% (35)</td>
<td>76% (38)</td>
</tr>
<tr>
<td>No Research Development Only</td>
<td>30% (15)</td>
<td>24% (12)</td>
</tr>
</tbody>
</table>

The NRDO firm and how its activities map onto the drug development cycle relative to the other major types of business models of firms is illustrated using the drug development continuum, in Figure 77.

NRDO firms do not have a business model based on a technological platform that would allow them to discover their own products or work on exploratory activities around early stage research related to discovering drugs. This was a surprising finding given that the literature on these companies and the development of this sector clearly discusses the research intensive nature of these small types of (hitherto classical biotechnology) firms. As noted above, one of the key differentiating facts in describing the small firms present in this sector and their business models is the presence of ‘discovery’ activities within the firm. These activities can be described as exploration-based activities (March, 1991; Levinthal and March, 1993; McNamara and Baden-Fuller, 1999; Gilsing and Nooteboom, 2006). They are generally resource intensive and will have a profound impact on the ability of the firm to develop products for its pipeline. This differentiating characteristic of the NRDO firms marks a key difference in the business models of these firms and a further notable change in the division of labour. However, it also follows that if these types of small firms are not generating products they are acquiring them from other firms. This indicates a change in the markets for technology.
**Figure 7. Types of Drug Development Firms in the Pharmaceutical Sector**

Phases of human therapeutic (drug) development:
- Target Identification
- Target Validation
- Lead Identification
- Lead Optimization

**Exploratory Phase**
- Timeline: Up to 6 years

**Exploitation Phase**
- Preclinical Development
- Phase I Trials
- Phase II Trials
- Phase III Trials
- Regulatory Approval
- Timeline: 1 year, 1 year, 1-2 years, 2-4 years, 1-2 years

**Large Firms**
- Classical Biotechnology Firms
5.3. **Characterising the New Firm and the Changing Division of Labour**

The combined database was then split into two cohorts of DD firms and NRDO firms for further analysis through a comparison of key firm characteristics. By comparing newly identified NRDO firms to the well defined DD firm, it was possible to gain a greater understanding of how firm characteristics differed (or were similar) between these two types of firms. Table 9, All Companies – Comparison of DD and NRDO Firms, presents key information about the two cohorts of firms based on the newly identified NRDO and DD models. The table highlights some interesting differences between these two types of firms but also illustrates the similarities where they might not have been expected.

The NRDO firm appears to be roughly the same age as the DD firm with a relatively similar number of products in development but the NRDO firms have higher numbers of marketed products. NRDO firms have considerably less development partnerships than their DD counterparts. In terms of their origins, NRDO firms are predominantly classified as Corporate Spin Outs (discussed further below) as many of them were not formed based on the traditional academic (public spin out – PSO) mode. In terms of the financial status of NRDO firms as public or private, the split is relatively even with a small majority of public firms. But more NRDO firms are public than DD firms.

**Table 9. All Companies – Comparison of DD and NRDO Firms**

<table>
<thead>
<tr>
<th>Dimension for Comparison</th>
<th>DD Firms</th>
<th>NRDO Firms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Average)</td>
<td>9.94</td>
<td>9.03</td>
</tr>
<tr>
<td>No. of Drug Candidates (Average)</td>
<td>4.31</td>
<td>3.81</td>
</tr>
<tr>
<td>% of Firms with Marketed Products</td>
<td>4%</td>
<td>33%</td>
</tr>
<tr>
<td>% of Firms with Alliances</td>
<td>80%</td>
<td>37%</td>
</tr>
<tr>
<td>% of Firms Origin – Public Spin Out (University and Government Laboratories) (PSO)</td>
<td>58%</td>
<td>37%</td>
</tr>
<tr>
<td>% of Firms Origin – Corporate Spin Out (CSO)</td>
<td>41%</td>
<td>63%</td>
</tr>
</tbody>
</table>
### Dimension for Comparison

<table>
<thead>
<tr>
<th></th>
<th>DD Firms</th>
<th>NRDO Firms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial Status – Private Co.</td>
<td>61%</td>
<td>44%</td>
</tr>
<tr>
<td>Financial Status – Public (stock market) Co.</td>
<td>39%</td>
<td>56%</td>
</tr>
</tbody>
</table>

#### 5.3.1. Firm Similarities

There were only two key dimensions where firms were broadly similar: Age and number of drug candidates in development. A new type of firm would suggest that they might be younger than the previously identified DD firms. However, the information gathered on firm age does not indicate a significant difference between the two cohorts of firms. The average age of both sets of firms is surprisingly similar possibly indicating that although a different type of firm is evident, these NRDO firms are not necessarily new. The classification is new but not the firm itself. This is discussed further in Section 5.4 on explaining the origins of firms discussing why this may be the case.

The number of drug candidates identified in each firm’s pipeline is not significantly different between the two different types of firm. This indicates that the lack of discovery capabilities does not necessarily mean that the NRDO firms have less products in their pipeline. It is possible that the number of drugs in development might be explained by the firms’ origins as well as their ability to buy in new products. Further analysis on firm origin indicated that some of these firms had in fact adapted their business model to change from being a DD firm to a NRDO firm. This might partially explain the similarity in the number of drugs in clinical development for the NRDO firm (18.5% of these firms which are NRDO firms were once DD firms). Hence the broadly similar numbers of products needs to be explored further to explain the similarity (discussed in Section 5.4).

With the discovery of the prevalence of the NRDO firm, analysis was extended to understand if the DD firm also obtained drug candidates from other corporate sources. The results indicated that a subgroup of these firms also in-licenses products from other organisations despite the presence of internal product generating capabilities. Surprisingly, 56% of all DD firms
obtain drugs for development from external sources indicating an interesting new development in the activities of these firms and thus changes in the markets for technology are also evident where the DD firm is concerned. This means that traditional research intensive DD firms are also changing their business models to acquire products from external sources to complement existing pipelines. Taken together, this represents a major shift in our understanding of the flow of knowledge, products and technology in this sector as well as a changing division of labour where over a quarter of small firms drug development firms are only concentrating on drug development and exploitation rather than drug discovery and exploration.

5.3.2. Firm Differences

The findings indicate differences in the business model of the NRDO and DD firm in a number of different areas related to: Marketed Products, Partnerships, Firm Origin and Firm Finance.

Marketed Products

There is a pronounced difference when it comes to marketed products. Over 33% of NRDO firms have marketed products compared to only 4% of DD firms. This finding in relation to DD firms is not wholly surprising as this business model was not focused on getting products to market for a range of reasons related to issues such as finance and capabilities. However, the focus of small firms on marketed products by NRDO firms overall is surprising given that this was not a focus of any small firms traditionally in this sector. It would appear that marketed products play a key role in the business models of NRDO firms and may provide evidence of the viability of this business model, particularly as these products are used to fund the operations of firms (who have historically faced financial constraints). This might also explain the ability to obtain development stage drug candidates if there is revenue available for purchasing products from marketed products.

Alliances

The role of alliances and collaboration with other firms has been widely discussed in the literature as an important feature of the way in which all
firms in this sector conduct their business (Powell et al, 1996; Powell, 1998).
So, information related to firm alliances (for the purposes of product development only) was gathered and used to try to find out if NRDO firms were engaged in the same level of alliance activity as DD firms. The data shows a very interesting difference in the extent of alliances between the two models. 80% of DD firms were involved in alliances compared to only 37% of NRDO firms. As discussed earlier, the DD firms’ business model is one where there is an internal organisation that includes discovery activities and provides new products for the firm’s pipeline. Historically, the generation of these products has provided the traditional basis for collaboration in the sector as acknowledged in the literature, forming the basis for prolific networks, particularly between large pharmaceutical companies and smaller newer companies (Orsenigo, 1989, Powell et al, 1996; Henderson et al, 1999; McKelvey and Orsenigo, 2001). Therefore, it could be argued that there would be a reduced basis for alliances with those firms that do not possess a technological platform to generate new products.

**Firm Origin**

The data above on the origins of both the DD and NRDO firms illustrate some interesting key differences between these two types of firms. When gathering the data on these firms, it was deemed important to understand exactly where the NRDO firm had come from given the new business model and absence of research focus. The majority of NRDO firms (63%) were formed as corporate spin outs (CSO) and not formed as public spin outs (PSO – 37%). Firms formed as academic spin outs (based on academic or publicly funded discoveries) was traditionally understood as a fundamental aspect of the formation of new firms in this sector. If firms were not formed in this way this indicates that there are obviously new explanations for the origins of these firms and thus this business model and division of labour. However, it is interesting to note that 41% of DD firms were also formed as CSOs and this makes the search for the alternate origins of these firms more compelling. The DD firm has been described as an academic spin out, exploratory research based business model with associated research capabilities but the evidence shows that there are other ways in which firms
are formed in this sector that have not been discussed in great detail. This is further explored in Section 5.4.

Firm Financial Status

There are also differences between the firms in terms of their financial operating status. The majority of DD firms are privately financed while the majority of NRDO firms are publicly financed through stock markets. The private/public finance split among the NRDO firms is less pronounced than that of the DD firms. Possible explanations are discussed in Section 5.5.

Revenue Generation

There are also important differences in the sources of revenue which generate income for the two types of firm. The table below illustrates the percentage of firms in the sample that were in receipt of revenue from one or more of the three major sources noted in Chapter four:

Table 10. Revenue Sources for Firms

<table>
<thead>
<tr>
<th>Corporate Finance Source</th>
<th>DD Firms</th>
<th>NRDO Firms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revenue – Marketed Products</td>
<td>4%</td>
<td>33%</td>
</tr>
<tr>
<td>Revenue – Licenses</td>
<td>61.5%</td>
<td>37%</td>
</tr>
<tr>
<td>Revenue – Research</td>
<td>64%</td>
<td>3%</td>
</tr>
</tbody>
</table>

The data indicated that 33% of NRDO firms are receiving revenue from marketed products which is surprising. Historically, the descriptions of the small firms in this sector have emphasised and illustrated their exploratory upstream product focus and yet a third of NRDO firms are engaging in downstream exploitation activities. However, if the NRDO firm is focused on the development stage with no research focus then this is perhaps to be expected that it would focus more on marketed products. It indicates that this is one of the key sources of revenue for these NRDO firms. As expected, the NRDO firm does not receive any revenue from research because it does not have exploratory capabilities. A third of NRDO firms receive revenue from licensing products. This is interesting because this indicates the essence of the new division of labour: the small firm only concentrates on clinical
development of drugs and so it must out-license or sell those products to obtain revenue. These firms are buying products, conducting clinical research and then out-licensing these products to generate revenue. This also points to a new set of capabilities of these firms given their focus on development rather than research, the former typically the realm of the large incumbent firm. This will be explored further in the following chapter through case study research and again in Chapter seven.

5.4. Firm Origin and Knowledge - Explaining the Division of Labour

Understanding the emergence of the NRDO firms, i.e. where they have come from, is a fundamental part of explaining their existence and how this new division of labour has taken place. It is necessary to understand how and from where firms are acquiring knowledge and products if they are not academic in origin nor internally discovering their own products. Understanding the origins of DD firms may also help to understand their behaviour in terms of their external product acquisition activities.

Traditionally, classical biotechnology firms (DD) were formed as a result of collaboration between scientists and venture capitalists (Kenney, 1986; Orsenigo, 1989; McKelvey and Orsenigo, 2001; Pisano, 2006). Firms in this sample with a similar origin were classified as Public Spin outs (PSO). However, analysis of information on company history and formation of the firms sampled revealed that not all firms had been formed as Public Spin outs (PSO). The diagram in Figure 88 shows how firm formation in the last 35 years in this sector can be understood and proposes how changes in our understanding of firm formation might be better understood moving forward. The top section of the diagram shows the dominant explanation of firm formation that has been historically utilised in the literature – that of PSO firms. The bottom part of the diagram illustrates that there are now two important ‘origins’ of firms – the PSO and the CSO, i.e., firms that have been founded as a result of spin out opportunities that are non-academic in origin and may be as a result of either actual spin outs or product divestment by other companies.
Importantly, the findings indicated that only 33% of NRDO companies could be classified as PSO firms compared to 58% of DD firms. What is surprising is that a significant proportion (48%) of all firms in the sample were not formed in the traditional manner as depicted in the top part of the diagram i.e., they were formed as CSOs. 41% of DD firms were formed as CSOs and this is in marked contrast to the existing literature and conventional understanding. The emergence of firms formed as a result of CSO activity represents a less well documented and understood explanation for the origins of firms in this particular sector. This suggests that there may be an important relationship between large firms, knowledge and the formation of firms for both NRDO and DD firms. It is possible to speculate that large firms have products and knowledge that they are willing to sell pointing to a possible surplus of unexploited knowledge. But the reasons why large firms are engaging in this type of activity must be understood. There are implications for the markets for technology and capital markets that will be further explored in Chapter 7.
**Figure 8. Firm Origin**

1975 – 1990s
Public spin-outs (PSO) Firms were primarily formed as a result of collaborations between academics / government scientists and venture capitalists.

1990s – 2000’s
Firms increasingly formed based on products and technologies from other companies. While PSO firms are still an important source of new firms, Corporate spin-outs (CSO) firms are now a significant new type of firm.
Overall, the picture that has emerged is a far more intricate and nuanced explanation for the origins of all small firms in the sector, NRDO firms in particular, which are not currently reflected in the literature. The more detailed review of firm origin indicates that there are a series of pathways that account for firm origin and adaptation patterns. The diagram below presents a summary of the various origins of NRDO firms that have been identified based on the two primary origins – PSOs and CSOs.

**Figure 9. Variety in Firm Origin – NRDO firms**

There appear to be 4 potential origin/adaptation pathways for NRDO Firms.

There are four potential ways in which NRDO firms may have been formed. While the majority of firms were formed directly as NRDO firms, both as either PSOs or CSOs, some were also formed as a result of a process of firm adaptation. Overall, 18% of NRDO firms were formed as a result of DD firms that discontinued discovery related operational activities as illustrated in the diagram above for both types of origin.

The process of firm adaptation and the reasons why firms change their focus and their business is a fascinating part of the story of the changing division of labour. As noted above, not all firms began as purely NRDO organisations. Some firms started out as DD firms but chose to stop their early stage activities. So, these firms morphed into NRDO firms from the DD business model. An example of firm in the sample that did precisely this was
ViroPharma. The firm was formed as a traditional DD firm but due to the failure of one of its major research programmes, abandoned all research activity and laid off personnel to focus on developing clinical stage compounds and marketing drug products. The rationale for these decisions warrants further inquiry and is addressed in Chapter six on case studies.

The origins of 41% of DD firms were also highlighted in the data presented above as they were not associated with academic or government (PSO) spin outs and this data was surprising because the origins of DD firms in this sector have been well documented. The surprising finding overall was the large number of firms that were formed as CSOs. However, it would appear that important changes are taking place in the sector with respect to firm activity in terms of product and knowledge acquisition. It is therefore necessary to understand more about these changes and how they may explain changes in the DD firms’ origins and their source of products and knowledge. This in turn has important implications for changes in markets for technology as well as the division of labour. This is explored further through case studies presented in the next chapter and discussed in Chapter seven.

5.5. The Role of Capital Markets in the New Division of Labour

One of the key differences between the two types of firms, DD and NRDO, is their financial status as illustrated in the table below:

Table 11. DD and NRDO Firm Finance

<table>
<thead>
<tr>
<th>Corporate Finance Source</th>
<th>DD Firms</th>
<th>NRDO Firms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finance – Public/Private</td>
<td>38%/62%</td>
<td>56%/44%</td>
</tr>
</tbody>
</table>

Understanding the extensive financial requirements of firms in this sector has made it is possible to speculate that financial considerations impacted the initial division of labour observed during the third epoch. It is also possible that one of the reasons for the emergence of the NRDO firm may be related to capital markets and funding drug R&D. The timelines are long in both the exploratory research stage as well as the development stage. Therefore, if firms are potentially shortening their whole product cycle by cutting out a
fairly significant proportion of it (discovery) this reduces the risk overall because the exploratory work has already been undertaken and that investment made but critically, by someone else. These NRDO firms are overtly focusing all of their available resources on the development phase rather than having to allocate some of that finance to the earlier exploratory stage activities. It may be that they believe this makes them more financially attractive to potential investors. The absence of the ability to generate research revenue on the part of NRDO firms and the sheer costs of drug development would also suggest that these firms need greater access to significant sources of funding such as that provided by public stock markets.

The role of finance may also potentially explain the type of in-licensing activity observed by traditional DD firms who normally would not need to buy in products to supplement their own discovery activities. This implies that while these firms possess the capability to develop their own products, they still engage in external technology/product acquisition and this raises questions around why internal generation of products is not sufficient for some firms and what might be driving this. However, these products may be further along the drug development continuum which would put the firm in better strategic position overall and would potentially have a positive impact on its ability to obtain more investment from either VCs or indeed an IPO. This is because having products that are further advanced in their development may make them more attractive to investors as the closer the product is to significant milestones, the more likely it is to succeed and firms are more likely to be rewarded for this.

This is particularly interesting when viewed in terms of the disappointing performance of firms in the last decade (Pisano, 2006). It may be that firms are searching for ways to make themselves more attractive to potential investors. The role of finance in this respect also warrants closer investigation to understand why this type of activity is occurring and why sources of finance support these activities in the firm. If significant resources are required for in-licensing, an increase in this type of activity suggests that financial support would be a pre-requisite given the evidence presented in
Chapter two related to the pervasive influence of the sources of finance, particularly venture capital and the speculations in Chapter three based on anecdotal industry information. These speculations warrant closer investigation which will be done through case study comparisons in the next chapter and the discussion in Chapter seven.

5.6. **The Role of Markets for Technology**

These findings from the database have prompted further questioning related to the markets for technology: if products\(^\text{18}\) are not discovered and developed internally by both the new type of NRDO firm as well as some DD firms, as was traditionally understood to be the case, then from where are they sourced, how are they sourced and why? The findings above with respect to firm origin and Corporate Spin Outs suggests that products are coming from either large pharmaceutical firms or other small firms both of which are unexpectedly 'spinning off' products and related knowledge. It was also unexpected that 50% of DD firms were externally sourcing products for internal development. This also implies that ‘buyer’ firms (NRDOs and DD firms) are able to capitalise on this availability of unexploited knowledge (Drug candidates) and bring these in-house. This is in complete contrast to our prior understanding of the flow of technology and products between large and small firms in this sector. The diagram below suggests how the markets for technology may be represented currently:

\(^{18}\) The term 'Product' is used throughout this thesis to denote drug candidates.
This reveals a greater complexity in the markets for technology than has been previously described. Large firms may have become suppliers of unexploited knowledge and products in contrast to their previously understood role solely as recipients of early stage products and knowledge. In addition, small firms are also trading unexploited products and knowledge between themselves, again in contrast to the current understanding in the literature. This change in the flow of knowledge and products also represents a key change in the relationships between large and small firms. It would seem that the availability of ‘surplus’ unexploited knowledge has caused a corresponding change in the markets for technology and technology and the reasons why this has happened warrant further investigation. Case studies are utilised to understand and explain this in greater detail in the following two chapters.
5.7. **Summary**

A new firm has been identified – the No Research Development Only firm (NRDO) and the business model is based on product development but does not involve exploratory research activities resulting in internal product generation. These NRDO companies are opting for a business model that seeks to focus on products that are in the later stages of clinical development or already marketed. Prior descriptions of the extant role of small firms solely as suppliers of upstream knowledge may no longer be entirely applicable in this sector given the finding that 27% of small firms sampled are no longer working at the early stage research end of the drug discovery and development spectrum. This provides evidence for a new division of labour in the sector. But as discussed in Chapters two and three, the changing nature of these firms is not wholly unexpected nor is the existence of a new division of labour. This new type of firm coexists in a system that has already witnessed changes in the division of labour.

The prevalence of firms that were formed with origins related to other companies (CSOs) was unexpected given prior evidence in the literature that illustrates the importance of the academic spin out (PSO). This new evidence suggests that a number of firms are formed based on products, knowledge and capabilities from other companies both large and small and this represents a change in the complexity of the markets for technology in this sector.

Nilsson noted that the main success factor for firms in this sector, regardless of the model chosen, is the ability to rapidly identify the latest research from academia and commercialise it (Nilsson 2001). However, it seems that while this may have been true for many firms’ business models in this sector in the past, it is not necessarily the case for all firms operating in the sector today. New firms that have developed during the last 35 years were traditionally characterised as a new breed of exploratory research focused high technology firms that were known for their embodiment of new knowledge and the generation and development of new products as a result of this knowledge (the classical biotechnology firm or DD firm). The evidence has
shown that this may no longer be applicable to over a quarter of firms operating in the sector. The reasons why this has happened will be explored further in the following chapter.

This research also presents new information on the innovation/product development strategies of Discovery and Development (DD) firms. The research illustrates that these firms also source products and knowledge from external corporate sources and not just academic sources as traditionally understood. The exchange of products and knowledge in this sector has become more complex than previously acknowledged. A closer examination of the changing complexity in the markets for technology is necessary to understand how and why markets are changing.

We must update our understanding of the pharmaceutical sector and particularly the small firms that operate within it as the evidence has shown a division of labour has taken place as well as changes in the markets for technology which are integral to the division of labour. However, the reasons why these changes have taken place will be explored further in the following two chapters. A series of case studies that examine both DD and NRDO firms to address the questions noted above around knowledge and origin, finance and markets for technology are presented.
Chapter 6. Case Studies

6.1. Introduction

This chapter presents information on eight selected firms that formed the cohort for further case study analysis. Cases are presented to better understand and therefore explain the following: why and how the new division of labour has taken place with respect to the newly identified No Research Development Only (NRDO) firm; what has caused the changes in the division of labour and changes to existing firms; what is the role of a possible surplus of unexploited knowledge and finance in these changes and how have the markets for technology changed. Selected information on the case study firms is presented to focus on the relevant information on the firms’ history and actions that helps to explain these issues. This includes major events in the firms’ history that were fundamental to their origin and operations and help to explain their business model orientation and activities. Case studies were selected as a research mode because the nature of this type of research methodology is most commonly used to answer ‘why’ questions (Yin 2003). By conducting in-depth reviews of company histories, achievements, activities and pipelines the case study approach with interviews provided a rich context for understanding those issues and answering those questions posed by the research.

This chapter is divided into two sections. The key aim of Section 6.2 is to present the pertinent case study data on NRDO firms as follows:

- To understand where NRDO firms have come from and why this particular business model has emerged – What prompted the formation of the firm? Why has it emerged?
- To understand what influences their product development and how this relates to knowledge and financial markets.

These case studies have been grouped to examine two pairs of NRDO companies. The first pair of companies presented are two NRDO companies that were formed as NRDO companies from inception and did not implement any changes to their business model orientation. Actinium Pharmaceuticals
Inc. and PanGenetics are discussed first and reviewed in terms of the aims outlined above. The PanGenetics case study provides insight into the birth of a young NRDO firm (only 5 years old) and illustrates how financial sources can play a key instrumental role in firm formation, determination of the business model and determining the innovation strategy of a firm through their involvement in corporate governance. The Actinium case study provides a contrasting story of a much older NRDO firm formed as a corporate spin out in the 1990s and tells a different story of how large pharmaceutical firms and financial sources can play a key role in firm formation, determination of the business model and the implementation of the innovation strategy within a firm.

The second two case studies presented are of two older firms that both went through changes to their business model but are currently NRDO firms. ProStrakan was formed as an NRDO firm but changed its business model for a short period during its history incorporating discovery activities into its business, only to return to the NRDO business model once again. The second firm in this pair, ViroPharma is also an interesting story of a firm that started off as a classical biotechnology firm with discovery activities but has since divested those activities and has become a NRDO firm.

Section 6.3 presents four case studies on selected US and EU small firms to better understand key changes that may have occurred in the traditional classical biotechnology firm (Discovery and Development) business model. These case studies enable the closer examination of why these changes have taken place in order to understand how these firms are different with respect to our prior knowledge in this area. Specific aspects of the firms’ origins and the subsequent operational characteristics with respect to the implementation of their product development strategies are reviewed. These aspects of the firms have been carefully selected in order to examine the role of the influence of finance and knowledge as well as the changing markets for technology.

The companies have been presented as two groups of two firms based on some common elements of their origin and formation. The first pair of
companies presented are two DD companies that were formed as academic spin outs. Pharmacopeia and Pharming are discussed first and reviewed in terms of the aims outlined above. The next two case studies presented are a pair of DD companies that were formed by scientists who had left other companies. But these two firms were formed based on compounds that they had obtained from large pharmaceutical companies. Cara Therapeutics and Actelion are also reviewed in terms of the key points mentioned above and again provide an interesting contrast in terms of why these firms consider discovery activities to be critical to their business in addition to obtaining external products.

6.2. No Research Discovery Only (DO) Firms

6.2.1. Actinium Pharmaceuticals, Inc.19

Actinium Pharmaceuticals, Inc. (Actinium) was formed in 1993 by a pharmaceutical company called Organon20. Actinium was formed to develop an idea to combine Alpha Emitting Isotopes (AEIs), Actinium and Bismuth, with Monoclonal Antibodies (MAbs) and then to test this combination in clinical trials. A group of Organon scientists helped to set up and run the company and Organon financed the company for the first seven years of its lifespan. However in 2000, Organon, as the company’s sole financial source, forced Actinium’s management team to look for new sources of financing to fund the company’s operations. A private equity group, General Atlantic, provided funding for the company for the next 10 years. The focus on the radioisotope/MAb product combination was sustained for that time period of the company’s history despite having been unable to publicly demonstrate the efficacy of these products over the combined period of 17 years since the company’s formation.

Actinium was chosen as part of this research because it is an NRDO firm and also because it was formed over 17 years ago and sustained operations

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19 Note: Efforts to contact the company for an updated summary of operations were not successful and all contact numbers for the company were not in use as of July 2010.

20 Organon was a mid size pharmaceutical company itself part of a larger Dutch company, Akzo Nobel was Specifically set up to produce insulin in 1923.
until 2010 despite a lack of proven clinical success with its products. Therefore, it illustrates that this particular business model is not necessarily new and it also illustrates the key role of finance and large pharmaceutical company influence in the formation and operation of a company such as this. The following key findings with respect to Actinium are discussed in more detail in this section:

1. Organon spun-out Actinium specifically to develop Radioisotopes rather than develop the idea in-house. Organon funded the activities of the company for 7 years.

2. New private equity financing supported the continuation of product development activities despite a lack of proven or published clinical success. This is in marked contrast to commonly received wisdom of the role generally played by financiers particularly in terms of time commitments.

1. **Actinium’s Formation as a Corporate Spin out**

Actinium was formed to develop a product. Organon’s therapeutic focus during that time was on reproductive medicine, contraception, psychiatry, hormone replacement therapy and anesthesia; it did not have any oncology programmes. Therefore, the creation of Actinium was the result of a decision to form a new company rather than develop a product to treat cancer, in-house. This suggests that the Alpha Particle therapy platform was not a strategic fit for the company nor part of the its current in-house research agenda at the time. Consequently, for Organon, the corporate spin out was the preferred mode of product development; something not well discussed in the literature covering this period in the sector’s history.

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21 This was considered a unique approach utilising a platform called Alpha Particle therapy. The company was formed based on an idea, put forward by the Head of R&D at Organon, that using Alpha Emitting Isotopes and attaching them to a Monoclonal Antibody which targets cancer cells would allow the isotope to get into a cell and facilitate the obliteration of that cell with minimal peripheral damage to the surrounding cells. Technically, this represents a huge leap in the world of cancer treatment where the effects of chemotherapy and radiation are known to have hugely damaging effects on the surrounding tissue. The discovery work had already been done at Organon.
Actinium’s business model presents an interesting contrast to what is known about new firms that were formed during this period of the sector’s history. It did not focus specifically on new product generation (discovery of new pharmaceutical products) utilising new technologies generated at an academic centre and therefore it has been classed as a NRDO\textsuperscript{22} firm. The company was formed based on an idea generated at a larger established firm. This type of transfer of knowledge is also in contrast to the commonly received wisdom from this period that new innovative ideas were passed from small companies to large companies. Clearly in this case, the discovery activities were conducted at a large firm, Organon, and then these products transferred to a small firm, Actinium, specifically set up to conduct further development of these products.

Organon was the sole financier of the company for the first seven years of its lifespan. Organon’s influence on the company’s development during this seven year time period was important because it provided financial and strategic support to the company which is longer than the traditional venture capital (VC) timeline of 3-5 years. During those seven years the company was able to remain committed to its approach to develop the radioisotope/MAb product because of Organon’s backing. During that time, Actinium conducted preclinical studies, worked on developing processes to manufacture the isotopes (AEIs) and began to conduct a proof of concept clinical trial (Phase II). However, after seven years, Organon made a decision that Actinium had to obtain a new source of funding and the company was forced to seek new financial backing.

The company’s problems in retaining Organon’s funding may have been related to the founding management team’s ability to run the company. According to the CEO that eventually took over:

‘These founding scientists had no real business experience and did not have a good understanding of the amounts of drug product required to treat

\textsuperscript{22} No discovery capabilities were part of the firm’s operation so the company was formed as a NRDO company – No Research Development Only company.
patients and no understanding of how material would be obtained to run large scale trials.’

It is worth noting that it was Organon that created the company with its own scientists and while the idea was new and exciting the operational and development skills of those scientists were questionable. Organon put in place a management team that were strong in their scientific capabilities but not in their company management, manufacturing or operational capabilities. Therefore the level of support that was required to help run the company was significant. This support had been provided for seven years and Organon recognized that a different set of skills were required to help the company in its operational goals that were better provided by a new set of financiers. Traditionally, VC support is not just financial in nature but also includes managerial, operational and strategic advice which may explain why the company were looking for new finance.

2. Sustaining operations and the role of private equity

In July of 2000, the management team approached a private equity group General Atlantic, primarily funded by Charles Feeney\textsuperscript{23}, and were successful in obtaining funding from this group on a long term basis. However, although the new financiers implemented changes to the management team, they did not fundamentally change the orientation of the firm in terms of its business model. After a review of Actinium’s accomplishments, the new financiers acknowledged that the technology was potentially very exciting. However, the sentiment expressed was that:

‘The company was being run by a group that couldn’t deliver.’

This signaled that the new financiers had problems with the management team’s ability to run the company and while Actinium agreed to the new financier’s terms and conditions\textsuperscript{24} this ultimately included implementation of changes to the company’s management team. The management team had

\textsuperscript{23} Known as the fourth largest philanthropist of the 20th century.
\textsuperscript{24} No funding amounts were disclosed
noticeably failed to make any progress with respect to the product development milestones.

However, despite these changes in financial management and support, the company has still not been able to demonstrate any notable clinical success since the new financiers took over which makes General Atlantic’s commitment to Actinium quite interesting and intriguing. Their commitment has lasted for almost 10 years despite no published clinical progress. Sources within the firm have suggested that General Atlantic’s commitment to the company was related to the attitude of one of its lead investors, Charles Feeney,

‘The funding process was made easier by the fact that the main financier believed in the product. Charles Feeney is behind this company as an individual.’

During this time period, there were no real changes to the overall focus of the business model (the company has remained a NRDO company throughout its lifespan). Actinium in-licensed two monoclonal antibody (MAb)\textsuperscript{25} products\textsuperscript{26} the second of which was acquired in 2005\textsuperscript{27} in an effort to supplement its pipeline. The new MAb would be used for clinical trials related to gastric cancer and solid tumours. Importantly, prior to this, the firm had only concentrated on the indication of Acute Myeloid Leukemia for the previous 12 years.

What is unusual is that the company has managed to sustain its funding during the last 10 years, despite no clinical success. Again this is a timeframe not typical for private investors in this sector who usually look for returns or an exit in a 3-5 year timeframe (Gompers and Lerner, 1999). This timeframe is double that normal period. This illustrates the critical importance

\textsuperscript{25} For use with their radiopharmaceutical drug products.
\textsuperscript{26} The first MAb came from Protein Design Labs (PDL), a small biopharmaceutical company, and was in-licensed in 2003.
\textsuperscript{27} It was discovered and characterized by researchers at the German National Research Centre for Environment and Health.
of the private equity investor in the role of financial and strategic support to this company in particular.

6.2.2. PanGenetics

PanGenetics was originally a firm first formed as a discovery and development (DD) firm in The Netherlands in 1996, focused on antibodies. However, the company was not successful in its development efforts and was in fact dormant when it was reinvigorated by Index Ventures, 9 years after its formation, in 2005. The firm was reformed as a no research development only (NRDO) firm by Index Ventures who were the primary force behind this reinvigoration. PanGenetics concentrated on the development of two products (out of its four) one of which was in-licensed as the result of financial influence (discussed later). The firm went on to successfully develop and sell the in-licensed antibody to Abbot late last year when the product successfully passed Phase I trials. However, the firm will be shut down following the closure of the successful Abbot deal (£170m) despite its success with this in-licensed product and the remaining 3 other products in the pipeline.

PanGenetics was chosen as part of this research in order to understand more about the younger NRDO Firm including its formation and subsequent product development strategy. This research is concerned with knowing more about how and why this type of firm is formed, how the role of finance interacts with these activities in the firm and changing markets for technology. The story of PanGenetics is a particularly interesting example of all of these research issues and so the following key findings related to PanGenetics are discussed:

1. Index Ventures was the main driving force behind the creation of the business model for the newly reinvigorated ‘PanGenetics’ known as the ‘asset centric’ NRDO firm.

2. Venture Capital financing imposed strict conditions for in-licensing that impacted the firm’s innovation strategy.
1. Index Ventures and the ‘Asset Centric’ Business Model

Index had originally decided to form a new NRDO company and was searching for suitable antibodies with which to set up a new company. They found these in a dormant company in Holland called PanGenetics\(^{28}\). Initially, Index considered buying the antibodies from PanGenetics and starting a fresh company. However, they decided that rather than forming a new company they would ‘restart’ PanGenetics with new management\(^{29}\) and new financing. A key reason for this decision to restart PanGenetics was related to finance. Index believed that the public markets in Holland were reasonably healthy at that time. Only a few biotechnology companies were listed on the Amsterdam exchange which appeared to be well supported by local investors. The decision was made to reinvigorate this existing company so that they would have a trading record in Holland which the firm considered to be key to a Dutch public stock market listing at a later date. This suggests that the influence of capital markets in this case was significant in two ways: the role of the venture capitalists was key to the survival of a firm and the influence of favourable public stock markets also was factored into the firm’s survival.

However, another critical aspect to this ‘experiment’ was that Index wanted to form the company around products; what they called an ‘asset centric model.’ They never intended to set up what they called a ‘technology based’ (discovery related activities) company and therefore, the premise of the formation of the company was based on the development of a product(s) and not the discovery of new products,

‘The asset was the centre of our investment case. We were investing in a product and not in a company. We wanted to invest not in a technology but in

\(^{28}\) Index’ involvement in PanGenetics was the result of an experiment. They wanted to set up a company alone so that they would be the main thrust behind the formation of a company. Index wanted to know if it could successfully set up a company itself, get it financed, operational and to a point where it would make money. Usually venture capitalists invest in a company or set up a company in conjunction with a founder based on someone else’s idea for a product or technology but in this case Index was not approached by anyone to fund a business, rather, they decided to create a business and then find the product to base the business upon.

\(^{29}\) The CEO was the only remaining management team member so new management was needed.
a specific product. All our due diligence would be around that product and its profile. There would be no technology component to that.’

This singular focus on a product rather than a technology platform for discovery was the most important facet of the business model and represents a new type of investment model for this sector. Historically, developments in technology have been the driving force behind the formation of many new firms and subsequent investment in those firms but in this case, it was purely the desire to develop products rather than the technology and discovery capabilities. This also meant that the company was only set up to develop products with a view to then ceasing operations once this had been accomplished. Therefore, this business model meant that the company was inherently transient and with a much shorter lifespan than is commonly acknowledged. The interesting aspect of this case is that this company was focusing on a later phase of product and clinical development than is commonly acknowledged for new small firms in this sector.


In March of 2006, less than a year after it was formed, the company raised €13 million through a new financing round including participation by Index Ventures as well as ABN AMRO Capital and Crédit Agricole Private Equity. However, this financing had a series of conditions attached that also impacted the ability of the company to implement its product development and innovation strategy: Kevin Johnson from Index Ventures had to take on the role of full time CEO (as this was a key condition of closing this finance round) and the company had to secure rights to an external product. As a result, the company entered into negotiations with Schering Plough in an attempt to secure new products for the company based on its contractual obligations to its financiers, despite the fact that it already had internal products in its pipeline. The company believed initially that these negotiations

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30. This exists in conjunction with other more established modes of investment.
31. Who hadn’t intended on becoming the full time CEO but was to go back to Index and ‘do more investing.’ A search for another CEO had been conducted but nobody suitable was found.
would be successful as Schering Plough had a number of potentially interesting compounds that they were willing to discuss for out-licensing. However, issues in the negotiation process became time consuming and in the end, PanGenetics did not in-license any products from Schering Plough.

'The Schering Plough deal was a ridiculous condition imposed by the new investors who wanted us to prove that we could get assets in, they didn’t care what asset, they just wanted the company to prove that we could get assets in. We did that as a demonstration project. It wasn’t a particularly valuable thing to do. We were wasting our time. We never picked anything up out of Schering Plough. The deal was a bust.’

While the PanGenetics management team did not necessarily agree with these conditions to obtain products externally, this illustrates that the conditions had to be met and the innovation strategy therefore reflected the wishes of these venture capital investors. It also illustrates another interesting point related to the beliefs of external investors and the role of in-licensing. Product in-licensing as both an exercise and a capability, was important to the new investors who believed that obtaining external products was critical to the firm’s success; enough to warrant a contractual obligation.

However, the company had also entered into negotiations with another small company, LayLine Genomics in pursuit of one of their products, a nerve growth antibody. Initially PanGenetics entered into a licensing deal\(^{32}\) with LayLine but as LayLine’s future looked uncertain\(^{33}\), they converted the license to a full purchase of the antibody that became the PG 110 product (that would later form the successful deal with Abbot). LayLine had serious issues with financial corporate governance which contributed to their closure and the sale of the PG 110 product. However, the evidence here indicates that there is greater complexity in the markets for technology than perhaps

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\(^{32}\) The founder of this company was known by Kevin Johnson for a number of years and was a former colleague at Cambridge University (Laboratory of Molecular Biology). The historical personal history was a key part of the reason for this deal.

\(^{33}\) The company was experiencing financial difficulties and could not pursue any further development of its products.
has been acknowledged as this case illustrates that small firms also trade products amongst themselves.

Figure 11. PanGenetics and the Development of the NGF Antibody

In 2009, PanGenetics publicised the success of a Phase I trial for PG 110, the nerve growth antibody that was purchased from LayLine. Abbott acquired the product in November 2009 for $170 million. Several companies bid for the product reflecting considerable competition and according to the company, the generous terms of this deal resulted from this competition for the product. PanGenetics had effectively undertaken a successful development programme which proved the worth of the product to potential buyers. Overall, the development of the PG110 product is interesting because of how it was passed from one company to another, each of which worked on a different aspect of its development. This particular type of product development pathway in this sector is not well documented in terms of the way in which multiple companies are involved in the iterative ownership and development process which is illustrated here. PanGenetics’ contribution was to effectively develop these products in readiness for their next stage of development, usually the remit of the larger firm. It is also interesting how the company was able to add value to a product where other companies had failed (LayLine).

The reinvigoration and development of the new PanGenetics and its subsequent financial corporate governance illustrates an interesting story
related to the financial provider influences on firm formation and development in this sector where the emphasis appears to be on external product acquisition. The company will not pursue further product acquisition and there are no plans to develop the remaining products\textsuperscript{34}. The company anticipates selling remaining products and assets while staff will look for other opportunities. PanGenetics will cease to exist in the relatively near future and will disappear into the history books of the Pharmaceutical sector making the story of this particular business model all the more interesting for its inherent transitory nature.

6.2.3. ProStrakan

The former CEO of Shire Pharmaceuticals and Professor John Kanis formed Strakan in 1995. The firm was based on a business model for developing generic products and it also in-licensed clinical stage products for development so it was a NRDO firm. Within four years the company had its first product on the market. For nine years Strakan operated as a NRDO firm initially focusing on generic products. Then in 2004 the company decided to become publicly listed on the stock market and embarked on an IPO. As part of this process, it merged with ProSkelia to add discovery activities and an early stage pipeline to the firm’s capabilities and changed their name to ProStrakan. However, the expanded pipeline and the clinical testing requirements of existing products put financial pressure on the firm and two years later, ProStrakan divested these discovery capabilities in a move to focus financial resources on the development of clinical stage compounds. ProStrakan\textsuperscript{35} continues to pursue the development only business model and has a number of products on the market.

ProStrakan is another interesting example of a NRDO firm but also illustrates how and why these types of companies may adapt and change their business model. While ProStrakan is now focused on achieving success

\textsuperscript{34} The company never pursued the clinical development of its two other products PG 120 and PG140 due to both financial constraints and inherent problematic product characteristics, but rather it concentrated its resources on its two most promising products, PG102 and PG110.

\textsuperscript{35} Now calls itself a Specialty Pharmaceutical company.
through marketing and late stage clinical product development, there was a period in its history when it believed that this business model approach was not adequate. The following key points in relation to the origin of this firm, the changes to its business model and the role of trade in products and knowledge are discussed in greater detail:

1. Strakan was formed as a generic\textsuperscript{36} company business model by an entrepreneur to develop and sell generic products as quickly as possible supported by in-licensing to fill the pipeline.

2. The company merged with a discovery company (ProSkelia) based on financier recommendations to add discovery capabilities to its business model.

3. The company’s acquired discovery subsidiary, Proskelia, was divested in order to fund investment in commercialisation resource needs and so the company became a NRDO firm once again.

1. Origin of Strakan and the business model approach using in-licensing

One of the founding principles was that Strakan would have the capabilities to develop products and get them approved and marketed. There were no discovery capabilities built for the company. The company wanted to focus on clinical development activities and in-licensing was the primary vehicle that the company used to build its product portfolio. This was certainly in contrast to the more widely acknowledged research and development model. According to the head of clinical development:

‘Shire and Strakan and some other companies started the other way round. They focused on getting some products to market and then doing the complicated stuff later. Harry Stratford’s success with Shire meant that he knew this particular product market well so he founded Strakan on the

\textsuperscript{36} In most cases, generic products are available once the patent protections afforded to the original developer have expired. Generic drugs are identical or within an acceptable bioequivalent range to the brand name counterpart with respect to pharmacokinetic and pharmacodynamic properties. By extension, therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use (www.fda.gov)
principle that if there was an opportunity to establish a product quickly and generate revenues then these opportunities should be the company’s main focus rather than spending 15 years ‘in the red’ wondering if the product will make it to market or not.’

For Strakan, this represented a less risky and less costly approach to drug development\(^{37}\) (in no small part because of the founder’s knowledge of the business) and due to the nature of generic product development regulatory requirements, these products did not require the complicated and extensive clinical trials associated with non-generic, New Chemical Entities (NCEs). The founders of Strakan made a conscious decision (initially) not to pursue discovery activities because of a more compelling belief in the need to first build a sound financial base for their company, which they did with the success of their first product and this is in marked contrast to the actions of many of its peers at the time. This approach, at the time, represented a very different business model characterised by the fact that it was not an academic spin out concentrating on research but a fully integrated small firm pursuing a generic and NRDO approach.

In-licensing was a key part of this strategy and the company has in-licensed five key products\(^{38}\) in the last 15 years. The extensive in-licensing activity demonstrates the importance of this method of acquiring products to this type of firm. It is interesting to note that the firm continued to in-license despite a new internal source of potential products (ProSkelia) acquired later on. The company was very careful in the selection of a particular type of product in terms of its in-licensing and this may also be a key explanatory factor in the company’s ability to maintain this business model,

‘We just keep a very simple focus on what we’re here to do. We are not here to win Nobel prizes for science we are here to come up with very suitable

\(^{37}\) Clinical trials are not generally required for generics. Companies need to simply prove bioequivalence and manufacturing capabilities in terms of quality and safety.

\(^{38}\) However, the rights to the sale of products in various markets have been obtained in separate licensing deals.
products for medical need and the simpler those products are the easier it is for me to develop them. If they’re more complex it adds risk into it. While that might not be very exciting – one of the rules is that products don’t have to be exciting or sexy to be good products. A good drug is a good drug.’

2. The Role of the IPO in the Merger with ProSkelia

The IPO was a critical funding mechanism to move the company forward in supporting and funding its development goals for the products that it had acquired. It was also critical for the company’s investors who had to have an exit strategy which the IPO provided (these were approaching their 3/5 year investment timelines). However, a year prior to the IPO, in 2004, Strakan was persuaded to merge with ProSkelia (an Aventis spinout formed in 2002). At the same time, ProSkelia was also being persuaded to merge in order to prepare for a public offering of their own. According to the head of clinical development,

‘The various investors and analysts pointed out that the so called wisdom at the time was that we needed to be more of an integrated company; in other words do everything from wall to wall. From a development/R&D point of view it (Strakan) was effectively unproven. The idea was that by putting the two companies together, you would have a discovery pipeline, a larger R&D group, a larger portfolio and that made you more complete in making the IPO possible whereas as individual companies it wouldn’t.’

So based on the recommendations of their financial supporters, Strakan merged with ProSkelia in 2004 (to form ProStrakan), illustrating that financial influence was key in terms of the development and business orientation of this company. The company’s investors brokered the merger with ProSkelia as the key investors in ProSkelia were also key investors in Strakan. Ultimately the merger was designed to enhance the new combined company’s valuation prospects. This is interesting and suggests that the financiers’ believed in the need for the company to be fully integrated i.e. to have discovery capabilities and consequently viewed it as being critical to the
success of the company’s public valuation. These financiers believed that there was more value in being a DD firm than being a NRDO firm.

3. **Focus on Commercialisation**

However, the merger with ProSkelia meant that the company was in possession of a much larger pipeline and to date, had very little attrition in its own pipeline. This created a financial problem for the company as it then had to decide how to allocate the limited financial resources in terms of early stage (exploratory) or later stage clinical development (exploitation) projects. However, the big commercial plans that the company had in terms of their marketed products were ultimately not financially compatible with their new discovery and development business model. The company also realised that they could monetise considerable value in ProSkelia and at the same time retain selected commercialisation rights to some products.

‘It’s important to be able to adequately support the launch of new products. It’s a big decision but it’s a very straightforward decision when you think about the pure business aspect. Clearly it then compromises your earlier stage pipeline but we all know that some of the earlier stage things in any discovery platform are going to be 12-15 years away from a product and the percentage chance of success is a small number. You wouldn’t compromise getting a new product to market to prioritise something that was in discovery.’

Two years later after the ProSkelia merger, the decision was made to prioritise financial resources and focus entirely on expansion and commercialisation of its later stage products that were hopefully due for marketing approval in the near future. Again, financial reasons played a key part in this next change to the business model which was for the firm to become a NRDO company once again. Reducing their spend on early stage clinical research would free up more financial resources that would be used for potential product launches (of which there were 5 hopefuls in Europe in the following 24 months and 3 potential product launches in the US in the following 30 months). The company recently received approval for a product in the US which resulted in a 20% gain in its share price.
6.2.4. ViroPharma, Inc.

ViroPharma was founded in 1994 as a privately held drug discovery and development company by a group of scientists\textsuperscript{39} from a range of companies. About a year after its formation, ViroPharma obtained the US and Canadian rights to a Phase I product, Pleconaril\textsuperscript{40}, from Eli Sanofi\textsuperscript{41} to supplement its discovery efforts. Pleconaril became the company’s lead product and full development efforts were made possible by an Initial Public Offering on the US stock market in 1997. During this time, the company had in-house generated compounds in late stage research for influenza, hepatitis C and viral pneumonia but Pleconaril was ViroPharma's first compound put into development and a primary indication for the common cold was ultimately pursued.

However, in 2002, a year after the company submitted its New Drug Application (NDA) for Pleconaril, the US Food and Drug Administration rejected the application for the product’s approval. This caused substantial changes to be made to the company, the most notable of which was the discontinuation of ViroPharma’s discovery efforts and the reorientation of its business model to become a NRDO firm. It in-licensed products from Lilly (Vancocin – an antibiotic which was a marketed product) and GlaxoSmithKline (Maribavir - an oral antiviral drug candidate in Phase I) and sold its rights to Pleconaril in addition to discontinuing its discovery efforts in-house. In 2009 the company reported 34% growth for the year in net product sales indicating that its recovery seems to be well on track.

ViroPharma represents yet another interesting type of NRDO firm. In this case, the firm did not start out as an NRDO firm but adapted its business model from the classical biotechnology business model of a discovery and development firm to that of the NRDO firm with no discovery capabilities. The

\textsuperscript{39} The founders were mainly experienced RNA virologists who had been laid off in the deal between Eli Sanofi and Eastman Kodak which saw the discontinuation of some discovery activities.

\textsuperscript{40} A novel compound that integrates into the capsid of picornaviruses, including enteroviruses and rhinoviruses, preventing the virus from attaching to cellular receptors and uncoating to release RNA into the cell.

\textsuperscript{41} This product ultimately came into Sanofi’s pipeline via Eastman Kodak.
following key points related to ViroPharma’s origin, changing product development and innovation strategies, its adaptation and subsequent revitalization and their relevance to this research are discussed in greater detail:

1. ViroPharma was formed by an independent group of experienced scientists who wanted to form their own discovery and development company. Scientists from large pharmaceutical companies and formed the basis of the company.

2. ViroPharma in-licensed drugs to support drug discovery efforts almost from its inception and then throughout its lifespan.

3. The firm made a deliberate decision to change its business orientation to ensure the survival of the firm by divesting its discovery capabilities and engaged in further in-licensing and acquisition efforts to support the development of the NRDO firm by obtaining marketed products and clinical stage products.

1. Origin of ViroPharma

ViroPharma's formation by a group of entrepreneurial scientists with corporate experience represents an interesting type of small firm in this era. The formation of the company was inextricably linked to the changes taking place in other large companies. Eastman Kodak sold off their prescription drug business to Eli Sanofi as they had scaled back on their discovery work. Consequently, the founders of ViroPharma were able to obtain equipment and recruit scientists as a result of these actions and this change in strategy. This is interesting because firm formation of this type is not well documented in the literature and although the extensive changes in the strategies of large pharmaceutical firms during this period have been discussed, the impact on the formation and development of small firms has not.

2. In-licensing to Supplement Discovery Activities

ViroPharma supplemented its discovery capabilities with the purchase of Pleconaril within a year of its formation. Pleconaril was originally discovered
by the same scientists who had since moved to ViroPharma (via Sterling Winthrop that had become part of Eastman Kodak and then Eli Sanofi) and it was these scientists that were influential in obtaining the product and bringing it to ViroPharma. Pleconaril was also an important strategic fit for ViroPharma which was formed to develop antiviral pharmaceuticals\(^{42}\) and the company believed that the addition of a clinical Phase I product to its pipeline would be financially beneficial also\(^{43}\). This was related to their valuation in terms of raising venture capital.

Pleconaril was in Phase I but what is interesting is this type of out-licensing activity from large pharmaceutical firms to small firms taking place in the mid 1990s. This type of knowledge exchange is not well documented in the literature on the related markets for technology in this sector and neither is the key role of scientists in the movement of these products between firms. Also, Eli Sanofi, (having just purchased Eastman Kodak’s prescription drugs business) was executing a product portfolio decision which meant that it did not consider Pleconaril a priority programme as it was willing to divest this product. This has implications for the markets for technology illustrating a different role played by both large and smaller firms; small firms as buyers rather than sellers of products of this type and large firms as sellers rather than buyers of this type.

3. The Transition to Becoming a No Research Development Only Company

In 2002, the FDA declared that the company had failed to show adequate safety for Pleconaril and the stock price fell dramatically (the stock price plunged from $22 a share to $.87 a share in 2002). Consequently the changes that the company had to make to its business as a result of the ‘not approvable’ decision were considerable. The firm implemented a series of new strategic decisions related to its product development effort. At this point in the company’s development, three key decisions were made: The first was to start the process of reducing and ultimately eliminating all early stage

\(^{42}\) ViroPharma’s capabilities included molecular target selection and assay development technologies to enable the development of proprietary chemical inhibitors and a specialized chemical library.

\(^{43}\) Pleconaril is active against viruses in the picornavirus family.
discovery activities and with that related capabilities in exploratory drug discovery, the second was to buy in drugs from other companies and the third was sell Pleconaril.

The company scaled back on its discovery operations and reduced their overall workforce by 70%. This move was designed to save money for the company. Overall, the belief was that it was better to try and save the company and keep it operational but with a different approach and new products. The new business model would be based on late stage clinical development and product marketing but not product generation through discovery. The expectation was that this would be the way in which the company would recover financially because they would obtain greater support from the public stock markets for this change in business model orientation away from discovery efforts. According to their head of corporate development:

‘We had to take into consideration the vagaries of the markets related to financing to keep us alive. We came to the conclusion that the market was simply not rewarding early stage research. We had to get ourselves closer to market and be perceived as a company that would likely be commercial sooner than we would otherwise have been. We changed ourselves around to be a late stage clinical development company. It’s rare that you make a plan like that and it actually works but it did for us. Today we still do not invest in discovery stage assets.’

Ultimately, this was done in response to a belief by the management team that the public stock market would support this decision (and thus the stock price would increase). The alternative was to retain discovery capabilities and with it the related expenditure and to also continue investment in Pleconaril. The company simply did not believe that continuing investment in its discovery assets would generate a suitable return in the timeframe required and wanted to free up financial resources to spend on other activities. This represents an unusual change in orientation for a firm such as this because their core capabilities and strengths are generally viewed in the
literature as lying in discovery based activities and not in later stage clinical development nor marketing.

Maribavir was purchased for $3.5 million in 2003 (prior to the sale of Pleconaril) and Vancocin was purchased for $116 million in 2004. Maribavir was in-licensed from GlaxoSmithKline and the rights to Vancocin were purchased from Eli Lilly. This deal was therefore critical for the company because it represented the opportunity to obtain a marketed product that would generate revenue. The head of corporate development remarked that this deal was important in facilitating the recovery of the company:

‘We went out and did a very complicated financing deal and were able to acquire Vancocin from Eli Lilly. And overnight, it dramatically changed our company.’

Within two years of purchasing this product, it provided significant revenue for the company. The company was obviously willing to invest substantially to buy new products which is interesting given their stock price collapse and their decision to shutter discovery operations in the name of cost cutting. It appears that this was more a decision to reallocate resources to other projects such as Vancocin. But it illustrates the conviction that this product acquisition was critical for the success of the company. Vancocin was an approved product with relatively no uncertainty. This justified the substantial investment required. However, what was also notable about this transaction was that the company was able to procure the rights\textsuperscript{44} to an already marketed product from a large pharmaceutical firm. This implies that Lilly was also making a product portfolio based decision to sell a marketed product which is somewhat surprising given that marketed products generate revenue. GlaxoSmithKline was also making similar portfolio management decisions around its products when it sold Maribavir.

\textsuperscript{44} In addition, the firm had access to manufactured product and ongoing manufacturing capabilities which was a bonus in terms of ease of production.
In November 2003, ViroPharma out-licensed Pleconaril to Schering-Plough for $10m. ViroPharma was ultimately not willing to make any further investment in the clinical development of Pleconaril and was able to convince Schering Plough to buy the rights to the product. ViroPharma ultimately made the same decisions that both Sterling, Eastman and Sanofi (see above) had made before it.

**Figure 12. Development of Pleconaril and the Role of ViroPharma**

The diagram shows the movement of Pleconaril from company to company illustrating how the development of a product can in fact be undertaken by more than one company and consequently how intricate the markets for products and knowledge can become in this sector. It also illustrates how products can represent value for some companies, but not for others and this value can and will change over time. ViroPharma made another substantial financial investment four years after the Vancocin purchase when they agreed to purchase another company for its product, Cynrize. This strategic decision to buy the company rather than the product was the preferred course of action for Lev Pharmaceuticals and ViroPharma agreed to the terms and conditions.
In February 2009, ViroPharma announced that the Phase III study for Maribavir failed to achieve its goal and development on this product has been halted. This has meant that the company no longer has any products in clinical development. ViroPharma is now concentrating its resources on its two main marketed products Cinryze and Vancocin focusing on expanding product markets abroad and conducting additional clinical trials as necessary. The reported growth and success of the company last year suggests that this business model and their particular focus on late stage development and product marketing have proved very successful for the company.

6.2.5. Summary

The case studies above illustrate a number of interesting issues associated with the NRDO firms. ProStrakan and ViroPharma illustrate the dominance of exploitation over exploration in terms of financial resource allocation. Both firms indicated that they discontinued exploratory discovery activities in favour of more certain outcomes from exploitation based activities. The formation of PanGenetics also illustrates the preference of financiers for the exploitation focused model while the Actinium story illustrates that this model was considered sustainable by its investors despite the lack of success. These case studies also provide compelling evidence for the changes in markets for technology and the role of surplus unexploited knowledge in their formation and development.

6.3. Discovery and Development Firms

6.3.1. Actelion

Actelion was founded as a discovery\(^45\) and development firm in December of 1997 by a group of scientists that had been working together at F. Hoffman La Roche (Roche). Soon after its formation, Actelion in-licensed Tezosentan from Roche which had been discovered by one of the Actelion founders. A

\(^{45}\) The discovery focus is the design, synthesis and optimization of small molecular weight drug-like molecules
successful IPO took place in April of 2000 and various co-promotion agreements strengthened the financial position of the company. The company continued to in-license products which it believed complemented its pipeline. It also spun out a company, Axovan, for the development of some products which was then re-acquired in 2003. The company remains a discovery and development firm and it has 3 marketed products as well as a range of products in various stages of discovery and clinical development. The following key points are discussed in relation to this case study:

1. Actelion was formed as a DD firm by a group of ex Roche scientists but in-licensed a Roche product within months of its inception.

2. Actelion has also continued to in-license products despite having a strong in-house research capability.

3. Actelion spun out a company for which a Roche product was in-licensed to supplement the spin out's pipeline.

1. **Formation of Actelion – The Role of Roche**

The founders of Actelion were committed to forming their own organization and dissatisfaction with various decisions related to product development that had been made at Roche appears to have been a key factor in the genesis of the new company. The new company was specifically formed to be a DD firm as the new management team believed that discovery activities were critical to their success. About five months after its formation, Actelion acquired Tezosentan from Roche who had made a decision not to pursue the development of this product. Roche was unfamiliar with the nature of the product in question and this was one of the key factors which influenced the decision by Roche not to continue development of the product:

‘If you have a new mechanism of action you are dealing with a lot of Intellectual uncertainty which is a key factor: If you have a lot of this, you have disagreement. Nobody can make a decision. You need not take ‘no’ from so called management. Make a proposal - that is what we did. We had already decided at the time that we wanted to create our own company.’
The acquisition of the Roche product by a small company like Actelion is unusual and provides interesting evidence of the changes in the markets for technology, in terms of the role of small DD firms and large firms. The acquisition of the product (they in-licensed it) was contingent on both the personal relationships with Roche management and the experience of the Actelion management team. Actelion convinced Roche management that they could successfully develop the product. The founders felt that because of their working history together and their combined network of contacts they could make the new company successful,

'We got Tezosentan based on the fact that Roche thought that we were the best group to bring Tezosentan forward (it was discovered by Martine Clozel, a founding member of Actelion). Ultimately it is a people business. It's knowing people and having the credibility with people. Obviously having inside knowledge and information with knowing the right people at Roche was important for this. This was not a normal in-license.'

The sale of the product by Roche to Actelion is unusual and represents an interesting mode of product development for large pharmaceutical companies also as well as a change in the markets for technology. Roche was putting the development of their product into the hands of another company as they did not want to pursue the development of these products. Again, this flow of products and knowledge from a large company to a small company is unusual in this sector.

2. Further In-licensing to Support Product Development and Innovation

The company has a mixture of products in discovery, pre-clinical and clinical development as well as marketed products. Its product development history is an illustration of an eclectic mix of strategies. These include in-house generated products in addition to in-licensed products, collaborative research programmes with other companies, acquisition of companies and products as well as out-licensing of products and a corporate spin out of its own. However, in-licensing has always been an important part of the company’s strategy and was also instrumental in the company obtaining venture capital
in its early stages. As noted earlier, Roche’s decision to discontinue development of two of its products played a key role in the development of Actelion. Actelion went on to successfully develop one of these products and later out-licensed the other thus profiting from Roche’s decision not to invest in the development of these products. In 2002, Zavesca (Gaucher’s disease) was in-licensed from Oxford GlycoSciences. Actelion’s next in-licensing deal in 2008 was with Nippon Shinyaku for Selexipag, for pulmonary arterial hypertension; the same indication as its lead marketed drug, Tracleer (Bosentan). This deal was important for the company because this drug was a potential competitor. The extent of the in-licensing activity is unusual for firms of this type (small DD firms) and not well discussed in the literature but it is especially interesting because in-licensing products is not typical for firms that have in-house discovery capabilities like Actelion.

Actelion has also engaged in a company acquisition to acquire a product which it believed was important for its product portfolio. Ventavis was acquired in 2006 through the acquisition of its license holder US company CoTherix. The acquisition was necessary as in-licensing was not an option (the product was the sole asset of CoTherix). Again, this type of activity is interesting to observe in smaller DD companies particularly for products that have already reached the marketing stage. It is interesting that the company was able to develop products in-house to reach the marketing approval stage and provides evidence that these small companies have competencies in areas such as clinical development and regulatory affairs; not something that is usually associated with these types of DD firms. The current literature focuses on these companies as upstream providers of knowledge and generally not market focused entities. The ability of these small firms to successfully develop and market products is not widely acknowledged.

46 A deal that was a result of networking and according to Dr. Fischli ‘...a golf course product’.
47 This product was for the same indication as Actelion’s main product and represented an important strategic marketing acquisition for Actelion because of its focus on the Pulmonary Arterial Hypertension market.
3. Alternative Product Development Strategy – Corporate Spin outs (Axovan)

In 2000, a group of Actelion scientists wanted to leave the firm and set up their own firm. Axovan was set up in 2000 and was formed by Actelion scientists with support from Actelion. The company was set up as a spin out of Actelion. In setting up the firm, Actelion had all the rights to those compounds put into the company. The creation of Axovan was viewed as a necessity in order to maintain important relationships with scientists who had expressed an interest in leaving the company,

‘How do you respond to the innovative push of a group of scientists within Actelion? If we don’t do anything, we will probably lose these people. Instead of losing them we created Axovan and supported it very much, letting these people work on relatively unknown targets. We licensed in Clazozenthan from Roche (reasons not disclosed) then when the deal to buy Axovan was done everyone benefitted.’

Axovan was later acquired in 2003 because they had successfully developed one of their core products to Phase II and Actelion wanted to ensure full ownership of that product48. This also suggests greater complexity in the markets for technology as the movement of products between Roche, Axovan and Actelion could be thus illustrated:

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48 This was an Endothelium Receptor Agonist product - an area in which Actelion was a leader.
This is an interesting example of how product development (and control over intellectual and human capital) can be managed – through the corporate spin out. In this instance, a new firm was formed to ensure that a core group of scientific personnel and their associated knowledge was not lost. The corporate structure of the spin out was constructed so that Actelion maintained exclusive rights to the products discovered. The role of corporate spin outs and the development of drugs is notable in the development of Actelion and it is remarkable how the company itself spun out a new organisation, 6 years later. Actelion’s development of the Roche products illustrates the changing markets for technology but the corporate spin out Axovan, illustrates the division of labour.

6.3.2. Cara Therapeutics

Cara Therapeutics (Cara) is a private company formed in 2004 by a group of scientists\(^49\) that had worked together at Arena. Cara was initially based on a

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\(^{49}\) These same individuals were among the founders of Arena Pharmaceuticals Inc, in San Diego which they left to form Cara.
molecule that was obtained from another company (Ferring Pharmaceuticals) but this was followed by the acquisition of discovery technology. The first lead product, the same product that was acquired from Ferring was out-licensed to Alza (a J&J subsidiary) in Phase I/IIa of its development within the first two years of the company’s formation. After out-licensing this product, the company then developed a compound internally which it has successfully developed in Phase II (announced in May of last year). Cara recently obtained a new injection of VC finance (July 2010). Cara is another interesting case study because of its formation, based on a product from another large pharmaceutical company and also because within the space of two years the company had effectively out-licensed this core product to a different company. This company’s approach to financing and its experiences with financing also illustrate alternative perceptions associated with the role of VC finance and how this may impact discovery activities at the firm. These key points are discussed as follows:

1. Cara was formed based on a molecule from another larger company but discovery technology was acquired after this initial product acquisition.

2. Cara’s management team made deliberate decisions on how to mitigate the control of Venture Capital in their company.

3. Cara has experienced negative perceptions of its some of its board members related to discovery activities perceived as a burden by some of these directors.

1. Formation of Cara – Ferring Pharmaceuticals and Finance

The company’s first (lead) product was obtained in a transaction with Ferring Pharmaceuticals; a company that the CEO had worked with at his last company. The founding members of Cara saw an opportunity to acquire a product through their relationship with Ferring Pharmaceuticals. This product was ready for Phase I clinical trials and this meant that Cara did not have to engage in any additional, research stage activities. Ferring was prepared to
give them the molecule as part of an equity transaction (whereby they didn’t have to pay for the product).

‘Ferring Pharmaceuticals put in the first molecule. They wanted a stake in a biotech company… We took in a molecule that had been developed all the way up to Phase I, in other words it was ready for Phase I. That was a cashless transaction for equity.’

Cara was founded on a molecule that was obtained from another company. Generally, this exchange of products/knowledge has been described as taking place in the other direction i.e. from small classical biotechnology companies to large pharmaceutical companies. The evidence presented here again illustrates that this is not necessarily a uni-directional flow of products and knowledge. What is also interesting is that the originating company (Ferring) chose this particular mode of product development. Rather than develop this product in-house, they opted to exchange all of the related IP in an equity transaction whereby they acquired ownership of a percentage of shares in Cara. This illustrates the changing markets for technology once again and the different type of origin (corporate spin out). This is very interesting as the roles of the ‘licensor’ firms such as Ferring Pharmaceuticals have not been widely acknowledged in the literature. Ferring traded their product for equity in a new company and believed that they would obtain greater benefit from the product by investing it in a new company rather than investing in the product themselves. It would appear that Ferring considered this trade-off as one that best served their interests. Implicit in this transaction is the fact that Ferring believed that Cara was capable of being able to deliver something back to Ferring to make it worth their while to exchange the molecule for equity in the company. This type of transaction represents a new type of relationship in terms of both the flow of knowledge in this sector as well as the fact that large companies may choose to have another company develop their product.

The intellectual property (IP) (drug compound) that was obtained from Ferring was critical to adding value to Cara from the start and the presence of the compound immediately added value to the firm.
‘We started the company with that IP; we took over the whole IP scheme. That was important in that most of the valuation was related to the value of the compound that we obtained. If I didn’t have that, I probably couldn’t have raised any money.’

Ferring’s role in providing the first molecule was important. The trade-off for Ferring was that they got their stake in a new and upcoming biotechnology firm. This transaction was also viewed favourably by the board.

‘The directors who don’t like the idea of enabling technology really like the idea that we ‘fished’ a molecule out of another company in a cashless sense and that someone else spent all the money on the research. So that’s the ideal model and you see more and more companies being funded along those lines.’

This indicates the importance of a molecule that was already primed for clinical development. From a financial perspective, this was very important for valuation and investment. Investors in the new company were willing to provide funding based on the acquisition of the drug from Ferring.

The product obtained from Ferring was entered into phase I clinical development in the first year of Cara’s formation. Results were obtained from the Phase I trial of the product, CR665\(^50\), in early 2005, a year after the company was formed. CR 665 was then out-licensed at the beginning of 2006. Cara entered into a worldwide licensing agreement with Alza Corporation, a Johnson & Johnson company and an unspecified sum was received in funding resulting from this transaction for CR 665. The following diagram depicts the product development path and illustrates the more complicated markets for technology:

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\(^{50}\) A pain drug candidate.
2. Financing the firm - Maintenance of Control and Venture Capital (VC) Fundraising at Cara

In its start-up phase, the Cara management team funded the company without VC money\(^\text{51}\). This funding scenario using the founders’ own money was a conscious decision,

‘It was deliberate. That was important for me from a control stand point. It was a question of making sure we could institute the business plan we started the company on without too much influence from VCs initially.’

Cara believed VC finance meant greater dilution of ownership and thus control and therefore this company made deliberate decisions on how to mitigate VC control within their company and the structure of the firm’s finances was the key way in which to do this. As the company chose not to initially finance with VC this indicates a couple of potential issues with respect to the prolific role of venture capital, particularly in this sector. The first is that VC as a funding mechanism might not necessarily be the most

\(^{51}\) The Ferring transaction was cashless. The company acquired shares in Cara in return for the molecule.
favoured type of capital. The second is that it would appear that VC conditional attachments are seen as a barrier to some firms as these conditions can prohibit the company owners’ decision making abilities with respect to their products and development decisions. There are conditions attached to VC funding that act as a disincentive for some companies and this example shows that it can influence how they structure their company’s finances in terms of limiting VC involvement and influence. This is interesting because this example shows how small companies view the disadvantages of VC and what they can do to mitigate these issues which was to look for other ways to finance initially.

3. Protecting Discovery Activities

The preference of some board members for obtaining clinical stage products from external companies was evident at Cara. The benefits from this type of in-licensing are believed to be based on the fact that another company has already financed the research stage of the product’s development. This means that these exploratory research activities don’t have to be financed internally making the product more attractive to investors in the licensee firm. Cara continues to pursue its discovery based activities but receives mixed support from its board on their discovery programme and as a result, has to defend the existence of these types of programmes;

‘We do have a technology that I brought in deliberately for finding drugs in a new area. It fits nicely strategically. There are some directors on the board that love it. There are some directors that hate it and that’s a running battle. …We’re spending money on basic research and discoveries and not spending money on clinical trials. …We’re trying to cloak the technology in with clinical development to fund it. It’s a minimal amount of what we spend but they want to see their money go as far as it possibly can.’

The firm remains committed to the discovery programme:

‘It’s worth having discovery because development does cost so much. The ‘Fee for service’ model does not have enough of a return. The margins are usually too small.’
This suggests that there is pressure on firms in this sector not to pursue discovery related activities. Overall it would appear that the company may struggle to continue to embed discovery related activities into their business due to resistance from board members on the value of such activities. This is where issues of control become critical for the company and the role of VC board members can result in an ‘anti research’ stance that may be translated into influential pressure to get rid of these types of activities. This suggests that certain types of financial influence may well be acting as a barrier to exploration based activities and potentially acting as a negative influence on the sector as a whole.

6.3.3. Pharming

The company was originally formed as Genfarm, a Dutch academic spin out founded in 1988 formed to commercialise recombinant DNA technology, utilised to create transgenic animals. It became public in 1998 and after the IPO, the company entered into a new phase of its development moving towards becoming more integrated and embarking on clinical development. Four years later, the company acquired another firm, DNage, in an effort to put renewed focus on earlier stage activities and to diversify its business. However, the ‘sale’ of DNage was recently announced, four years after its acquisition, on the basis that the company’s finances have to be prioritised in favour of its commercialisation activities. This 22 year old company represents an interesting story of how the classical biotechnology business model is adapted in order for firms to survive and illustrates how financial pressures and changing financial fortunes can impact the firm’s product development and innovation strategy.

The following key points are discussed in relation to how and why the firm changed its business model and the role of finance in these changes:

1. Pharming adapted its business model to become both a discovery and development focused company, post IPO and it has re-orientated its

52 Formed by Professor Herman De Boer
business model three times between 2002-2010 alternating between its identity as a research and development focused company and that of a development and commercialisation focused company.

2. The most recent decision to divest DNAge has meant that the firm is focusing all of its efforts on becoming an exploitation oriented firm in the face of pending marketing authorisation of one of its products.

1. Changing Firm Orientation

This company was formed as a new technology based research firm (GenFarm) in the classical biotechnology business model when the Rijks Universiteit of Leiden was given a subsidy from the government to research the production of proteins by transgenic cattle\(^{53}\). In 1995, a decision was made to restructure the firm once again\(^{54}\) and create a new separate company, Pharming, (the Dutch subsidiary). Ten years after the company was formed the new organisation conducted a successful IPO in 1998. Although the funds received from the IPO made the pursuit of clinical trials possible, the financial viability of the company was eventually destabilized. Clinical development activities were proving very costly and the firm was forced to make significant changes to its business model during 2001 and 2002 due to the escalating costs of its operations.

This restructuring began in 2001 and prompted the complete out-licensing of the lead product, Human Alpha Glucosidase\(^{55}\), to Genzyme in 2001. The number of research products in clinical development proved to be too much for the company and they eventually had to make major restructuring changes in a big effort to recoup operating losses and move forward in a bid to become a financially viable enterprise. The company had been running at

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\(^{53}\) The Pharming scientists were/are able to breed animals that produce human-like proteins in their milk that were essentially used for enzyme replacement treatments.

\(^{54}\) Financial needs forced the company to seek changes to its business a year after it was founded as there was no venture capital market in The Netherlands. Once the restructuring took place, (two companies were formed, a US holding company GenPharm International, GPI and a Dutch subsidiary GenPharm BV.

\(^{55}\) In 1998, the same year as the company’s IPO, they entered into a collaboration with Genzyme for the first human trials of their lead product, alpha-glucosidase (HAG), (produced in the milk of rabbits) a protein used in the treatment of a rare disease (Pompe’s disease).
a significant loss since its IPO in 1998 and its revenues were not enough to cover the various costs of operations including subsidiaries in various locations (Finland, Belgium).

The company decided to scale down on its operations significantly. It refocused its efforts onto three of its remaining projects and made significant cuts to staff and operations. The company labelled its new focus as the ‘Product Focused Business Model’ and this suggests that the firm was orienting itself towards the NRDO business model. Most of the projects that were de-prioritised were early stage projects. This was in direct response to financial pressure and clearly illustrates the impact of finance on the firm’s product development strategy, particularly their early stage assets. The new ‘product focused business model’ (NRDO) meant that the allocation of resources was not prioritised towards any exploratory/discovery stage projects. It illustrates that the balance of exploration and exploitation will change in favour of exploitation particularly when scarce financial resources have to be allocated among projects.

Interestingly, once these changes had been made, 2 years later the company started obtaining a series of financial injections through additional stock offerings suggesting that the financial markets were rewarding the decisions made by the company. Between 2004 and 2006, the company raised over €53 million representing significant injections of capital that coincided with a series of product and technology transactions as well as clinical development milestones. The most notable change during this period was the acquisition of DNAge, a research focused firm. DNage was founded as an academic spin out in 2004. Its early stage research capabilities provided Pharming with a more diverse portfolio of products in terms of therapeutic area and application. It also helped to shift the balance of exploration and exploitation back in favour of exploration. However, the acquisition of DNAge was seriously challenged by employees and caused substantial problems within the company. Most unusually, employee shareholders sued on the grounds that this was an unnecessary and poor decision for the company. This was based on its expenditure on the
transaction which was not well received given that the firm had managed to turn around its financial situation by becoming more ‘product focused’ and thus oriented towards exploitation activities that would benefit the firm in a more timely fashion. Acquiring DNAge was seen as an immense setback for the firm.

2. Becoming a Development Focused Company

In May of 2010, four years after it acquired DNAge, Pharming recently announced that it would ‘reduce its financial interest in this wholly owned subsidiary.’ In other words, it would no longer be the sole financial support to the company. The pending marketing authorization for their lead product Rhucin is a very important factor in this decision. Rhucin is the company’s oldest internally generated product for the treatment of Hereditary Angio Edema (HAE). The company’s regulatory filing for Rhucin was rejected in 2007 and the company has spent the last 3 years working on resubmitting the regulatory package. The company has invested in various activities to ensure its regulatory approval:

‘We have to make this a priority. In a way, it’s like growing up. We are now a commercially focused company. You can’t fund everything.’

Pharming has indicated that it will refocus its business on the commercialization of this product in particular:

‘We have spent 22 years in research and now we have the opportunity to market our own product, we have to ensure that our resources are aligned to this goal. The work that had to be done on the regulatory package was substantial and expensive but we knew we had to get there.’

In contrast, DNAge projects are reaching the point where they require significant additional investments to fund clinical trials but Pharming management believes that they are no longer in a financial position to support the range of both early stage activities and pending clinical stage activities being undertaken by their DNAge subsidiary.
DNage will require new sources of funding who will bear the risks while Pharming takes a financial step back. The funding required for the marketing of Rhucin will consume a great deal of resources but ultimately the company believes that this will lead to profitability and so early stage work and clinical programmes simply have to be put aside in favour of the product marketing finance needs. In the 12 years since its IPO, the company has yet to make a profit but it believes that this is now possible with the marketing of Rhucin\(^{56}\). The decision to allocate funding away from DNage is inevitable and necessary, according to the management team as the company’s new focus has to be on the appropriate support of commercialization activities. For this company, this has meant that early stage research funding is cut in favour of the later stage marketed product as financial resources are allocated in favour of these commercial activities. Once again, this illustrates how the balance of exploration and exploitation will shift towards exploitation when firms face scarce financial resources.

### 6.3.4. Pharmacopeia

Pharmacopeia was initially part of a larger company formed in 1994\(^{57}\). The company was spun out in 2002/3 when the parent company split. Pharmacopeia was spun out as a public company. Initially this was a discovery stage company dedicated to identifying compounds for larger companies. It conducted fee for service discovery activities but it moved into clinical development with the acquisition of clinical stage products which were in-licensed from a large pharmaceutical company, three years after the firm was spun out. The chief scientific officer championed an in-licensing deal with Bristol Myers Squibb which put the company into the clinical development sphere and substantially changed the range of activities. However, the number of products that required investment in clinical trials prompted the company to reduce its discovery capabilities (50%) in 2008.

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\(^{56}\) Rhucin was approved late last year.

\(^{57}\) The company’s discovery capabilities include ECLiPS® Technology which was licensed exclusively from Columbia University and Cold Spring Harbor Laboratory in 1993. ECLiPS® enabled the company to generate hundreds of thousands of small molecule compounds at a fraction of the cost of traditional chemical synthesis methods enabling the build-up of a library of over 500,000 small molecule compounds.
because of financial pressures. Then towards the end of 2008, they agreed to be bought out by Ligand Pharmaceuticals.

The development of Pharmacopeia into a clinical stage firm is interesting because two critical changes took place for the company based on this change in business model and these are discussed in detail below:

1. The orientation of the firm changed to incorporate clinical development but this was contingent on the in-licensing of two key products from a large pharmaceutical company and also contingent on the prior knowledge of these compounds by senior personnel at the company.

2. The changing focus of the firm to include clinical development activities ultimately placed a large financial burden on the firm and forced the firm to reduce its early stage discovery activities by 50%.

1. **Becoming a Clinical Development Stage Firm – The Decision to in-License**

Collaborative working with large pharmaceutical companies in discovery based activities was the cornerstone of the company’s strategy for the first 2-3 years of its life. However, in March 2006, the company entered into an exclusive licensing agreement with BMS and obtained the rights to two compounds discovered by BMS (including one product which was put into phase I trials in early 2007). This transaction did not involve any payment by Pharmacopeia to BMS; Pharmacopeia agreed to provide a set of compound libraries as well as milestone payments upon the achievement of successive clinical and regulatory events in the United States and certain other jurisdictions, and royalties on sales of products. This type of transaction would appear to be unusual for a company of this type that was so strong on discovery activities.

However, there were several reasons why Pharmacopeia in-licensed two products. Pharmacopeia was a publicly funded company and having a clinical stage product meant that its chances of obtaining further financing through additional stock offerings would be greatly increased in addition to future revenue from the sale of the products. The company recognized that
speeding up its development timetable by in-licensing products would be rewarded by the public stock markets in terms of increasing its share price. It needed to do this because none of its products were close to the clinical development milestone. The head of research noted that:

‘You go from being a discovery company and being 3 or 4 years from phase I, to all of a sudden you’re in phase I and it’s in phase I and it’s been vetted, and could be in phase II in another year and then the company drops into a place where Wall street can recognise that value. 3% royalty is not a great business\(^{58}\). You don’t get rich, at least not quickly.’

This meant that the company would move faster towards a point where the products would hopefully provide a better financial return either through out-licensing or successful marketing authorization and sale. The in-licensing strategy was intended to supplement the company’s own pipeline and illustrates the importance of this activity to a company which was a discovery stage company.

However, the decision to in-license these products was not straightforward and there were extensive discussions at the company in terms of whether or not this transaction should take place. The head of research answered that there was a lot of persuasion needed:

‘Yes it took a lot; an awful lot and I’m not sure that everyone is still persuaded. Before these two compounds the company had never done anything in development. The furthest we had gone was to hand off in lead optimization.’

The hesitation in terms of the decision to in-license appears more to do with concern over the company’s capabilities in conducting clinical trials rather than any belief that the company should be self-sufficient in terms of generating in-house products. The company were used to doing fee for

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\(^{58}\) They indicated that the business of providing compounds to other firms in early stages was not optimal in terms of revenue generation.
service discovery activities and consequently, clinical development wasn’t necessarily something that many felt comfortable doing. In addition, the business of in-licensing was no easy task:

‘Most of the time if you go out and you look for packages, most of it is garbage. The good news is that 90% of it you can look at and see where it’s flawed. The real challenges are that the ones that are the 10% and you can still pick one that is flawed but you won’t figure out what’s wrong with it until you spend your money. There is almost nothing good out there. You don’t know what you’re buying.’

However, there was another aspect to the deal with BMS that played an integral part in Pharmacopeia’s decision to in-license these products. The company’s new executive Vice President (VP) of Research and Chief Scientific Officer was the head of Worldwide Chemistry at BMS and been in charge for 20 years and as a result he was familiar with the products in question:

‘He knew that they had certain assets on the shelves (BMS) and so he was able to bring those into Pharmacopeia pretty cheaply. So David brought in these things, he was the key influence because he had the information and he knew that these assets were there and he was able to lobby and win the day.’

It would appear that this prior knowledge of the new VP and his experience with these products was also a key factor in the decision to in-license and suggests that this was integral to the entire transaction. It was noted that the process of in-licensing any products from external sources is a difficult one because of lack of knowledge about the product but the discussion above illustrates that despite this prior knowledge, the company was still reluctant to embark on this transaction because of its lack of capabilities in clinical development.

This connection between its senior executive and the newly in-licensed products was key for the firm and enabled the transaction to take place.
However, without the decision by BMS to sell the products, there would have been no transaction. BMS had shut down its endocrine and bone division and consequently there were products that would not be developed in-house any longer. BMS had made a strategic decision to discontinue development of any products related to endocrine and bone therapeutic areas and therefore any programmes related to these products was shut down. This created an opportunity for other companies to obtain these products. As the head of research noted,

‘It’s sitting on the shelf so anything we give them for it is good. We could get it for a pittance…’

Pharmacopeia was able to negotiate terms that it was satisfied with and obtain two products in the clinical development phase directly resulting from another company’s prioritization and portfolio initiatives once again illustrating the changes in markets for technology.

2. Financial Pressures – Changing Business Model Focus and the Reduction of Discovery Capabilities

In early 2008, the firm determined that the cost of its clinical development programmes was having a serious impact on its financial circumstances. By 2008, there were two programmes in clinical development with another programme pending clinical development and not enough available financial resources to fund these programmes. As a result, a decision was made to lay-off 50% of personnel and reduce spending on discovery during that year. In this case, Pharmacopeia had to make a choice between investment in its discovery stage assets or in its later stage clinical assets. Given that the firm is more likely to recoup costs from sales of a marketed product or out-licensing, the choice was made to invest their limited financial resources in clinical development stage assets. As Pharmacopeia was a publicly listed company, its board and shareholders had input into this decision and therefore influenced the outcome which was to reduce investment in early stage research. Given that the firm was so strong in its discovery capabilities, this decision was surprising but it illustrates the influence of financial resources in terms of forcing firms to make decisions related to their product
development goals. It also illustrates once again that the balance of exploration and exploitation will shift in favour of exploitation particularly when financial resources have to be prioritised. Pharmacopeia was sold in late 2008 to Ligand Pharmaceuticals.

6.3.5. Summary

The case studies on the DD firms illustrate a number of interesting issues that challenge the current understanding of how firms in this sector operate: they provide evidence for a the role of finance in the changing balance of exploration and exploitation in the firm, the role of finance in these decisions, the role of a surplus of unexploited knowledge in the development of these firms and the increasing complexity of markets for technology. Three out of the four firms in-licensed products to bolster pipelines for financial reasons and despite in-house capabilities for drug discovery. Two of the four firms have sustained their discovery operations while the two other firms have announced plans to cut their exploratory operations illustrating that the balance between exploration and exploitation within some of these firms has shifted towards exploitation.

6.4. Conclusion

Chapter three outlined four key areas for research related to the following: The changing division of labour, the role of finance in the changing division of labour, the role of a surplus of unexploited knowledge in the changing division of labour and how the markets for technology have changed. The case studies were undertaken to learn more about these four key areas and how they impact upon each other and the essence of that interrelatedness. A selection of DD and NRDO firms were chosen because the trade literature suggested that changes were also taking place within traditional DD firms and that a new type of firm was evident, the NRDO firm. Chapter six provided evidence for the NRDO firm and outlined some key points with respect to the origins of these firms and the nature of these firms. Chapter six also provided supporting data related to key changes in DD firms.
These case studies have provided empirical evidence that changes to firms are indeed visible and that the role of finance and a surplus of unexploited knowledge play a key role in these changes to firms and the sector as a whole. The evidence indicates that financial pressures have caused firms to seek a different mode of operation, the NRDO firm and caused the DD firm to in-license clinical stage drugs. The evidence also indicates that this is related to a surplus of unexploited knowledge which is being traded by large and small firms. Details of product development indicate a deeper complexity in markets for technology as products are traded between two or more firms for development. None of these issues have been discussed to any great extent in the literature on the sector but this does reflect the literature on Distributed Innovation Processes and Open Innovation. The following chapter will analyse these findings in greater detail to complete the up to date picture of the sector.
Chapter 7. Understanding and Explaining the New Division of Labour and Changes in Markets for Technology

7.1. Introduction

Chapter two discussed the nature of the pharmaceutical sector and illustrated the roles of the two major types of firm in this industry: that played by the small, classical biotechnology firm and that of the large, fully integrated firm. The complementary roles played by these two types of firms illustrate the current understanding of the division of labour and the markets for technology in this sector. The rate of adoption of the new biotechnologies by large firms varied but their relationships with the smaller, new 'classical biotechnology firms' (operating in the industry as harbingers of new technologies, tools and processes) were prolific. Chapter two also reviewed studies that analysed adaptation of firms, in particular, the small classical biotechnology firms. It discussed the heterogeneity of firms within the overarching classical biotechnology firm business model indicating that changes to firms was an important part of the sector landscape. The primary aim of this research was to examine a potentially new division of labour with respect to the small classical biotechnology firm and to understand what were some of the major influences on that changing division of labour and the related changing markets for technology.

The research design reflected the need to analyse the division of labour from a quantitative and qualitative perspective to be able to achieve the goals of ascertaining the extent of the division of labour, understanding the division of labour and understanding changes in the markets for technology. The research results from both types of analysis have been presented in Chapters five and six together with the initial responses to the findings. Evidence for the existence of the No Research Development Only (NRDO) firms is presented in Chapter 5 together with evidence of changes to the Discovery and Development (DD) firms and related changes to markets for technology. Case study evidence in Chapter 6 provided explanations for the reasons behind the formation and development of these NRDO firms, changes to existing DD firms and changes in the markets for technology.
purpose of this chapter is to now examine these changes in detail and explore the reasons why these changes in the division of labour have taken place and the major influences that are visible from the evidence presented. This chapter will also examine the changes in the markets for technology and discuss why these changes have taken place and their relationship to the division of labour. A discussion on the implications for the sector is also presented.

This chapter is divided into a further seven sections. Section 7.2 provides an overview of the main findings in relation to the changing division of labour. Section 7.3 discusses all evidence from the case studies and the database to illustrate the financial influences of capital markets on the changing division of labour. Section 7.4 discusses changes to DD firms specifically. Section 7.5 discusses the availability of ‘surplus’ unexploited knowledge in the sector - the results of large scale exploration activities as a key factor that has influenced the changing division of labour and markets for technology but this section also discusses how this is closely aligned with the influence of capital markets (Venture Capital and Public Stock Markets). Section 0 discusses changes in the markets for technology and how they are related to the changing division of labour in the industry and also examines the relationship between capital markets and the surplus of unexploited knowledge with markets for technology. Section 7.7 reviews the implications of all of these changes particularly on the changing balance of exploration and exploitation within the section. This section also reviews changing core competencies and capabilities within the firm that have resulted from the changes in the sector. The final section, 7.8 concludes the discussion and analysis.

7.2. **The Changing Division of Labour in the Pharmaceutical Sector**

The trade literature discussed the emergence of a new type of exploitation focused NRDO firm in addition to changes to existing firms also undertaking more exploitation focused activities (not evident in the academic literature). This research set out to ascertain the existence of this new type of firm and
therefore a new division of labour in the sector. A quantitative analysis of the sector was undertaken and a random sample of drug development firms was compiled. The firms were analysed based on their activities, their pipeline and their technological platforms. The drug development continuum (see Figure 1515) was utilised to facilitate the appropriate identification of exploration and exploitation activities (as discussed in Chapter 4) and to divide the sample into two distinct cohorts: firms that were only focused on exploitation activities (NRDO firms) and firms that were focused on exploration and exploitation activities (DD firms). The results showed that 27% of firms in the sample were NRDO firms.

This NRDO firm represented a new type of firm within a new division of labour precisely because of its focus on exploitation activities. The findings from the quantitative analysis showed that over 33% of the NRDO firms also had marketed products. This is in contrast to its peer, the discovery and development (DD) firm that has activities in both exploration and exploitation (predominantly) activities. Only 4% of DD companies in the quantitative sample had marketed products. Many small classical biotechnology firms in this sector were formed to commercialise new developments in the fields related to biotechnology and informatics. This was the essence of the division of labour that initially took place in the third epoch. New small classical biotechnology firms concentrated on new exploratory knowledge and technologies and formed extensive relationships with large incumbent firms in order to transfer this knowledge. Their contribution to the development of these new technologies and this exploratory research was critical to the wider dissemination of this new knowledge.
Figure 15. The Changing Division of Labour in the Pharmaceutical Sector – NRDO and DD firms
However, the role of these exploratory focused firms was contingent on their relationships with large firms in the sector who predominantly provided exploitation based activities and knowledge, their complementary strength. This was the basis for a symbiotic relationship and the resulting division of labour whereby the new small classical biotechnology firms focused on the exploratory activities on the drug development continuum related to target identification, target selection, lead identification, lead selection and incumbent firms focused on the exploitation focused pre-clinical and phase I-III clinical trials. However, the situation has now changed with a new type of firm and a new division of labour. The new NRDO firms now concentrate on the exploitation activities, previously the bastion of the large incumbent firms. The questions that now must be tackled are as set out in Chapter 4: What has influenced this changing division of labour? Why has this change occurred? How has this impacted the markets for technology?

7.3. The Role of Finance in the Changing Division of Labour

The NRDO has been characterised as a firm that concentrates its activities on the development and/or marketing of drugs. The new division of labour is recognised because these firms do not engage in exploratory research as previously understood. Having established the existence and also the prevalence of the NRDO firm, it was necessary to understand why they were formed in this way and what influenced their formation. Questions related to the role of finance in emergence and growth of these firms is a central concern of this research and both the database and case study approaches were utilised to understand the role of finance in the division of labour and changes to existing firms. The findings from the quantitative analysis illustrated a key difference between DD and NRDO firms in terms of their financial status: 56% of NRDO firms were publicly listed firms while only 39% of DD firms were publicly listed. The findings also indicated that NRDO firms earned considerably less revenue from licenses than DD firms (37% - NRDO firms and 61.5% of DD firms) and as expected, almost no revenue from research. This section looks at how the origins and development of the NRDO firm has been impacted by financial considerations and sources of finance:
7.3.1. NRDO Firm Origin – The Role of Finance

Understanding the origins of these firms and what they were set up to do makes it possible to understand more about why the division of labour has occurred. The case studies produced some interesting findings but most importantly they illustrated the heterogeneity of the origins of these NRDO firms. However, there were some important commonalities related to the role of finance and its influence on the formation and development of the NRDO firm (or in the case of ViroPharma, its orientation towards the NRDO business model). Table 1212 examines this interaction of finance with the formation/adaptation of the firms.

Table 12. Summary of NRDO Firms and the Role of Finance

<table>
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<tr>
<th>NRDO Firm</th>
<th>Funding Type</th>
<th>Origin</th>
<th>The role of finance</th>
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<tbody>
<tr>
<td>Actinium</td>
<td>PRIVATELY FUNDED</td>
<td>Organon spun-out Actinium specifically to develop the Radioisotopes rather than develop the idea in-house. Organon funded the activities of the company for 7 years.</td>
<td>Organon was the sole funder for 7 years.</td>
</tr>
<tr>
<td>Formed in 1993</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PanGenetics</td>
<td>PRIVATELY FUNDED</td>
<td>Index Ventures restarted ‘PanGenetics’ but specifically as an NRDO firm in contrast to its prior DD orientation.</td>
<td>A VC firm, Index Ventures was the primary driving force behind the creation of the business model for the newly reinvigorated ‘PanGenetics’ known as the ‘asset centric’ no research development only firm.</td>
</tr>
<tr>
<td>Re-Formed in 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProStrakan</td>
<td>PUBLIC – STOCK MARKET</td>
<td>ProStrakan was set up as a ‘Generic’ company formed by the ex Shire CEO. No Products were spun out into the firm. It was not set up to research and explore the creation of new biologic or NCE</td>
<td>The ability to be self sufficient financially was a key goal and influenced the way in which this firm was founded. The manufacturing and sale of generic products as quickly</td>
</tr>
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</table>
Actinium’s formation was based solely around the development of a product that had already been discovered and no further research activities were deemed necessary within the firm for the generation of new products. In this respect, the source of funding (the parent company Organon) was the most influential factor in the genesis of this business model. This represented a corporate spin out firm. This is the only example of a NRDO corporate spin out where the firm was actually formed by another company based on one of their products.

The evidence suggests that the role of Venture Capital (VC) in the case of PanGenetics is a particularly interesting example of the influence of VC in terms of the formation of the NRDO business model. As discussed in the case study, Index Ventures made an important strategic choice to invest in more NRDO firms because they believed that this model was more efficient and less costly than the traditional ‘technology’ centric firm that engaged in exploratory research. Index’ stance was that investment in ‘technology’ based firms did not produce an acceptable rate of return. This reflects a change in the balance of their portfolio of firms. Historically, the role of VCs as supporters of exploratory technology oriented firms has been acknowledged but this suggests that firms such as Index are making changes to the types of firms in their portfolio to balance the risk-return ratio. ProStrakan’s founding team also did not believe that discovery activities were part of their vision for a self sustaining financial business model and

<table>
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<th>NRDO Firm</th>
<th>Funding Type</th>
<th>Origin</th>
<th>The role of finance</th>
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<tbody>
<tr>
<td>ViroPharma</td>
<td>PUBLIC – STOCK MARKET</td>
<td>Scientists from other large firms came together and formed ViroPharma to discover and develop products. No products were spun out into the firm at the outset.</td>
<td>However the firm adapted to become an NRDO based on financial pressures to allocate resources toward development and marketing activities for financial stability.</td>
</tr>
</tbody>
</table>
chose not to have these activities as part of their business. They chose to focus on generic and development stage oriented business model as a way to become financially self sufficient.

However, ViroPharma’s story of becoming a NRDO firm is in contrast to the others as it was formed as a DD firm. This firm adapted its business model to become a NRDO firm. It is an important example because it illustrates another way in which the role of finance provides an explanation for why the firm is currently a NRDO organisation. In the case of ViroPharma’s transition to becoming a NRDO firm the key issue was the regulatory failure of their lead product which caused the stock price to plummet and the value of the company to decline rapidly. ViroPharma indicated that they ceased discovery operations and chose to focus financial resources on later stage in-licensed products (including one marketed product) because it made more financial sense to prioritise its remaining financial resources towards development activities. ViroPharma was formed with the expectation that it would discover and develop products, however, it had to change that focus and adapted to become a NRDO firm because financial pressure on the company meant a need to focus on later stage products for revenue generation. As a public company, they believed that the stock market would be more inclined to support exploitation activities and so the decision was made to shut down discovery and exploration in favour of development and exploitation.

The findings certainly confirm the heterogeneity in the way in which these firms were formed but some common themes can be further explored. Undoubtedly, three out of the four firms examined were formed specifically with an exploitation focus that was to develop products rather than discover them using ‘academic’ science. The reasons why they were formed in this way are apparent for two of the firms: PanGenetics and ProStrakan. The case of ViroPharma also illustrates the preference for the NRDO business model based on financial constraints, similar to that of ProStrakan prior to its divestiture of Skelia. The evidence from these firms strongly suggests that financial considerations were a key influence and that the NRDO model was a financially desirable way in which to organise a company.
The ViroPharma case study also supports earlier research that exploitation activities will drive out exploration activities (Levinthal and March, 1993). However, this research adds more to this particular body of work and provides support for the notion that firms can survive and grow and prosper despite the absence of exploratory activities. This is in contrast to the commonly received wisdom that firms who can’t maintain this balance will not survive. However, the longer term sustainability of this model remains to be seen and as discussed in the Section 7.5, is dependent on the availability of drug candidates for sale from other firms.

7.3.2. NRDO Firm Development and the Role of Finance

The evidence from the case studies also suggests that finance plays an important part in the continuing development of the firm and the decisions that are made around external product acquisition, development and innovation. The following table summarises the findings from the NRDO case studies:

Table 13. The Impact of Finance on NRDO Firms

<table>
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<tr>
<th>NRDO Firm</th>
<th>Development and the role of finance</th>
<th>Development and the role of finance</th>
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<tr>
<td>PanGenetics</td>
<td>Venture Capital financing imposed strict conditions for in-licensing that impacted the firm’s innovation strategy. The view taken by the VCs of in-licensing and its critical role in the firm is interesting.</td>
<td>The firm has indicated that it will cease operations now that it has sold its primary asset. It also indicated that the plan was always to set up a ‘transitory’ organisation that would not be expected to remain in business for a lengthy period of time.</td>
</tr>
<tr>
<td>ProStrakan</td>
<td>The company merged with a discovery company (ProSkelia) based on VC recommendations to add discovery capabilities to its business model prior to the IPO.</td>
<td>Ultimately, Proskelia was divested in order to fund investment in commercialisation resource needs and so discovery capabilities were no longer part of the company’s business model once again.</td>
</tr>
<tr>
<td>ViroPharma</td>
<td>Within a year of its formation, ViroPharma</td>
<td>The firm made a deliberate decision to change its business</td>
</tr>
<tr>
<td>NRDO Firm</td>
<td>Development and the role of finance</td>
<td>Development and the role of finance</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td></td>
<td>in-licensed to financially support drug discovery efforts and improve its valuation.</td>
<td>orientation to ensure the survival of the firm based on scarce financial resources and a perception that stock markets would be more supportive in terms of this business model.</td>
</tr>
</tbody>
</table>

**Actinium**

New private equity financing supported the continuation of the business model and product development for a further 10 years despite no proven or published clinical success in marked contrast to commonly received wisdom of the role generally played by financiers as well as the time commitments.

There is evidence from all firms to suggest that the role of finance (in terms of the influence of specific sources of finance as well as financial considerations) was an integral part of all decisions made with respect to their product development and innovation strategies. While this is not necessarily a new revelation, the extent of that involvement and influence in terms of the balance of exploration and exploitation in a firm is significant. It has implications for the ability of a firm to manage product development and innovation and adds to the knowledge of the role of finance and how it impacts firms specifically.

For PanGenetics, their VC financing dictated that the had to in-license another product despite the existence of several products in house. The provision of new finance was contingent on their acquisition of an external product. This suggests that in-licensing was deemed critical by their financiers for the continuing success of the firm. For ViroPharma, acquisition of products was deemed critical for financial survival and this was related to the perception that the stock market would support this rather than the continuation of discovery and exploration. ProStrakan too had to choose
between allocating financial resources to research or later stage clinical development and marketed products. Interestingly, the case of ProStrakan provides contrasting evidence to that of PanGenetics in that the source of finance (VC) was an important determinant of the firm also becoming a DD firm, albeit, for a short while. Prior to embarking on its IPO, ProStrakan’s VC investors advised that they thought the IPO would be more successful (and therefore the capital markets more receptive to the IPO) if there were discovery capabilities in the firm and thus the firm merged with ProSkelia who were a discovery firm. This is in contrast to the role of Index Ventures who at around the same point in time believed that research based activities would not create value for the firm.

However, as discussed, the discovery assets of the new ProStrakan firm were spun out only two years later. The decision was made based on financial resource constraints. ProStrakan’s story is remarkable in that it changed its orientation from NRDO to DD and then back to NRDO. It also shows that different VC firms attach different value to the role of research in the firm and consequently it is difficult to ascertain an overall picture for the role of VC with respect to the NRDO based on these examples. Nevertheless, it does suggest that some VC firms are willing to back a firm that is not founded on cutting edge technology but rather on the promise of successful product development. The view taken by Index Ventures to specifically invest in NRDO companies reflects a decision to allocate more financial resources towards NRDO firms rather than solely towards DD firms with exploratory capabilities. The influence of public stock market funding in the re-orientation of ViroPharma towards an NRDO focused business model was that the company believed that the markets would not support their continuation unless they made serious changes to their business. ViroPharma and ProStrakan indicated that in order to fund the development and marketing of their products they felt that they had to discontinue their investments in their discovery activities as the funding would not stretch to both. But these decisions are less about the influence of specific types of finance and more about the value that the firm attaches to its exploratory and exploitation related activities.
Another curious aspect to the NRDO story is that of the role of a Private Equity firm in the development of Actinium (General Atlantic assumed the role of primary financier once Organon had made a decision to cease being the sole funder of the firm). This Private Equity firm continued to finance Actinium for almost 10 years despite any visible clinical success of the product. The example illustrates that the unwavering financial support was integral to the survival of the company and its ability to continue down its NRDO path.

The role of finance in the development of these firms could be summed up as follows:

Table 14. Summary of Impact of Finance on NRDO Firms

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>PanGenetics</td>
<td>-</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>ProStrakan</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>ViroPharma</td>
<td>✅</td>
<td>✅</td>
<td>-</td>
</tr>
<tr>
<td>Actinium</td>
<td>-</td>
<td>-</td>
<td>✅</td>
</tr>
</tbody>
</table>

Financial considerations are of paramount importance to firms particularly when it comes down to a matter of survival and the choices that have to be made with respect to exploration and exploitation. In three out of four of the cases presented, the firms believed that their success and survival was contingent on an exploitation focused business model. This evidence provides support for the prior findings related to the balance of exploration and exploitation in firms as past research has shown that exploitation will

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59 Private equity is defined as any investment made in a firm that does not involve the issuance of any public offering of stock in a firm and is an overall term used to include all forms of private equity investment such as venture capital and business angels. Not all private equity investments are venture capital.

60 General Atlantic defines itself as a ‘leading global growth investor’ that engages in a variety of investments not limited to venture capital investments.
dominate over exploration (Levinthal and March, 1993). This appears to be the case for these NRDO firms and is particularly well illustrated by the examples of ViroPharma and ProStrakan who found themselves having to discontinue their exploratory operations in favour of funding exploitation for survival.

7.3.3. Summary
The evidence presented and discussed has indicated a number of important findings with respect to the role of finance and capital markets in the changing division of labour. The primary change in the division of labour is the focus on exploitation activities by the NRDO firm. It is important to emphasise what these specific activities mean from a financial perspective in order to understand why finance plays an important role in this division of labour. These exploitation activities are focused on the testing of a drug candidate in animals and in humans. A drug candidate at this stage has already gone through a lengthy process of identification, characterisation and formulation and thus the investment related to these activities is both substantial and for the NRDO firm, has been made by someone else. Thus their risk is reduced and from a financial investment point of view this is critical and represents both a cost saving and a risk reduction. This was why Index chose to configure PanGenetics as a NRDO firm and why ProStrakan also chose to focus on both the NRDO and generics model. The findings illustrate that firms will allocate financial resources in favour of later stage clinical development activities over exploratory activities because these activities bring the firm closer to the market, quicker and this reduces risk. This also explains why firms will invest in external products: to reduce risk and exposure by investing in products that have reached a particular point in their development. The final observation is on the importance of the direct influence of investors such as VC and Private Equity firms. The criticality of the role of Index in the decision to form PanGenetics as an NRDO firm is notable. While the role of VC firms has always been understood to be influential, this particular example illustrates a central role in the firm’s direction technological orientation.
7.4. Understanding and Explaining Changes to the Discovery and Development (DD) Firm

7.4.1. In-licensing

The evidence from the discovery and development (DD) case study firms presented in chapter 6 illustrates some interesting findings in relation to changes to the firm. The most notable of these is related to the extent to which these firms acquire external products for development. The quantitative analysis indicated that over 56% of DD firms acquired products externally for development with the firm. This raised significant questions about the activities of the DD firms which were explored through case studies. The pertinent findings from the case study analysis have been summarised in the table below:

**Table 15. Summary of Impact of Finance on DD Firms**

<table>
<thead>
<tr>
<th>DD Firms</th>
<th>Origin</th>
<th>Development and the role of finance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actelion</td>
<td>Actelion was formed by Roche scientists as a DD company. They later in-licensed products from Roche.</td>
<td>Actelion has continued to in-license products, despite having a strong in-house research capability, for revenue and valuation purposes</td>
</tr>
<tr>
<td>Cara</td>
<td>Cara was formed by Arena scientists as a DD company but the company was based on a drug from Ferring Pharmaceuticals.</td>
<td>Cara was able to successfully develop their externally acquired product internally and sell it on to another company.</td>
</tr>
<tr>
<td>Pharming</td>
<td>Formed as an academic spin out from University of Leiden</td>
<td>Pharming has since re-orientated its business model three times between 2002 and 2010 alternating between its identity as a research and development focused company and that of a development and commercialization focused company. Pharming has announced its divestment of a significant part of its research organisation to redirect</td>
</tr>
</tbody>
</table>
Table 15. Summary of Impact of Finance on DD Firms

<table>
<thead>
<tr>
<th>DD Firms</th>
<th>Origin</th>
<th>Development and the role of finance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacopeia</td>
<td>Formed as an academic spin out</td>
<td>The in-licensing of two key products from a large pharmaceutical company brought the company further along the drug development continuum faster and the expectation was that this would bring the company greater revenue, quicker. The changing focus of the firm to include clinical development activities placed a large financial burden on the firm and ultimately forced the firm to reduce its early stage discovery activities by 50%. However, the firm was later taken over.</td>
</tr>
</tbody>
</table>

It is very interesting to observe the way in which two of these DD firms were formed. Cara, while formed as a DD firm, was based on a product from Ferring. It was not an academic spin out firm. It acquired its discovery technology and assets once the Ferring drug was acquired. This would appear to be more in line with the NRDO firm formation but in contrast, the company acquired exploratory discovery based assets believing that these were a necessary part of its operations. However, changes in the markets for technology are evident because Ferring conducted the exploratory work on the drug prior to selling it to Cara who then worked on the exploitation and development of that drug. These are also related to changes in the division of labour and a surplus of unexploited knowledge. The role of finance in this transaction is also notable because Cara’s management indicated that the acquisition of the Ferring drug greatly improved their valuation. This is an interesting example of a Corporate Spin Out (CSO) firm and illustrates the heterogeneity in the origins of firms in this sector which is also evident in the
other case study firm Actelion. While Actelion was not founded specifically with a product from Roche, it did acquire a product from the company and was formed by company scientists but not as a direct CSO, again representing a different mode of CSO formation. These types of origins of firms have not been discussed in the literature and represent an updated picture of how firms are formed in the industry.

The story of Actelion is also similar to that of Cara whereby the company was formed by a group of scientists that had left another company. Actelion also built up discovery capabilities and then in-licensed a product from Roche within a year of its formation. These examples provide evidence for distinct changes in the markets for technology with respect to their acquisition of technology (products) from large firms. There is also further evidence in support of key changes in the markets for technology and the surplus of unexploited knowledge provided by the example of Pharmacopeia. This firm acquired products from a large firm specifically to enhance its clinical development stage pipeline and therefore positively impact its financial valuation.

Acquisition of external products for DD firms also appears to be a critical part of the DD firm product development strategy, not something that is currently acknowledged in the literature on small firms in this industry. This is especially interesting given that over 56% of firms in the sample acquired products externally. Three of these case study firms out of four acknowledged that in-licensing products was integral to improving the financial prospects of their firms. Firms indicated that the presence of later stage clinical products brought them closer to market in one or both of two ways: closer to regulatory approval and thus revenue generation through product marketing or closer to sale of the product to another firm and thus revenue generation. Thus the role of finance as a key influence on this decision to acquire products from external sources for development must be acknowledged. This suggests that financial pressures even for DD firms are influencing product development decisions in a significant way. The
corresponding implications for the markets for technology are dealt with in Section 0.

7.4.2. Changing DD Firm Orientation – Financial Considerations

Two of the DD firms interviewed were in the process of making changes to the orientation of their business model and they indicated that their investment in discovery activities was being reduced considerably. In essence, these firms were beginning to orient themselves towards the NRDO model. The need to ensure continued financing from the Public Stock Market was closely related to the firms’ decisions to reduce their discovery based activities and focus instead on commercialisation related activities.

- Pharmacopeia, a publicly funded firm, was forced to reduce discovery activities by 50% because of funding issues and shareholder pressure to allocate resources away from discovery and towards development.
- The case of Pharming, another publicly funded DD company, also illustrated how competing resource pressures meant that their discovery assets (DNage) were spun out in favour of funding their commercial activities.

Firms explained that their decisions to focus more resources on development stage products rather than earlier stage products were a matter of resource prioritisation (cited by both ViroPharma and ProStrakan in the same situation). Pharmacopeia and Pharming both indicated that they faced financial resource constraints and were moving towards allocation of finance to commercialisation activities (exploitation) rather than research (exploration). Costs of marketing products and scale up of required activities were provided as the key pressures. The reasons why some of these firms are redirecting resources towards clinical and market development and thus reorienting towards the NRDO model are clearly related to issues of finance. Once again, these examples clearly illustrate the domination of exploitation over exploration particularly when it comes to decisions related to investment of financial resources. The table below summarises the impact of finance on the DD firms:
Table 16. The Impact of Finance on DD Firms

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Actelion</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Cara</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Pharming</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacopeia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

There are key similarities between the cases of Pharming, Pharmacopeia, ViroPharma and ProStrakan. The findings suggest resources have to be allocated in the firm between earlier stage discovery and later stage development, regulatory and marketing activities but resources will be predominantly allocated towards those activities that firms believe will produce the most financially advantageous result in the quickest time. Firms in this sample believed that exploitation related activities will produce more financially advantageous results as this involves products that are closer to milestones that are associated with product sale, market launch and revenue overall. All four firms cited above are publicly funded companies. This suggests that the pressures resulting from this form of finance may influence firms and their orientation towards the NRDO business model, especially when they have products that are ready for approval and marketing. Publicly funded firms are subject to the perceptions/wishes/vagaries of a range of shareholders that want to see dividends and will therefore likely support actions that result in greater dividends. ViroPharma is a prime example of how negative perceptions of shareholders based on performance can almost financially ruin a company when their share price fell from $23 to $.83. ProStrakan also saw their share price halve recently because of negative publicity related to clinical development milestones. Publicly traded companies face serious financial pressures as result of the relationship between stock price and information that comes from the company’s operations. Pressure to deliver significant dividends in a timely fashion exists
and if this means cuts to spending on other areas, such as earlier stage research, then clearly, some firms will take this course of action. The evidence suggests that publicly funded firms are more likely to take this course of action.

7.4.3. Summary

The evidence from DD firms suggests that overall the role of finance has played a key role in changes to these firms and suggests that there are also changes occurring in the markets for technology which are significant. Out of four DD firms, three (Actelion, Cara, Pharmacopeia) in-licensed products to enhance financial prospects by obtaining products in a more advanced stage of development. Two out of the four case study firms have indicated that they have reduced exploratory operations in favour of exploitation related development operations primarily because of the need to prioritise financial resources in favour of these activities (Pharming and Pharmacopeia). Two different types of firm (NRDO and DD) provide compelling evidence for the role of finance in their decisions to allocate more resources to exploitation rather than exploration activities and also provide evidence for changes in markets for technology and a surplus of unexploited knowledge, discussed further in Sections 7.5 and 7.6.

7.5. Surplus of Unexploited Knowledge and the Changing Division of Labour

The evidence presented so far has pointed out the role of finance in the changing division of labour but it has also illustrated the importance of externally sourced products for firms. This implies that there is a given ‘surplus of unexploited knowledge’ in the form of potential drug compounds that are for sale because firms have not developed these products themselves. These compounds have passed through the lead optimisation stage of development and have been traded in either the pre-clinical, phase I or in the case of ViroPharma, the marketing stage. Therefore the availability of products at this later stage of development (ready for human clinical trials) also emerges as a part of the explanation for the new division of labour. Again, the evidence so far shows that firms are willing to trade these
products because they have chosen not to develop them internally. This section presents the evidence for the surplus of unexploited knowledge and discusses the reasons why this surplus has emerged and why firms are willing to trade this unexploited surplus knowledge.

7.5.1. Large and Small Firms – Surplus Unexploited Knowledge and the Role of Finance

The database that was created for the purpose of ascertaining the existence of the NRDO firm also facilitated the collection of other important data in relation to the activities of both NRDO firms and DD firms. This data pointed to some interesting findings in terms of the origins of firm products and suggested that further examination of these findings in relation to the origins of these products be undertaken. The evidence indicated that large and small firms now have a range of roles to play in the changing markets for technology and in the division of labour. But why firms are playing these various roles can also be understood to a large extent by reviewing why they have spun out products. The large sample of firms illustrated that 56% of firms were obtaining products from other firms for development in-house. Case studies have revealed that all eight firms obtained products from other firms, both large firms and small, in contrast to what has been written about the activities of both in this industry.

The table below summarises those firms that have spun out products in relation to the firms presented in the research case studies and the main reasons why (when available) large and small firms have spun out products. The table is in date order.

Table 17. Trade In Products Between All Case Study Firms

<table>
<thead>
<tr>
<th>Product Originator Firm</th>
<th>When</th>
<th>What</th>
<th>Why?</th>
<th>Receiver Firm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organon</td>
<td>1993</td>
<td>Radio isotopes</td>
<td>Development in a different organisation</td>
<td>Actinium Pharmaceuticals</td>
</tr>
<tr>
<td>Eastman Kodak</td>
<td>1994</td>
<td>Pleconaril</td>
<td>Portfolio Management</td>
<td>Eli Sanofi</td>
</tr>
<tr>
<td>Product Originator Firm</td>
<td>When</td>
<td>What</td>
<td>Why?</td>
<td>Receiver Firm</td>
</tr>
<tr>
<td>------------------------</td>
<td>------</td>
<td>------------</td>
<td>-------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Eli Sanofi</td>
<td>1995</td>
<td>Pleconaril</td>
<td>Portfolio Management</td>
<td>ViroPharma</td>
</tr>
<tr>
<td>Roche</td>
<td>1997</td>
<td>Tezosentan</td>
<td>Portfolio Management ‘New knowledge’ difficulties</td>
<td>Actelion</td>
</tr>
<tr>
<td>Strathmann AG</td>
<td>1999</td>
<td>Adcal D3</td>
<td>N/A</td>
<td>ProStrakan</td>
</tr>
<tr>
<td>ValPharma /Galen</td>
<td>2001</td>
<td>Isotard</td>
<td>N/A</td>
<td>ProStrakan</td>
</tr>
<tr>
<td>Oxford GlycoSciences</td>
<td>2002</td>
<td>Zavesca</td>
<td>Financial difficulties</td>
<td>Actelion</td>
</tr>
<tr>
<td>PDL</td>
<td>2003</td>
<td>MAb</td>
<td>Financial Difficulties</td>
<td>Actinium Pharmaceuticals</td>
</tr>
<tr>
<td>Roche</td>
<td>2003</td>
<td>Bosentan</td>
<td>Portfolio Management ‘New knowledge’ difficulties</td>
<td>Actelion</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>2003</td>
<td>Maribavir</td>
<td>Portfolio Management</td>
<td>ViroPharma</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>2003</td>
<td>Vancocin</td>
<td>Portfolio Management</td>
<td>ViroPharma</td>
</tr>
<tr>
<td>Ferring Pharmaceuticals</td>
<td>2004</td>
<td>Pain (CR665)</td>
<td>Development in a different organisation</td>
<td>Cara</td>
</tr>
<tr>
<td>Cellgry</td>
<td>2004</td>
<td>Rectogesic Tostran</td>
<td>N/A</td>
<td>ProStrakan</td>
</tr>
<tr>
<td>Orexo</td>
<td>2005</td>
<td>Rapinyl</td>
<td>Financial Gain and complementary assets (marketing)</td>
<td>ProStrakan</td>
</tr>
<tr>
<td>Schering Plough</td>
<td>2005</td>
<td>MAbs</td>
<td>Portfolio Management</td>
<td>PanGenetics</td>
</tr>
<tr>
<td>LayLine</td>
<td>2006</td>
<td>PG110</td>
<td>Financial Difficulties</td>
<td>PanGenetics</td>
</tr>
<tr>
<td>BMS</td>
<td>2006</td>
<td>Hypertensin e</td>
<td>Portfolio Management</td>
<td>Pharmacopeia</td>
</tr>
<tr>
<td>CoTherix</td>
<td>2006</td>
<td>Ventavis</td>
<td>N/A</td>
<td>Actelion</td>
</tr>
</tbody>
</table>
Table 17. Trade In Products Between All Case Study Firms

<table>
<thead>
<tr>
<th>Product Originator Firm</th>
<th>When</th>
<th>What</th>
<th>Why?</th>
<th>Receiver Firm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lev Pharma</td>
<td>2008</td>
<td>Cinryze</td>
<td>Financial Difficulties</td>
<td>ViroPharma</td>
</tr>
</tbody>
</table>

In total, 18 companies spun out products consisting of nine large and nine small firms.

7.5.2. Explaining the Surplus of Unexploited Knowledge - Diversity of Knowledge

As the evidence above has shown, large and small firms have been trading in products that they have generated internally but chose to sell or trade. Again, these are products that are drug candidates that have passed through the discovery and lead optimization phase into the pre-clinical and phase I in many cases. In total, 18 companies spun out products consisting of nine large and nine small firms. The prolific changes in the knowledge base of the pharmaceutical sector have been discussed in chapter two to explain the division of labour that occurred during the third epoch but there are further implications arising from this that must be revisited here because of their relevance for the arguments presented. The increasing diversity of the scientific landscape has resulted from multiple discoveries in molecular biology, cell biology and biophysics and in addition, medicinal chemistry remains an integral part of the scientific landscape (Pisano, 2006). This is significant because the changes in the biotechnology knowledge bases of this industry and in the chemistry knowledge bases mean that there has been an increase in the amount of knowledge that has been generated but not exploited via internal development by those firms that have generated that knowledge. These changes have impacted the range and indeed the number of potential drugs as well as the corresponding number of potential targets.

A number of important and interlinking developments in biology, chemistry, process technologies and informatics essentially resulted in the development of industrialised high-throughput screening (HTS) platforms, combinatorial
chemistry and improvements in bio-based assays. These were all critical developments (Nightingale, 2000). Together, these enabled generation and rapid screening of extensive chemical libraries against a greater number of new targets created by significant advancements in genomics (Hopkins et al, 2007). The new developments also created a significant focus on quantity over quality (Hopkins et al, 2006; Pisano, 2006). As a result, a larger number of potential clinically active compounds have been identified. This is reflected in changes in the total number of patents granted in the US61 over the period 1978–2002 (these are patents for therapeutically active compounds). This can be used as an indicator of the number of compounds considered ‘attractive enough to warrant patent protection, but not necessarily viable enough to enter development’ (Hopkins et al, 2006). During this period, the number of patents rose from less than 2,500 in 1978 to over 20,000 in 2003 representing an 800% increase in the number of patented compounds, however, the most significant increase has taken place over the last 10 years.

While the new knowledge has created a greater number of potential drugs and greater knowledge of drug targets, it has potentially created a dilemma for large companies in particular. Faced with the ever increasing vast array of new knowledge (the most recent of which has resulted from discoveries related to genomics and proteomics) and coupled with increasing financial costs of drug development, companies have had to make decisions with respect to those products they retain and develop internally versus those products they don’t. References to an increasingly narrow range of therapeutic area focus on the part of large companies (Hopkins et al, 2006) are supported by some of the findings of this research that indicate that some larger companies have indeed been closing down research in some therapeutic areas (Bristol Myers Squibb was shuttering its bone and endocrine divisions when Pharmacopeia obtained their drugs from the company). Ultimately this array of new knowledge and products has led to

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61 This was in patent classes 424 and 514 for potentially therapeutically active compounds
difficult decision making in relation to product portfolios and overall company strategy. The following section 7.5.3 illustrates just how this surplus of knowledge has resulted overall, creating opportunities for new companies and indeed opportunities for existing companies.

7.5.3. Explaining the Surplus of Unexploited Knowledge – Financial Considerations

Interviews with executives from case study companies revealed important insights into the reasons behind why firms are selling drug candidates to other firms. These findings were then substantiated with another interview with a representative\(^\text{62}\) from a large firm, GlaxoSmithKline (GSK). The interviewee was in the business development group and a discussion was initiated to review the firm’s actions in relation to portfolio management, out-licensing, and corporate spin outs. Several interesting findings emerged from the interview related to these three areas. With respect to portfolio management the firm noted that the lack of adequate financial resources prevented investment in everything that was developed and as a result, prioritisation decisions had to be made. Strategic decisions were made at a corporate level to prioritise therapy areas and therefore make cuts by closing sites and shuttering entire therapy areas. This resulted in products that were selected for out-licensing in a specific bid to generate additional revenue for the firm as these products were ‘lying around.’ In therapy areas where the company had exited, scientific personnel were encouraged to take drug candidates and set up spin-out firms (funded with external financing) while retaining an equity share in these new firms.

The findings from the case studies and this interview indicate that the role of portfolio management is a key factor which is in turn driven by financial considerations related to resource allocation and risk. Portfolio management is a process whereby firms must evaluate and select which new products to develop and then prioritise the sequence in which to develop them. The ‘portfolio’ must ‘maximise the expected economic returns at an acceptable

\(^{62}\) B. Carr. Director, Drug Discovery Transactions, GlaxoSmithKline
level of risk for a given level of resources in a new product development pipeline’ (Blau et al, 2004). Large firms have for some time practised ‘portfolio management’ whereby they are constantly reviewing their complete range of products in their various stages of development to make informed decisions on what products they should develop, continue to develop or discontinue.

The complexity inherent in drug development is an issue common to every therapeutic area. However, the nature of disease and epidemiology means that each therapeutic area (e.g. cardiovascular, cancer, central nervous system) has biological and chemical complexities that mean that knowledge of the mechanisms of cells and tissues within one therapeutic area may not necessarily mean that the same knowledge can be applied to the development of drugs for another area. In many cases, the economies of scope are particularly limited. Some of the firms connected with these case study firms have reduced the number of therapeutic areas in which they are active and it is possible that this explanation is relevant. For example, Bristol Myers Squibb sold their hypertensive product to Pharmacopeia as they were shutting down their Endocrine therapeutic area to reduce their breadth of therapeutic areas. Eastman Kodak also sold part of their key drug business to Sterling Winthrop in the 1990s in a bid to decrease their areas of focus. Most recently, GlaxoSmithKline indicated earlier this year that it would reduce its work on depression and pain which has subsequently resulted in the creation of a number of spin-outs63.

7.5.3.1. Portfolio Management - Development Costs and Revenue Maximisation

The literature on large firms in this industry has described how firms during the second epoch of the development of this industry were able to generate huge libraries of compounds (drugs) for potential screening. In addition, those firms that internalised capabilities in biotechnologies to aid in the search for new products were also able to generate large numbers of

63 Based on information from an interview with B. Carr at GSK in September 2010.
potential products. Large firms in this industry have traditionally worked in a range of therapeutic areas and produced a range of products and as a result of the combination of these factors, the discovery efforts of large firms have resulted in a prolific number of drug candidates (Nightingale, 2000; Walsh, 2004). However, only a limited number of these products can be selected for development because of the need to manage an entire portfolio of existing marketed, development stage and discovery stage assets. The portfolio is limited by the extent of both capital and human resources available to develop the products but particularly the availability of resources to pay for the development and or marketing of products within the entire portfolio. Increased financial pressure on large companies due to patent expirations and reduced revenues from products, for example, has potentially made large companies more sensitive to costs of development. As a result, products in various stages of development, including those that may just be ready for Phase I, are discontinued in light of the entire portfolio. This has resulted in firms having products ‘sitting on shelves’ as evidenced by the table above.

These firms realised that there was an opportunity to extract value from these products financially and this was also noted as a particular reason for the actions of GSK in out-licensing their products. By allowing other firms to obtain these de-prioritised assets (through a variety of transaction types) and develop them, large firms can still obtain value from these products but without risk to themselves. The pressing revenue needs as discussed throughout Chapter two, three and six, have forced large firms to look for more ways from which to extract revenue from products to fund existing research and development activities. This was also linked to the growing financial pressures on large companies resulting from drugs coming off patent. The prioritisation of some products over others can be offset by the ability to trade these products left ‘on the shelf’ and obtain revenue from them.

64 Glaxo is expected to lose patent protections on drugs such as diabetes drug Avandia, osteoporosis treatment Bonviva, and cancer drug Hycamtin that all generated 2008 sales of $2 billion
This is essentially another form of product development through the reduction of risk but maximising revenue potential at the same time and this has been discussed in the context of markets for technology, distributed innovation processes and open innovation. The fact that large firms in this sector are also engaging in trade of drug candidates is somewhat surprising because of the extensive literature that has concentrated on the way small firms sell technology and not large firms. The extent to which it appears to be an activity pursued by many firms in this industry was a surprise especially given that the movement of products was always been characterised as a one way exchange from small to large firms. However, the activity should not be entirely surprising given the current level of attention and discussion related to open innovation, distributed innovation processes and markets for technology tackled in greater detail in the following section (Coombs and Metcalfe, 2000; Arora et al, 2001; Chesbrough, 2003). The growing output from the research activities from large firms has potentially influenced the growth of in-licensing by small firms and the growth of the NRDO firm and thus the division of labour and markets for technology. In turn, the role of both the availability of this surplus knowledge for sale and financial considerations subsequently represent an important element of both the division of labour and changing markets for technology in this sector.

7.5.4. Summary

The findings of this research have indicated that a new division of labour is evident but a key element of this division of labour is the role of a surplus of unexploited knowledge in the form of clinical stage drug candidates. Firms developed capabilities (high throughput screening and combinatorial chemistry) to generate a substantial number of products for development but face resource pressures related to costs of development which means that not all products can be developed fully in-house. These ‘intermediate’ products are being sold by large companies to small companies as part of portfolio management decisions and by small companies who can no longer afford to develop them. Large companies are maximising value from products that they would not have otherwise developed and this provides support for the need for growing markets for technology to ensure efficient
use of products that would not otherwise be developed by firms (Arora et al, 2001). Financial considerations are a key part of the decision by both large and small firms to sell intermediate products. These new trading patterns represent changes in the markets for technology to which the focus now turns.

7.6. Changes in the Markets for Technology in the Pharmaceutical Sector

The pharmaceutical sector has been characterised by a sharp rise in the number and type of arrangements for trading and exchanging technology/knowledge during the third epoch of this industry (Powell, 1996; Arora and Gambardella, 2001; McKelvey and Orsenigo, 2001; Hagedoorn, 2002). These markets for technology\(^{65}\) have been a key characterisation of this industry but historically, this characterisation has described particular roles played by large and small firms in these markets for technology (also noted in Chapter two). Small firms have been consistently described as providers of technology while large firms have been described as receivers of technology (Galambos and Sturchio, 1996; 1998; Henderson et al, 1999; McKelvey and Orsenigo, 2001; Walsh, 2004; Pisano, 2006). The novelty of biotechnology created a role for small firms as transfer agents for the new knowledge from academic institutions and the applicability of this new knowledge to the pharmaceutical industry enabled them to become conduits of this new knowledge (Orsenigo, 1989; Powell, 1996; McKelvey and Orsenigo, 2001).

7.6.1. Characterising Changes in Markets for Technology

The information gathered from both the database and the case studies illustrates that there are identifiable changes in the markets for technology. 56% of DD firms are obtaining products from other firms for development and 100% of NRDO firms obtain products for development from other firms. This means that of the whole sample, 67% of firms obtained products externally.

\(^{65}\) Arora et al define technology as ‘an imprecise term for useful knowledge rooted in engineering and scientific disciplines, but also drawing from practical experience from production.’ Arora et al 2001.
for development. Trade in products in four key directions not previously discussed in the literature have been identified as follows:

1. From large firms to small firms (DD)
2. From large firms to small firms (NRDO)
3. Between small firms – DD to NRDO
4. Between small firms – NRDO to DD

This type of movement of products for development has been taking place for at least the last 15 years and as a result, this does not indicate any sudden or recent changes in behaviour as the evidence suggests that these strategies have been executed since the mid 1990s. This movement of products (drug candidates) represent a variety of transactions that have taken place between these firms including: licensing fees only, licensing with milestone payments, equity stakes with no upfront fees, and equity and upfront fees. However, these findings also represent the fact that markets for technology in this sector have invariably become more complicated than were previously acknowledged. The diagram below is an attempt to illustrate how this complexity has changed.
The complexity in the markets for technology and the division of labour can be illustrated together with four interesting examples from the case study firms. The diagram in Figure 17 maps the path of the drug candidates in terms of the number of companies that were involved in their discovery and development. These examples show the movement of products between firms and the stage at which the next firm took over development as well as the stage completed by each firm. Both NRDO and DD firms are represented in these examples where the division of labour is also evident.

Prior experience with the product and a key relationship with the ‘seller’ also emerged as another key reason for six of the case study firms obtaining products (from both large and small firms):

1. Actelion – Roche
2. Actinium – Organon
3. Cara – Ferring Pharmaceuticals
4. PanGenetics – LayLine Genomics
5. Pharmacopeia – Bristol Myers Squibb
6. Pharming – DNAge
Figure 17. Increasing Complexity in the Markets for Technology and the Division of Labour
As described in the case studies, another key part of why some of these firms wanted to obtain these products was precisely because they had knowledge of or extensive experience with the drug. Powell acknowledges that in many cases licensing is based on prior knowledge and relationships and this evidence confirms these prior findings (Powell et al, 1996). This was particularly relevant for ViroPharma and Pharmacopeia whose executives had direct experience with the products. Findings have indicated that locating good products to in-license is difficult because of lack of in-depth knowledge of the products, something particularly difficult to ascertain when trading in drug products. However, two of these firms also indicated in interviews that they had a prior relationship with the seller which also influenced their decision to acquire products. Cara and PanGenetics both noted that their decisions to obtain products were also related to their prior relationship with the seller rather than specific knowledge of the product. Conversely, however, firms were allowed to purchase these products because the seller deemed them capable of developing the products. In addition, as these products emerge from the strength and calibre of a large pharmaceutical discovery effort, they are typically better characterised\(^{66}\) and carry less risk than traditional early stage programs, which also makes them a more desirable acquisition.

### 7.6.2. Trade in Unexploited Knowledge by Large Firms

As noted previously, the historical portrayal of the movement of products and knowledge was a simplified relationship between public research institutions, small firms and large firms. This was based on the key notion that the new knowledge generated from these public institutions was then transferred to small firms who then developed it further and ultimately transferred it to large firms. The markets for intermediate technological inputs has been a key feature of the pharmaceutical sector (Arora et al, 2001) and this evidence provides continuing support for this. However, the findings from this research show that the picture is more complex particularly with respect to large firms.

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\(^{66}\) A phrase used in the industry to denote the amount of information known about the drug candidate including physiological and structural information.
The evidence shows that large firms in this sector also develop technology they don’t utilise providing support for the arguments put forth by Arora et al with respect to the need for markets for technology (Arora et al, 2001).

Large firms are increasingly under financial pressure and will also look to maximise value from products that have historically ‘sat on the shelf’. The evidence confirms licensing as a mechanism of revenue generation, particularly for large firms (Autio, 1994; Kollmer and Dowling, 2004). Large firms will generally out-license technology to firms in markets in which they don’t typically operate (Arora et al, 2001) as evidenced by cases such as GlaxoSmithKline and Bristol Myers Squibb, who out-licensed technology related to therapeutic areas in which they no longer intended to operate. But in their discussion on markets for technology, Arora et al also point out that the presence of small firms (who are usually more aggressive licensors) may induce larger potential rival firms to also license more aggressively (Arora et al, 2001). These authors point out that large firms must also become ‘effective technology licensors and compete in the market for technology’ if they are to maximise value from technology (in this case drug candidates not being developed). The extensive out-licensing behaviour by small firms in this sector has demonstrated that licensing is an effective mode of trade so the evidence from this research illustrates that this is potentially applicable for large firms also in this sector. Large firms have technology in the form of drug candidates that they are willing to trade to maximise the financial gain while reducing their risk which has been the strategy pursued by small firms.

7.6.3. Trade in Unexploited Knowledge Between Small Firms

While the literature on networks has provided extensive accounts of the relationships between small firms and between large and small firms, there has been less said on the actual markets for technology in terms of the trade of drugs candidates between small firms in this industry. The evidence from these case studies noted in Table 1717 suggests that small firms are trading products amongst themselves also indicating the importance of markets for technology between small firms as a means by which firms can maximise the value from technologies that may no longer hold value for them. A key
example noted in the PanGenetics case study was that of LayLine who sold their lead product to PanGenetics because financial difficulties meant that they were unable to develop the product internally. Actelion’s acquisition of Zavesca was for the same reasons. While the literature focuses on other positive issues such as complementary capabilities and sharing of risk, the references to financial difficulties suggest that the relationship between product development and innovation and finance warrants much closer examination. Small firms are increasingly under financial pressure to add value to their organisations and have shown that they will in-license products in order to fulfil those expectations. The rationale presented in Table 1717 also indicates that financial difficulty is cited as a key reason for why firms trade products.

7.6.4. Summary

There have been important changes in the markets for technology in this sector as evidenced by the database findings and the case studies. The evidence also reveals that relationships between firms are also a key factor in the markets for technology. Intermediate technologies - drug candidates - are being traded and developed by a number of firms and markets are no longer confined to the one way trade of products from small firms to large firms. Large firms are trading their own internally developed drug candidates (and marketed products in some cases) with small firms and small firms are trading products amongst themselves. The importance of the findings discussed above that related product sale/product acquisition to finance means that it would appear that markets for technology are inextricably linked to finance and a surplus of unexploited knowledge. The availability of products for sale is related to a need for revenue and to maximise the return on investment in a product that might not necessarily be considered for internal development by the firm. The propensity to buy products is correspondingly related to financial needs – acquisition of products means greater value is associated with the small firm. The reasons for these changes in the markets for technology are closely related to the changing division of labour also which has been partly explained by the arguments
related to the surplus of unexploited knowledge and the financial needs of companies in the present day.

7.7. **The Implications of the Research Findings**

7.7.1. **Modelling the Relationship Between the Division of Labour, Finance, Surplus of Unexploited Knowledge, and Changing Markets for Knowledge**

The evidence from the discussion and analysis of the research findings from the database and the case studies provides support for the model of these interrelationships as proposed in Chapter three. The following model was proposed in Chapter three denoting the proposed interrelationships between all of the four factors discussed:

**Figure 18. Association of all Factors – The Division of Labour – Surplus of Unexploited Knowledge – Finance – Markets for Technology**

The arrows have been positioned as multidirectional to reflect the two way relationships between each of the four factors. Each factor has an impact on the other and there is no one-way causality in effect. This model supports the
evolutionary perspective with respect to way in which industries grow and change and is supported by the findings of this research.

7.7.2. Changing Balance of Exploration and Exploitation Within the Firm

The combined case study and database evidence shows that the changing division of labour has important implications for firms. Evidence suggests that the balance of exploration and exploitation has completely changed in some firms that have become exploitation focused (27% of the database sample were NRDO firms). While in other firms, the balance has shifted with more emphasis on exploitation of resources along with the retention of exploratory activities. When allocating financial resources, the firms studied as part of this research had to make a choice between the extent to which various activities would be funded: exploratory or exploitation activities. The evidence suggests that financial pressure on firms results in the allocation of resources towards those activities that will bring it closer to market, sooner; what have been described as exploitation activities.

Firms have demonstrated that when it comes to this type of funding choice, they will reduce or even cease funding discovery (exploratory) activities in favour of funding later stage exploitation activities. ViroPharma, Pharmacopeia, Pharming and ProStrakan are all examples of firms who had to make these decisions and who chose to allocate their resources toward exploitation activities. The cost pressures on firms for product launch and marketing have been cited as the main reasons for these decisions as firms have to find ways to fund drug launch and marketing. This usually results in cutting earlier stage activities related to exploration. This may have further implications for the level of research/exploratory activity in this sector. The data indicated that 27% of firms in this sector are no longer carrying out research activities amounting to over a quarter of the firms in the sample. The implication is that this may be impacting the level of exploration in the sector overall if less firms are carrying out exploratory as well as exploitation activities. Further empirical work on this may well be warranted to understand if an overall shift is apparent in the sector. This is particularly
relevant for a sector that has been closely associated with a high proportion of exploratory research and scientific activity in firms.

These findings support earlier research work carried out by Levinthal and March that indicates that as a firm matures, exploitation of current knowledge drives out exploration of new ideas (March, 1991; Levinthal and March, 1993). However, some of the findings of this research differ from one of the fundamental parts of the Levinthal and March argument. They propose that the likelihood of firm failure is increased due to this changing balance in favour of exploitation but the findings of this research show that firms that have undergone this changing balance towards exploitation for some time, are still in business today (ViroPharma, ProStrakan). They also emphasise that this takes place in the mature firm while the firms in this sample were arguably not necessarily ‘mature’. Overall the findings from this research indicate that for some firms in this industry, the orientation towards exploitation related activities can mean success rather than failure. It also suggests that financial considerations are a major cause of this change in activity and thus the potentially declining level of exploration in the sector as a whole.

7.7.2.1. Finance and the changing balance of exploration and exploitation within the firm

The database findings indicated that over 90% of all firms had received VC funding at some point in their history suggesting that VC funding is a critical resource for firms. The findings from two of the case studies in particular provide some interesting observations related to the role of VC finance and the support for research (exploratory) activities in the firm. In Cara’s experience, the attitudes to discovery and the allocation of financial resources to those activities, meant that they felt they had to ‘cloak’ discovery because of variations in their board’s support. As noted in the case study, some board members felt that spending on discovery activities was not an efficient way to allocate funding within the firm, suggesting a decline in VC support might be apparent for exploratory activities. This was echoed in the PanGenetics case study. PanGenetics also represents another interesting example in terms of VC support for exploitation rather than
exploratory activities. PanGenetics was specifically set up by a VC company as an exploitation only (NRDO) focused company with no exploratory activities included in their business model. This was because of the view taken that investment in exploratory activities did not bring the required return on investment soon enough. It was also revealed that the VC (Index Ventures) view was that there was a more robust market for later stage assets, based on knowledge of what prospective buyers (large pharmaceutical firms) were looking for. This suggests that financiers may have a bigger role that has been acknowledged in the past in terms of how they impact the overall level of exploratory activity in the sector. In conjunction with the earlier discussion on the importance of financial considerations and financial support, this evidence also suggests that there is a considerable impact on innovation that can be related to financial control in firms.

The database findings indicate that 56% of NRDO firms are publicly listed while only 39% of DD firms are publicly listed representing a sizable difference between firms in the sector. The case studies illustrate that managing financial expectations as a public company are difficult and result in trade-offs having to be made around the allocation of scarce financial resources in the firm which has implications for exploratory activities in particular. The evidence presented in this chapter therefore suggests that publicly funded companies face financial pressures that will negatively impact the level of exploration in the firm. In four of the publicly traded case study firms – Pharmacopeia, Pharming, ProStrakan and ViroPharma, the prioritisation and allocation of resources was made towards later state ‘exploitation’ activities rather than early state exploratory/research based activities. The rationale provided by the firms in all of these cases strongly suggests that the firms had to focus resources on these activities. The need to fund activities that result in the firm being able to generate revenue as soon as possible was the most compelling argument for this allocation of finance away from exploration and research.
It is also notable that for ProStrakan and ViroPharma, this decision meant that absolutely no remaining internal resources would be allocated towards research activities. While this provides further support for the exploration/exploitation arguments proposed in the literature, this evidence adds to this debate with the more compelling finding that exploration activities can disappear completely from the firm. This has not explicitly been dealt with in the literature to date. In essence, there appears to be a demand for exploitation activities more than exploratory activities form the capital markets overall.

7.7.3. Exploration and Exploitation in the firm: Changing Capabilities and Core Competencies

The capabilities related to exploration and exploitation within the NRDO and DD firms in this sector have shifted. Capabilities and core competencies that are required by NRDO firms to execute product acquisition and development strategies for effective exploitation of products are in contrast to the capabilities required for research and early stage discovery. DD firms have had to adapt their capabilities as they have concentrated more of their resources towards development, regulatory and marketing efforts for their products. These findings (particularly as they relate to the NRDO firm) offer a marked contrast to the conventional understanding of capabilities in the small traditionally understood classical biotechnology firms operating in this sector. Rothaermel and Deeds notes that ‘biotechnology firms focus on the ‘R’ of the research and development process whereas large pharmaceutical companies focus on the ‘D’ (Rothaermel and Deeds, 2004). However, this generalisation can no longer be applied to all firms in this sector as indicated by the findings of this research related to the NRDO firm whose focus is the ‘D’ in research and development. Firms have already demonstrated that they have these capabilities that were traditionally only associated with large pharmaceutical firms.

Baden-Fuller and McNamara noted in the Celltech case study that ‘new capabilities needed to be developed to focus on new product development, rather than technical excellence’ (McNamara and Baden Fuller, 1999). In the
case of Celltech, this firm had to make ‘a fundamental switch from technological capability to a more therapeutic-based capability’ and this provided a considerable challenge for the firm (McNamara and Baden-Fuller, 1999). This study illustrated how the firm specifically needed new and different capabilities in order to change its exploration/exploitation balance and provides a valuable frame of reference for the findings of this research.

DD firms have had to augment capabilities in development, regulatory affairs and marketing in addition to their early stage research capabilities while NRDO firms have had to be built with these capabilities from the outset.

### 7.7.3.1. New and Renewed Capabilities

It is important to note that the traditional core competencies of the DD firms in particular were perceived to lie in research (Kenney, 1986; Orsenigo, 1989; Pisano, 1991; Henderson et al, 1999; McKelvey and Orsenigo, 2001). But in fact the core competencies of NRDOs and indeed some DD firms have shifted to include a concentrated focus on downstream activities as noted above. The following table illustrates the key capabilities observed within the case study firms:

**Table 18. Changing Capabilities of Firms**

<table>
<thead>
<tr>
<th>Firm</th>
<th>In-licensed / Acquired product(s)?</th>
<th>Success?</th>
<th>New Capability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinium</td>
<td>CSO – No</td>
<td>No</td>
<td>❖Clinical development</td>
</tr>
<tr>
<td>Actelion</td>
<td>Y</td>
<td>Y - Licensed to Genentech Y - Marketed</td>
<td>❖In-licensing ❖Co. acquisition ❖Clinical development – Phase I-III ❖Regulatory affairs ❖Marketing</td>
</tr>
<tr>
<td>Cara</td>
<td>Y</td>
<td>Y - Developed through Phase I, Sold to ALZA</td>
<td>❖In-licensing ❖Clinical development Phase I, II</td>
</tr>
<tr>
<td>PanGenetics</td>
<td>Y</td>
<td>Y - Sold product to Abbot</td>
<td>❖In-licensing ❖Pre-clinical development</td>
</tr>
</tbody>
</table>
Table 18. Changing Capabilities of Firms

<table>
<thead>
<tr>
<th>Firm</th>
<th>In-licensed / Acquired product(s)?</th>
<th>Success?</th>
<th>New Capability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacopeia</td>
<td>Y</td>
<td>No</td>
<td>◆Clinical development Phase I</td>
</tr>
<tr>
<td>Pharming</td>
<td>Y – Acquisition of co.</td>
<td>Y – regulatory success</td>
<td>◆In-licensing ◆Clinical development Phase I, II</td>
</tr>
<tr>
<td>ProStrakan</td>
<td>Y</td>
<td>Y - Marketed a range of products</td>
<td>◆In-licensing ◆Clinical development ◆Regulatory Affairs ◆Marketing</td>
</tr>
<tr>
<td>ViroPharma</td>
<td>Y</td>
<td>Y – Marketed two products</td>
<td>◆In-licensing ◆Clinical development ◆Regulatory Affairs ◆Marketing</td>
</tr>
</tbody>
</table>

The core competencies of the firm have arguably thus changed in the following ways:

a. New In-licensing capabilities have become critical – the ability to obtain products
b. Changing capabilities of large firms to out-license products
c. Some existing capabilities have become more important = Development capabilities have become critical – While this is not necessarily new, the focus on the importance of these activities is.

1. Ability to Obtain Products from Other Companies

The capability to attract ideas from research universities and government laboratories was cited as a key factor of growth in small firms operating in this industry (Enright, 1998; Kenney, 1986; Prevezer, 2001; Niosi, 2003) but there is evidence to suggest that there has been a shift in the nature of this capability. While it is still important, obtaining products from other firms may
create the need for a different type of capability related to in-licensing from other firms in contrast to academic sources and out-licensing which has been previously associated with small firms (Kollmer and Dowling, 2004). This implies capabilities that are necessary to complete a transaction to successfully obtain a product from another firm. This is identified as a new capability because historically, this capability was not observed but it is an integral part of the new division of labour and changing markets for technology as such is identified as a new core competency of the firm operating in this industry.

2. **Out-licensing as a Capability**

While point one above makes reference to the importance of being able to acquire products, this capability focuses on the opposite end of this transaction which is the capability of firms to ‘sell’ products. As noted in the interview data collected on GlaxoSmithKline and in the case of PanGenetics and Schering Plough, the ability of firms to transact on the sale of their product also reflects a particular set of capabilities required to be able to divest a product successfully to another firm. Both firms noted serious issues with this process (PanGenetics and GlaxoSmithKline). Nevertheless, this capability has been identified as distinct and necessary for firms if they are to obtain value from products they wish to sell\(^{67}\). Arora and Gambardella noted that problems of appropriation may hinder the division of innovative labour and this certainly warrants greater consideration in the present.

3. **Ability to develop products**

Evidence from the case studies suggests that some of these firms were able to execute better product development strategies than other large and small firms implying that these firms had superior capabilities in this area (Pangenetics, Actelion, Cara, ProStrakan). The role of PanGenetics in the successful clinical development of its product where its peer had failed

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\(^{67}\) Interestingly, there is perhaps some relationship to the extensive literature that has abounded on the difficulties of alliances and firms trying to work together where documentation of failure was estimated at around 60%. 

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(LayLine) illustrates that the firm was able to execute a superior clinical development strategy. PanGenetics was able to do with the PG110 product what LayLine could not and that was successfully develop, produce and test this product to produce favourable results. Actelion demonstrated their capabilities in clinical development, regulatory affairs and marketing when they took a Roche product and managed to take it all the way through to approval. Cara demonstrated their capabilities by successfully developing the Ferring product and selling that to Alza. ProStrakan also proved their capabilities in regulatory affairs and clinical development when they were able to assess the data from their acquired products, have a dialogue with the FDA and re-design clinical studies (Cellegy failed to get Celegesic and Tostran in the US approved) turning those products into successes via their own development strategy and thus capabilities. These types of capabilities (regulatory affairs and marketing for example) have usually been attributed solely to large firms and not something that small firms are credited with, however, the evidence here shows that these firms have these capabilities.

This may also be explained by the presence of scientists and executives from other companies in the formation and management of these firms which is an important common element. This in itself is not necessarily a new finding in terms of the involvement of these types of individuals (Kenney 1986, Orsenigo 1989, Pisano 1993, McKelvey 1996). However, these founding members and managers with corporate experience in a large firm (Bristol Myers Squibb, Eastman Kodak, Roche, Schering, Shire) or experience in multiple small firms (Cara, PanGenetics management teams) bring expertise and experience in important activities related to the range of drug development needs which has been systematically applied in a new range of activities within these small firms. These individuals have brought important competencies to these small firms with respect to drug development and their organisations benefit from these capabilities as illustrated in the table above.

Teece’s discussion on complementary assets concluded that successful commercialisation of an innovation requires that the know-how in question be
utilised in conjunction with other assets such as services (Teece, 1986). Being able to obtain a new product is only one part of the process; being able to develop the product utilising clinical development and regulatory expertise represents those critical complementary assets. The majority of the firms interviewed as part of this research have demonstrated those capabilities and complementary assets (ViroPharma, ProStrakan, Cara, PanGenetics, Actelion).

7.8. **Exploration and Exploitation in the Pharmaceutical Sector – A System Level Summary Review and Conclusions**

Important changes within the sector have been discussed throughout this chapter and this thesis related to the division of labour, why this has occurred and changes in markets for technology. These changes can now be viewed at a system level utilising the lens of exploration and exploitation for the sector as a whole. A key argument based on the evidence from this research has posited that an outcome of the previous focus on exploration in the sector produced a surplus of unexploited knowledge in the form of drug candidates. The development of a range of technologies related to high throughput screening, combinatorial chemistry, and the myriad developments in genomics (to name but a few) contributed to greatly improved productivity of search processes for drug candidates (Nightingale, 2000). These activities were focused on the upstream discovery and thus exploratory areas. They are best evidenced by the growth in the number of classical biotechnology firms that emerged throughout this epoch who focused on these exploratory activities.

However, this concentrated focus on exploration has now resulted in a surplus of drug candidates produced by this system level concentration on search efforts. As Nightingale also notes, ‘productivity improvements have produced a series of shifting bottlenecks and excess capacity within the system’ (Nightingale, 2006). The findings of this research as evidenced in Table 1717 above clearly indicate that firms have produced more drug candidates than they can develop internally. This system level focus on exploration has essentially created a deficit of exploitation capabilities at the
system level. Thus the massive system level exploratory focus has ultimately opened up the opportunity for NRDOs to enter the sector as a new and distinct class of firm that concentrate on the downstream exploitation activities necessary to develop and market drug candidates.

The cycle of discovery proposed by Nooteboom has been utilised to explain how changes have already occurred in the pharmaceutical sector and this may help to explain current changes proposed as a result of the findings from this research (Nooteboom, 2000). A system level cycle of discovery68 explains how exploration and exploitation build on each other and illustrates how various phases within the overall exploration/exploitation cycle progress from exploration to exploitation and vice versa. These authors explain how exploitation starts when the variety of content that emerges from exploration is reduced in a ‘consolidation’ phase (Gilsing and Nooteboom, 2006). A division of labour is associated with this phase and an increase in specialisation by firms that possess more specific knowledge on a narrower range of issues is apparent. This may explain the current changes being witnessed in this sector with the identification of the NRDO firm and its concentration on exploitation. This represents a division of labour and the specilisation that Gilsing and Nooteboom are referring to in their description of how a sector moves through the phases and ultimately between exploration and exploitation. The changes evident in the pharmaceutical sector today indicate that the sector may be moving towards an exploitation phase overall to take advantage of the levels of surplus unexploited knowledge and the opportunities for exploitation overall.

The original impetus behind the formation of small new firms in this industry was related to a need to bridge a gap between basic university research and discovery/clinical development of drugs (Henderson at al, 1999) driven by new knowledge that arose from discoveries in molecular biology. A market for know how was built up with small firms as upstream suppliers of technology and R&D services and incumbents (large firms) positioned as

68 Discussed in Chapter 2.
downstream buyers who could provide capital and access to other competencies required for successful development and marketing (Pisano and Mang, 1993). This latest division of labour, however, appears more to do with issues of efficiency, self sufficiency and viability of the firm on an economic level. The role of capital markets has been presented as a critical influence on this changing division of labour in concert with the corresponding surplus of knowledge. Financial considerations as well as cost pressures on firms exerted by both public stock markets and VC firms have emerged as key influences on all three types of firms discussed: NRDO firms, DD firms and large firms. However, a supply of products available for in-licensing is also critical factor that has enabled this changing division of labour.

The markets for technology have grown increasingly more complex as illustrated by the flows of products between firms studied as part of this research. Universities are no longer the only the major suppliers of knowledge and products to small firms operating in this industry. An increase in the available level of products and knowledge has greatly impacted the surplus of knowledge related to advanced (exploitation/development stage) drug candidates in the system but this surplus is comprised of drug candidates that have progressed through several important milestones and as such are more developed products. The emergence of this new NRDO firm and the changing strategies of DD firms have provided a key way in which the surplus knowledge can be redistributed. This becomes a more compelling argument when viewed with evidence that relates to financial pressures and constraints on firms. As firms face more and more pressure to be a success financially, they find themselves in need of advanced stage products to positively impact their financial position. Thus a need for products arises and is fulfilled.

Arora and Gambardella noted that ‘the body of knowledge and information for innovation has become more ‘divisible’ pieces of knowledge, and bodies of expertise and information can be ‘separated into different organizations and re-assembled at a later stage’ (Arora and Gambardella, 1994). This
certainly appears to be the case in the pharmaceutical sector as the NRDO firm, changes to the traditional DD firm and changes in the outlicensing activities of large firms illustrate a new division of innovative labour that has been made possible by this ‘divisibility’ of knowledge and expertise. Large firms are undertaking important strategic changes that are influencing the innovative strategies of smaller firms but not necessarily in the way that has been historically described. The evidence suggests that the creation of these new NRDO firms may also be a response to an increase in the number of opportunities for product development created by a surplus of knowledge from large firms with an excess of unexploited drug candidates in more advanced stages of development.

If, as the evidence suggests, more efficient markets for technology are apparent, then there are more exploitation opportunities available for firms and it is possible that there will be an increase in the numbers of NRDO firms. The case of PanGenetics implies that there may also be a shift in the expectations of these firms in terms of their organisation, their goals and ultimately their longevity. PanGenetics was specifically reincarnated by Index for development of products only. Once that goal was achieved, the firm was essentially dissolved. Firms may be consciously set up as temporary or ‘project based’ organisations to fulfil a specific purpose. Arora et al suggest that this would also mean that once their purpose is achieved, assets can be allocated elsewhere and the firm dissolved (Arora et al, 2001). Whether or not this type of transitory firm will become more popular in this sector remains to be seen but forms an interesting avenue for future research.

Serious problems exist with current business models in the sector where the returns to R&D investment have decreased (McKelvey 2008) and this provides an important context for these findings. Pisano also has noted that persistent poor performance of firms in the sector has created a real need to organise firms differently to address this fundamental performance issue in the sector. This becomes particularly important in terms of the very large sums of money that have followed many firms into decline and closure (Pisano, 2006; Lazonick and Tulum, 2010). The arguments provided by
Hopkins et al in 2007 were also significant in that they pointed out compelling reasons to think that the pace of technological change in the sector has been both disappointing and not at all revolutionary (Hopkins et al, 2007). These observations in the literature provide an important foundation for the relevance of the findings from this research: namely that the emergence of the NRDO firm and the changes to DD firms are ultimately the sector’s response to the pervasive issues of disappointing performance from a technological and financial point of view. This becomes a more compelling argument when viewed with evidence that relates to financial pressures and constraints on firms. As firms face more and more pressure to be a success financially, they find themselves in need of advanced stage products to positively impact their financial position. Thus a need for products arises and is fulfilled. How the overall performance of the sector will ultimately change now based on these new organisational changes and fundamental changes in the division of labour and markets for technology remains to be seen.
Chapter 8. Conclusions of the Research

The literature provided a frame of reference that indicated change is to be expected because of the dynamic and evolutionary way in which firms and industries evolve. A new division of labour has taken place in the pharmaceutical sector. The No Research Development Only (NRDO) firm has been identified as a new type of firm within the division of labour of the pharmaceutical sector. The evidence indicates that a surplus of unexploited knowledge and the demands of capital markets as well as the corresponding response by firms to financial pressures have an important role to play in this division of labour. This has also been accompanied by a change in the markets for technology whereby markets have become more complex than previously understood. A model was used to illustrate the important connections between all of these areas that were studied as part of this research.

8.1. Main Findings of the Research

8.1.1. Changing Division of Labour

The literature illustrated how a division of labour emerged from the 1970s onwards within the pharmaceutical sector. The new small classical biotechnology firm fulfilled a key role in the dissemination of new knowledge from the academic centres to the private commercial sector. These new small firms concentrated primarily on upstream exploratory research and became providers of this technology and knowledge to large firms thus illustrating the division of labour as these firms were essentially ‘research boutiques.’ However, evidence from the trade literature suggested that there was yet another change in the division of labour that was not related to upstream exploratory activities but rather downstream exploitation related activities including clinical development, regulatory affairs and product marketing (in some cases). This research looked for evidence that a new type of firm had emerged that represented a new division of labour.

The No Research Development Only (NRDO) firms were identified through a quantitative study that examined a range of firms from the sector. A random
sample of firms from the sector was collected to determine if there was a division of labour evidenced by a new type of firm. The creation of the categorisation of NRDO companies was based on the analysis of a sample of companies that examined the span of drug discovery and development activities together with a review of their product pipeline and the existence of any platform technologies. The results indicated that 27% of the firms sampled were NRDO firms. The primary focus of these firms was on clinical development (and in some cases marketing) of products rather than exploratory discovery activities leading to the creation of products. This exercise provided an indication that the operations of the NRDO company were not focused on the discovery of products in contrast to that of their peers and the characterisation in the literature as noted in chapter two. Case studies confirmed this understanding and revealed that the development of each of these firms was in inextricably linked to finance, a surplus of unexploited knowledge and changing markets for technology. The range of activities of NRDO firms spanned multiple product platforms and multiple therapeutic areas and indicates that the formation of these NRDO firms is not peculiar to one particular product type or therapeutic area. This provides evidence for the changing division of labour.

However, the rationale for why this division of labour has happened in terms of NRDO firms is related to the role of capital markets and availability of surplus unexploited knowledge. These are two key factors that have been identified as a result of this research. Changes in the markets for technology have also become apparent and are related to the changing division of labour. None of these areas can be viewed in isolation as they are all linked.

8.1.2. The role of capital markets as an influential factor in terms of the new division of labour

Sources of finance including Venture Capital (VC) and Public Stock Markets were important in the emergence of the initial division of labour that took place during the third epoch of the pharmaceutical sector. During the 1980s, 1990s and early 2000s, for the most part, the markets ‘directed’ capital to early stage exploratory research activities being carried out by many firms in
the hope that new exciting knowledge and products would emerge. These sources of finance supported the growth of the classical biotechnology firms who were research intensive exploratory firms in need of capital to fund their research based activities. The public stock markets provided an exit for VC firms and way of raising substantial amounts of capital for these classical biotechnology firms.

However, there has been a change in the nature of firms operating in this sector and thus a change in the division of labour. A new type of NRDO firm has emerged that only concentrates its resources on development (exploitation related) activities while existing firms are also adding later stage products for development into their portfolios. These firms do not require resources for discovery (exploratory) activities and their product development timelines are consequently not as long. These attributes make them attractive to both venture capitalists and public stock markets.

The evidence presented from this research has indicated that the capital markets (sources of finance such as Venture Capital and Public Stock Markets – the most prolific sources) have played a role in the emergence of a new type of firm, as well as changes to existing firms and thus the new division of labour. The evidence illustrated that venture capital was instrumental in setting up a new type of NRDO firm and ensuring that external product acquisition was undertaken while public stock market considerations influenced firms' decisions to discontinue exploratory activities. The acquisition of external products by DD firms for development was based upon the need for improved financial valuation of the firms.

The literature has indicated that the costs associated with drug development are excessively high and consequently firms need a great deal of capital investment. In addition, the nature of these firms means that risk is inherent in any investment made. The capital markets have supported many of these sorts of firms but the performance of the sector overall has been called into question over the last number of years. The evidence indicates that the need for firms to be closer to the market in terms of the stage of development of their products was a key consideration related to financial sustainability.
and was linked to the value of the firm as perceived by its investors. But because successes were so few and far between, ultimately, some experimentation in the business model was needed and some financiers in the capital markets have turned to funding later stage products in different types of firms. Finance was consistently cited as a key factor in discussions with firms as to why they sourced products externally and why they did not have research related exploratory activities as part of their business model. Financiers want better results in terms of their return on investment. More advanced products represent a faster chance of success. The role of capital markets is visible in the changing division of labour.

8.1.3. Surplus of Unexploited Knowledge as an Influential Factor in the Division of Labour

The role of new knowledge was critical in the development of the new small classical biotechnology firm during the third epoch of the pharmaceutical sector. This new knowledge was the reason for the foundation of many firms (including various different waves of new firms throughout the third epoch). Firms traditionally sourced new technologies from public laboratories and academic centres. Various developments in a range of areas within molecular biology, chemistry and information technologies created many opportunities for firms but also added to the body of knowledge of drug targets and how to search for new drugs. Some of the key developments included High Throughput Screening and Combinatorial Chemistry. As a result, large firms in particular were able to produce vast libraries of compounds for testing. However, not all drug compounds have been exploited by firms and this has resulted in a ‘surplus’ of drug candidates that were not internally exploited by firms. Excess knowledge has been produced in the sector due to these exponential discovery related developments and also because firms face resource constraints in terms of their development portfolios.

However, this has also created opportunities for the formation of new firms with those products that firms have chosen not to develop. This has formed the basis for the start up of other firms. Firms studied as part of this research
have illustrated that this mode of corporate spin out is another way for firms to extract value from their surplus stock of knowledge.

Trade in these products has grown and consequently enabled the division of labour to take place whereby firms with ‘surplus’ products offer them for sale and development by other firms for reasons related to portfolio management and financial resource constraints. It is possible that discovery activity has (for the moment) reached a critical mass where a bolus of products has been produced but resources need to be applied to develop them. Consequently, this division of labour in terms of development activity is the natural answer to the problem as new entrants focus on clinical development at this point in the sector’s lifecycle. The literature illustrates that there has always been changes to firms (large and small) usually in response to changes in knowledge in the sector. The findings of this research help to update our understanding of how firms appear to have changed most recently and how that is related to a surplus of knowledge rather than new knowledge. The critical problem remains with successful clinical development.

8.1.4. Increasingly Complex Markets for Technology

One of the distinguishing features of this epoch of the pharmaceutical sector has been the role of markets for technology as part of the vast networks of various types of linkages between companies. When new technological developments took place, small firms were the primary conduits of this new knowledge from universities and government laboratories to the commercial sector where they developed these technologies further in the pursuit of product discovery and development. The slow uptake of the new technologies by large incumbent firms enabled the creation of a market for this technology and related knowledge whereby large firms essentially bought products and know how from small firms to ensure they had a ‘window’ on this technology.

But as noted in the previous section there is evidence of a surplus of unexploited knowledge in the sector and firms have opted to trade these drug candidates. Large firms have opted to trade this knowledge for financial reasons to capitalize on the value of these products. They have sold these
products to other small firms for development because of portfolio management decisions whereby scarce resources can only be allocated to some projects. Traditionally, these large firms were only associated with buying in products and knowledge from small firms where as now they are buying and *selling* products and knowledge to small firms.

Conversely, while small firms have historically only been associated with selling products and knowledge to large firms, the evidence showed that there is also trade between small firms. Small firms are trading products and knowledge amongst themselves and citing financial pressures and issues as the main reason for this trade. The need for other small firms to acquire products in later stages of development has been acknowledged and is related to financial reasons also. These new trading relationships add up to a complex picture of trade in the sector where existing relationships with academic institutions are still an important source of new knowledge but the picture is more fine-grained with new sellers and buyers in the market.

In addition, the evidence gathered also indicated another important change that was related to the activities of the Discovery and Development firms and related to the markets for technology. The anecdotal evidence in the literature also suggested that DD firms might also be acquiring products externally for development in-house. The database was set up to gather information on the external product acquisition by all firms and the findings illustrated that DD firms (who are traditionally known for discovering their own products) were also acquiring products from external firms to complement existing in-house pipelines despite having the capability to discover products in-house. This, again, is in marked contrast to what is currently understood about how these sorts of classical biotechnology firms conduct their business in terms of internal product generation and product development.
8.2. **Contributions to Knowledge**

8.2.1. **Overall Theoretical Contribution**

Prior studies on the pharmaceutical sector have provided much valuable knowledge on the structure and dynamics of the sector and the roles of the various firms that make up the drug development sector in particular. However, this research has proven the existence of a new type of firm in the industry and makes an important new contribution by updating knowledge of the various firms in the sector and how they participate in markets for technology. It provides support for existing theories that the dynamics of industrial structures will continue to evolve in response to various pressures and situations and that the pharmaceutical sector itself is dynamic and responsive to a range of changes (Nelson and Winter, 1982; Malerba and Orsenigo, 1996; McKelvey and Orsenigo, 2001, McKelvey, 2008). Changes in markets for technology within the sector have been identified and an updated understanding of the range of exchanges taking place in the sector by accounting for a new type of firm and the changing behaviours of existing large and small drug development firms.

These research findings add to the stock of knowledge on the industry by illustrating the activities of the new type of NRDO firm. This research contributes to the stock of knowledge on the reasons why new firms are apparent in this sector by illustrating the role of finance and the surplus of unexploited knowledge in the sector. The research also illustrates new knowledge with respect to the fact that existing firms will continue to evolve in response to the same factors as those impacting NRDO firms including the unexploited surplus of knowledge and financial considerations. The knowledge in relation to the innovation strategies of firms has also been updated and a greater understanding of the role of finance and financial pressures and the actions of financial providers is made explicit by the research. The research shows how the range of firms in the sector have capitalised on the availability of unexploited knowledge and how this relates to financial considerations.
These contributions to knowledge were made possible by an original research approach that used a quantitative and qualitative information gathering process to establish the existence of a new type of firm and some of the key reasons for the existence of the firm. The existence of the new firm was confirmed by a random sampling approach but was supported by the range of qualitative data that was gathered on each of the firms in a large 100 firm sample. A database captured a range of information on each firm that made it possible to ascertain key activities of the firms including the evolving DD firm. Case study qualitative approaches usually involve only one or two firms but a total of eight firms were used to establish and verify the reasons for the changes taking place within the firms operating in the sector and overall this made it possible to confirm the role of finance and the surplus of unexploited knowledge. This unique combination of quantitative and qualitative methods has enabled the range of research questions to be addressed successfully and provided different types of data and evidence required to make a series of important contributions overall.

8.2.2. Identification of a New Organisational Typology

It has been noted throughout this thesis that significant challenges are inherent in the integration of science and business (Pisano, 2006) and evidence has shown that novel organisational experiments are evident as a result. The evidence presented here indicates that a new organisational arrangement, the NRDO firm, is visible and it makes up over a quarter of firms in the sector. This is an organization that is oriented towards exploitation, focusing on the development of drugs. This organizational form has not been formally identified in the literature to date and this research presents this finding as a major contribution to knowledge.

8.2.3. Identification of a New Division of Labour

The pharmaceutical sector has witnessed many changes throughout the third epoch and it appears logical that still more changes are evident in the division of labour. The most well known division of labour was the role of small firms as research and exploration focused businesses while large firms took on the role of developers, regulatory experts and marketers. However, a
new division of labour is now evident where some small firms are focusing on a different part of the drug development continuum – that concerned with clinical development of drugs rather than discovery of drugs. This represents an important updated understanding of the division of labour in the sector.

8.2.4. Identification of Increasing Complexity in the Markets for Technology

This research findings show that there have been changes in the markets for technology. These were previously characterised as one way transfers of knowledge and products from academic centres to small firms and from small firms to large firms. These markets for technology are now more complex as small firms and large firms engage in new types of transactions that are different to the current understanding with small firms buying products and large firms selling products. This research has provided a more up to date view of the markets.

8.2.5. Financial Considerations are an Important Influence on the Changing Division of Labour

The drivers of the new organisational type and changes in the division of labour are, in part, directly linked to financial considerations. This research is not claiming that this is the only driver of this new changing division of labour but rather that this particular influence is significant and noteworthy. The evidence has shown that financial pressures will result in firms’ decisions to allocate resources towards more developed products at the expense of exploratory work. The need for firms to extract the maximum financial value from their portfolios appears to be a key concern implicit in the new division of labour. The more central role of finance has not been well discussed as a key factor that influences a firm’s innovative direction or the division of labour but it has emerged as a key consideration in this research that warrants more attention in the future.
8.3. **Extending This Research**

### 8.3.1. The Transitory Nature of the NRDO

According to Levinthal and March, an organisation that engages exclusively in exploitation will ordinarily suffer from obsolescence (Levinthal and March, 1993). However, one of the interesting findings that has resulted from this research is that the firm’s primary goal may not necessarily be long term survival, in which case the firm’s focus on exploitation is not necessarily a problem because long term survival is not actually a fundamental part of the firm’s strategy. The case of PanGenetics illustrates this point. The long term survival of the firm was never part of the overall plan of its creators, Index Ventures. The firm was specifically engineered to be a transitory organisation that was created for successfully developing a product(s) that would be sold to another firm.

But how transitory is the NRDO business model and division of labour as a whole? Is it here to stay or will they in turn be forced to turn to exploration when the supply of unused drugs runs out? Maybe increasing specialization can’t be maintained, or maybe it’s a transitory phase in the market similar to the way in which discovery only firms have changed and become discovery and development firms. Arora et al suggest that the transitory nature of firms may be a useful organisational arrangement for any industry as firms arise specifically for a project (Arora et al, 2001) and then resources are re-allocated once the project has been completed (such as PanGenetics). This area represents an interesting avenue for considerable future attention.

### 8.3.2. Changing Levels of Exploration in this Sector

These findings indicate that the balance of exploration and exploitation in the sector as a whole may be changing. The level of exploration may be declining (with the growth of NRDO firms and in-licensing of DD firms) which will have consequences for the sector as a whole. This trend away from exploration must be reviewed further. The findings suggest that the influence of capital markets may be impacting the overall level of exploration activities in this sector but this needs to be substantiated with additional research that would examine the overall level of exploration in the sector. This could be
combined with research to ascertain the extent of the influence of sources of funding on the level of exploration in the sector. In the context of the findings of this research, there is a need for future researchers to be more aware of the impact of finance on basic science and research activities.

8.3.3. Social Network Theories and the Role of the Serial Entrepreneur

The role of ‘serial entrepreneurs’ moving from company to company to found and develop firms appears to be important given these particular findings. ‘Scientist entrepreneurs’ are spotting opportunities and persuading companies to give them products for development. These findings illustrate that the presence of an academic founder or indeed the intellectual property from an academic institution are no longer the sole prerequisites for firm formation in this sector. Therefore, the extent and importance of the role of human capital in moving products around from company to company poses an interesting avenue for future research.

8.3.4. The Role of Corporate Spin outs as a New Mode of Division of Labour

One firm in the sample, Actinium, was created specifically to pursue the development of products that the parent firm had decided not to pursue internally. While this is the only example of this type of firm in this set of case studies, Skelia, (whom ProStrakan merged with) was a spin out from Aventis. GlaxoSmithKline also noted that they were becoming more active in setting up spin out firms with products that did not make it into their development portfolio. The portfolio management issues faced by large pharmaceutical companies are becoming more and more topical in the sector today as companies are scaling down operations and narrowing therapeutic area focus. The trade literature has noted many other examples of companies that have engaged in this activity. In terms of future research, the creation of a new company specifically to develop a parent company’s product or series of products represents an interesting avenue of further research in this sector because this is an under researched topic. The advantages and disadvantages of such a mode of innovation are not well discussed but
would represent an important line of inquiry from a management and strategic perspective.

8.3.5. The Role of Finance and its Impact on Innovation

The findings from this research point to a more direct role between finance and its role in innovation and its value as an explanatory factor in how and why firms make various decisions related to innovation. This could be better understood by looking at other industries. The role of finance should be given more prominence in terms of the links between financial decision making and innovation strategy. Future research could focus on other industry examples of this type of division of labour to ascertain the role of finance and how it impacts innovation.

8.3.6. Understanding how Firms Change Capabilities

The division of labour is fundamentally characterised by a change in firm capabilities. As these ‘buyer’ firms are able to bring these products in-house, these findings would imply that different capabilities are a key aspect of this process but the exact role and relative importance of these capabilities have yet to be ascertained. Future research could help to ascertain how these capabilities have changed and how firms have internalised these new capabilities.

8.4. Summary

This thesis is about the dynamics of an exciting sector – the pharmaceutical sector. It is about industrial change on a macro level (the division of labour, changes in markets for technology) and firm change on a micro level. It is about how firms adapt to survive the range of pressures and expectations, particularly financial pressures, that surround them in their quest for success. But it is also about how firms respond to various opportunities; in this case, the availability of unexploited knowledge in the form of pharmaceutical drug candidates. Firms are buying in drugs (56% of DD firms) that have already been discovered (and generally passed through the important phases of drug discovery) from other companies to develop internally. A significant number of firms are dedicated to developing rather than discovering products (27%)
while others are balancing the dual demands of exploration and exploitation in an attempt to have the best of both worlds. Why is this happening? Because these firms recognise two things: That there are opportunities out there in the form of drug candidates and that these opportunities greatly improve the chances of obtaining capital. When these products are obtained and integrated into a pipeline it puts them closer to the market and to success and ultimately, they benefit and their financiers benefit. Poor performance has been an issue for the sector but it is now possible to recognise that there are potentially many unexploited opportunities that have resulted from the prolific exploration that has been taking place. A market for these products has arisen as firms on both sides (buyers and sellers) have something to gain. These changes also represent very interesting variations in how we understand the way in which knowledge and products are traded. Overall, the markets for technology have become more complex and variable than previously understood.

The landscape of this sector is changing. More than a quarter of firms analysed were NRDO firms. More than 50% of all firms analysed were not formed based on academic discoveries and were instead formed as standalone entities by various scientists and venture capitalists or angel investors. More than half of all firms in the sample sourced drug candidates externally. This is a dynamic sector and increasingly, firms are being formed by entrepreneurs who see new opportunities with existing products combined with the need to reach profitability as soon as possible. They are also responding to greater financial demands particularly in an era when poor performance is becoming less acceptable. The NRDO firm is a new organisation concentrating solely on development but the established and well understood traditional DD firm is also buying in these more advanced stage products. The activities of these firms are shifting with an ever increasing emphasis on financial success. It remains to be seen how long the NRDO model will form part of the landscape but one thing is for sure: there is nothing more certain than change itself. As Gary Pisano has said ‘There is no more important challenge for both scholars and practitioners in twenty first century economics than contributing to our evolving knowledge of
the business of science’ (Pisano, 2006). It is greatly hoped that this research has made such a contribution.
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