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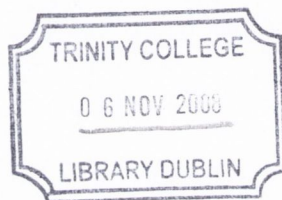
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**Exploring the Connection Between R&D and Supply Chain
Management in the Branded Ethical Pharmaceutical Sector**



Submitted for Ph.D. in Business Studies

July 2008

By Erin E. Sullivan

THESIS
8620

Statement of Original Authorship

I certify that the work in this dissertation has not previously been submitted as an exercise for a degree at this or any other University.

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Erin E. Sullivan
July 2008

Executive Summary: Exploring the Connection Between R&D and Supply Chain Management in the Branded Ethical Pharmaceutical Sector

Research Problem: This investigation, in the field and in the literature, aimed to describe how SCM functions in terms of new product R&D in the ethical branded pharmaceutical industry. The literature review revealed little extant research on SCM practices in this sector; it also revealed the potential benefits of a tight linkage between R&D and SCM. This, in turn, prompted this study's central research question: *To what extent is SCM considered by R&D within the branded ethical pharmaceutical industry?*

To answer this question, the inquiry considered how a pharmaceutical firm's pipeline and development management (otherwise known as Research and Development) impact the supply chain, the relationship between upstream (R&D) and downstream (SCM) activities, and any available evidence of coordination or collaboration between the two in new product development.

Problem Context: The context of this research encompassed several strands of management literature: supply chain management; industry-based work on pharmaceuticals (including R&D and SCM) and knowledge management. However, there is a lack of a literature on ethical branded pharmaceutical SCM in relation to new product R&D; in fact, coupled with supply chain management's status as an emerging discipline, this indicated that this was an area suited for exploratory doctoral research. The large and profitable reality of the ethical branded pharmaceutical industry suggested that this was an arena that had remained insulated from the pressures that cause firms to create efficient and effective supply chains.

Many supply chain management strategies have focused on the operations side of the enterprise, with minimal connections to product development. Some authors, however, suggest that supply chains should coordinate with R&D. My initial case studies set within the branded ethical pharmaceutical industry indicated that this was not necessarily happening in this environment. There was little evidence of what the literature described as a shift away from managing

individual functional processes, to managing integrated chains of processes in order to achieve improved business operations. Thus, it became compelling to consider the extent to which SCM was considered by R&D in ethical branded pharmaceuticals.

Methods: In investigating the relationship between SCM and new product R&D in ethical branded pharmaceuticals, this empirical exploration investigated top pharmaceutical firms and focused on three that were representative; these three are presented as case studies that examine the internal workings of upstream (i.e. R&D) and downstream (manufacturing, SCM) activities. The exploratory nature of this research warranted such an approach, which involved semi-structured interviews conducted at each site focused on R&D and SCM practices. The data revealed existing relationships and flows between these two areas and enabled extensive analysis.

Findings: Analysis involved an open approach to synthesizing the case research findings with the literature to develop conclusions with respect to the nature of the relationship between new product R&D and SCM within the branded ethical pharmaceutical sector. While the literature recommends that firms need coordination and collaboration between R&D and SCM to achieve benefits for both sets of activities, this is not manifest in the case study firms. The analysis led to the conclusion that SCM is not extensively considered by R&D- it is not a major priority. The case studies suggest, however, that the lack of extensive SCM consideration is due to the sector's prioritization of R&D, the nature of SCM challenges within the industry, an absence of lean or agile supply chains found in other industries, and an underdeveloped comprehensive knowledge management strategy that would allow R&D to consider SCM in new product development.

For my parents, who gave me everything.

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Chapter 1: Introduction

This research is set in the context of the branded ethical drugs segment of the pharmaceutical industry; more specifically, the research considers how new drugs move through the product life cycle to product launch, and how research and development (R&D) works with supply chain management (SCM). The industry choice and theory area for this study were predetermined by a project in the Institute for International Integration Studies before I arrived at Trinity College. The first two years of research were spent learning about the industry, the supply chain management literature and, in particular, how international supply chains operated. Initial field research, combined with exploring the literature, revealed that instead of focusing purely on pharmaceutical SCM, a more interesting story may result from looking upstream at R&D and how new products are developed. That insight prompted the study's central research question: *To what extent is SCM considered by R&D within the branded ethical pharmaceutical industry?*

Because Research and Development comprise a significant and critical portion of a branded ethical pharmaceutical firm's activities, to answer the research question, the scope of the inquiry aimed to consider how a pharmaceutical firm's pipeline and development management (otherwise known as Research and Development) impacted the supply chain. By reviewing additional management literature, the investigation for this research was redefined in terms exploring upstream (R&D) and downstream (SCM) activities. I observed a disconnection between what was written in SCM literature, suggesting that supply chains should coordinate with R&D (Balasubramanian 2001; Singhal and Singhal 2002; Haque 2003; Hult 2003; Fine, Golany et al. 2005; Power 2005), and my observation that this was not the case in my initial case studies set within the branded ethical pharmaceutical industry. It was this curiosity that drove two additional years of doctoral research, which resulted in the development and execution of the four-year project presented within this dissertation.

1.1 Research Context and Literature

In recent history, the branded ethical pharmaceutical industry¹ has been challenged by Wall Street to re-think its business model and improve its pipelines. Government regulators have challenged the safety and integrity of the industry's products. The generic pharmaceutical sector has grown increasingly aggressive in challenging ethical pharmaceutical patents. Payers (governments or health maintenance organizations) have demanded lower product pricing and improved efficacy guidelines. The industry, however, has not found a fail-proof way to address the complaints from this myriad of constituents. As such, the heated, volatile and changing nature of this industry made it a compelling choice for an in-depth study.

The lack of a mature literature base on SCM within in the pharmaceutical industry, coupled with supply chain management's twenty year history as a discipline in its own right (Burgess, Singh et al. 2006; Cousins, Lawson et al. 2006; Harland, Lamming et al. 2006; Storey, Emberson et al. 2006; Vachon and Klassen 2006), indicated that this was an area suited for exploratory doctoral research. The large and profitable nature of the branded ethical segment, combined with recent pressure to re-think its business model and increase cost-savings indicated that it would be interesting to explore the industry's supply chains to see if they were comparable with descriptions of efficient and effective supply chains from the management literature. Further, an initial investigation of one the industry's top and most well known pharmaceutical giants, Pfizer, suggested a low degree of SCM practice present within the industry.

The supply chain management literature reveals that supply chains are fundamentally about flows and the movement of tangibles (i.e. materials) and intangibles (i.e. money and information). Most SCM discussions take an engineering or technical point of view, in which SCM problems can be solved using an optimal-solution approach (Mouritsen, Skjott-Larsen et al. 2003). As such, many supply chain management strategies have focused on the operations side of the enterprise, with minimal connections to product development (Balasubramanian 2001; Vachon

¹ Also referred to simply as "the industry."

and Klassen 2006). Some authors, however, contend that SCM requires a shift away from managing individual functional processes, to managing integrated chains of processes in order to achieve improved business operations (Kotzab and Otto 2004; Power 2005; Tracey, Lim et al. 2005).

Considering supply chain practices in light of upstream activities, such as product development, transports SCM from a singularly downstream function (Balasubramanian 2001; Singhal and Singhal 2002; Haque 2003; Hult 2003; Fine, Golany et al. 2005; Power 2005). This stretches SCM frameworks, but supports a more conceptual and broader approach to SCM, which incorporates upstream as well as downstream activities. This approach includes an evolving awareness of the supply chain and its interfacing components, suggesting that actions taken in one area might affect upstream activity, and thus, the performance of the whole. Hence, organizations need a higher degree of integration between firm activities and information, material and financial flows (Fisher 1997). Integrating supply chains with other up and downstream activities means deconstructing organizational silos and replacing them with a greater level of cross-training across functional boundaries, so that managers have enough in-depth expertise in one discipline (i.e. SCM) combined with the ability to identify connections with others (i.e. product development) (Mangan and Christopher 2005; Swink 2006).

Thus, the literature's recent suggestion of a link between SCM and other firm activities supported expanding the scope for this research from investigating pharmaceutical SCM to exploring if branded ethical pharmaceutical R&D and SCM worked together. This was particularly interesting in light of the way products move through drug discovery and development to manufacturing by being handed from one functional unit to another, also known as "tossing over the wall."

1.2 Research Approach

The context of this research encompassed several strands of management literature: supply chain management; industry-based work on branded ethical pharmaceuticals; and new product processes, with a focus on R&D and SCM. The industry-based literature on branded ethical pharmaceuticals revealed the knowledge-intensive nature of the industry and as such, some areas of knowledge theory were added to the literature review. In investigating R&D and SCM in branded ethical pharmaceutical companies, this research used case studies to examine new product R&D activities and new product SCM activities. Case research facilitates the description of events and outcomes to allow other researchers to understand processes and environment (Finch 1999). Further, case research helps bridge the gap between academia and industry; each side has the opportunity to learn something from the other. Thus, findings from case research are recognized as generally valid by both academic and industry audiences.

The qualitative study succeeded in recruiting three international, branded, ethical, top-25 pharmaceutical firms for the purposes of this research. Interviews were conducted at each site regarding both R&D and SCM practices, in order to determine the existing relationships and flows between these two areas. After completing data collection at the case firms, extensive case write-ups were created with an emphasis on developing descriptive, narrative accounts, central to the generation of insight (Gersick, 1998; Pettigrew, 1988). Such descriptive cases are particularly helpful in assisting researchers with the volume of data collected during site visits/interviews (Eisenhardt 1989) and provide an initial method for organizing and understanding qualitative data (Bryman and Burgess 1994). With fieldwork complete, the data was coded and analyzed on a case by case basis, and in comparison to one another in order to allow insights to inductively emerge.

1.3 Research Contribution

This work contributed to both management theory and practice. While pharmaceutical R&D has been extensively covered in the literature, and a distinct body of supply chain management literature exists, the issue of pharmaceutical supply chain management has been largely unexplored. Thus, even before moving to the analysis stage, the case descriptions, as empirical evidence, made a contribution by providing an in-depth perspective of new product development and SCM in three successful pharmaceutical firms. At the same time, the use of case research for this investigation generated extensive and descriptive case write-ups for analysis, thus supporting the value of case studies, or case research, for new areas of research.

In terms of theory, a set of common characteristics that exist across branded ethical sector pharmaceutical firms was identified. Outlining these characteristics also contributed to understanding the industry's environment and complex nature of the industry's business: drugs are an integral product and the human body is an integral system (Pisano 2006), which is but dimly understood--as a system or in individual manifestation. Following from this, the industry does not have a clear-cut, reliable approach to consistently and successfully discovering and developing drugs to deal with this complexity; and that, in turn, poses significant strategic challenges. R&D operates with incomplete information, as the science of the "druggable universe" and knowledge of how the human body and disease mechanisms operate are constantly evolving, not to mention highly complex. The development process also involves lengthy timelines (10-12 years) and high rates of failure, which makes it difficult to make predictions and plan downstream manufacturing.

Industry regulations also trigger a number of barriers given that this industry's product could *kill* a patient. Firms must worry about much more than just meeting customer demands or creating the next big product. They must create new drugs in an environment that lacks some of the prototyping and experimentation opportunities available in most other industries. The market for drugs is not the same as the market for an iPod (or a new Toyota). Pharma's end customer is

even unclear- is it patients, doctors or payers (governments, health insurance companies, HMOs)? Further, gaining manufacturing approvals from various regulatory bodies around the globe makes it difficult, and even prohibitive, to make changes to products if that means a further expense in both time and money for a re-approval; attaining approvals is already a long and expensive process.

In light of the industry environment, looking closely at new product R&D and SCM practice at three branded ethical firms uncovered practically oriented strategies that firms attempted for a variety of reasons, such as to address the changing industry landscape or decrease operating costs. These included, but were not limited to, the following:

- Re-organizing parts of the R&D process;
- Introducing manufacturing or pilot plant activities earlier in development;
- Finding more predictive methods for supply chain planning and design;
- Increasing the transparency of information;
- Improving organization-wide communication mechanisms;
- Standardizing procedures and technologies; and
- Omitting or condensing steps within the product lifecycle.

Achieving a complete understanding of why the three firms implemented any of the above practices required iterating between the reviewed literature and the data collected at three firms so that observations and conclusions could inductively emerge over time. Because the conclusions were rooted in “living and breathing” pharmaceutical companies, it is difficult to designate the conclusions as either practice or theory specific.

1. The branded ethical pharmaceutical sector maintains a strong focus on upstream activities, namely R&D. Pharma’s inherent upstream focus stems from a necessity to fill the product pipeline with discoveries that begin in R&D. Developing new products, however, typically is facilitated by collaboration between upstream and downstream knowledge workers; this is particularly the case in a knowledge-based industry where coordination of upstream knowledge significantly impacts downstream activities (Balasubramanian 2001; Hong, Doll et al. 2004; Mangan and Christopher 2005; Tracey, Lim et al. 2005)

2. The priorities for the pharma supply chain are not to attain operational efficiencies, but rather strategic or design-level efficiencies. In an industry where making operational-level SCM improvements is markedly constrained by regulatory approvals and testing to guarantee product safety, the attempted SCM efficiencies exhibited by the case study firms focus on improving strategic and design level supply chain issues. The case research suggests that pharma is focusing on strategic and design level changes, more than strictly operational ones, grounded in effective management of knowledge and supply chains, to result in reduced levels of uncertainty, decreased cycle times, lower cost, improved quality and better management of complexity. So, for example, R&D processes will be redesigned to more reliably and predictably feed the downstream functions.

3. Industry pressures and structure create SCM challenges. Focusing part of the research on identifying current SCM practices gave some insight into branded ethical firms' reluctance to revolutionize or significantly change SCM practices. Part of the hesitation to make SCM changes is a direct result of regulatory requirements and the associated costs to obtain regulatory approvals for new process steps or materials. Further, adopting strategies such as outsourcing manufacturing or moving production to lower cost locations remain unattractive ways of attaining cost-savings; such strategies lead to firms giving up complete control over a product for which the ultimate responsibility for any adverse patient outcomes is theirs and theirs alone.

4. Piecemeal knowledge management strategies support firm activities. Firms operate in an environment that relies on knowledge from a number of interdisciplinary sources. Knowledge seems to be managed within teams or silos, but no firm exhibited a comprehensive, organization-wide knowledge management strategy, which would, at least in theory, seem critical for functioning in a knowledge-intensive industry. The firms do employ, however, a number of strategies for knowledge management, referred to as piecemeal because they do not extend throughout the organization: leverage accumulated experience and informal networks; share

knowledge; recruit a talented staff; create a team that synthesized knowledge. This approach, however, contrasts with the suggestion in the literature that successful new products typically are facilitated by the integration of upstream and downstream knowledge workers.

These conclusions, rooted in the data collected on both the new product R&D and SCM sides of branded ethical pharmaceutical organizations, illuminate how these two units function within the firm. Using the field research and literature to reflect upon the original research question, it is possible to not only answer the research question, but also to consider the forces at work within these firms which cause R&D and SCM to operate in a particular way. SCM is considered by R&D, but not extensively. The literature suggests much tighter coordination and collaboration between the two than is manifest in the case study firms (Balasubramanian 2001; Singhal and Singhal 2002; Haque 2003; Hult 2003; Fine, Golany et al. 2005; Mangan and Christopher 2005; Power 2005; Tracey, Lim et al. 2005). However, the case studies demonstrate that perhaps the lack of extensive SCM considerations, which would be found in other industries, is due to a number of factors. One of these factors is the way firms prioritize R&D, but this is because without successfully developing new products, there is no need for SCM. Another factor that contributes to the level of connectedness between R&D and SCM is the fact that the case study firms do not seem to seek the operational benefits of lean or agile supply chains in the same way firms do in other industries. This directly links to the SCM challenges which make changing or re-designing downstream activities more of a burden than an opportunity for cost-savings. Finally, the lack of a coherent organization-wide knowledge management strategy, would, in theory, pose a problem in R&D being able to comprehensively consider SCM in new product development.

1.4 Structure of Dissertation

In the chapters that follow, this dissertation will consider the relationship between R&D and SCM within the branded ethical pharmaceutical sector and what, if any, consideration R&D gives to SCM in new product development. First is a literature review which provides a deeper

explanation of the industry, with special attention to common industry characteristics, and a discussion of the strands of knowledge theory relevant to this research. The second literature review chapter reviews supply chain management literature and places it in the context of the branded ethical sector. The research methodology and methodological choices which governed the fieldwork and data collection phases is detailed in chapter four before the the three case study descriptions are presented in chapters five through seven. The penultimate chapter considers the themes which emerged in reviewing the case data and how the case study findings resonate with the literature. Finally, the concluding chapter summarizes the project and highlights its contributions to theory and practice.

Chapter 2: Pharmaceutical Industry Literature Review

This chapter, the first of two literature review chapters, is grounded in a thorough study of the ethical branded segment of the pharmaceutical industry and aims to provide a basic understanding of the setting for this research. After presenting an overview of the industry², the chapter concentrates on the two key up and downstream activities within pharmaceuticals that are at the center of this research: Research and Development (R&D) and supply chain management (SCM). R&D and SCM are heavily knowledge-based activities that impact multiple units involved in the drug development process. As such, the chapter also explicates pharma's characterization as a knowledge-intensive industry. Pharma's heavy reliance on knowledge prompts a consideration of the most applicable concepts from the knowledge management literature, including how knowledge impacts supply chains within this industry.

While the chapter is neatly divided into four sections, italicized statements appear in sections 2.1 and 2.2, denoting industry characteristics that were derived during the literature review. In developing an understanding of the industry, certain issues, challenges and pressures consistently recurred within the pharmaceutical industry literature; thus, they were collected and developed into a set of branded ethical pharmaceutical industry characteristics. This pharmaceutical industry literature review presents, explains and links a set of definitive industry characteristics to the industry literature; these characteristics, an outcome of the literature review, are a research contribution which factored into the case analysis process.

2.1 Pharmaceutical Industry Overview

Pharmaceuticals is one of the largest and most lucrative industries in the world, with annual sales exceeding \$400 billion (USD). The industry is well known for its size, power, profits, legendary marketing strategies, R&D pipelines, as well as its battles with the FDA, government and each

² The literature reviewed for this chapter focused on the branded ethical segment of the pharmaceutical industry; however, in keeping with conventions within the reviewed literature, "industry," "pharma," and "pharmaceutical industry" refer (interchangeably) to the branded ethical segment unless otherwise noted in the text.

other. As an industry with over a century of history, the industry says its focus is to “predict and prevent” disease (Saftlas 2003), improve quality of life, lower health care costs, reduce hospitalizations, and decrease disease complications (PhRMA 2003). It has been heavily criticized for relatively low research productivity, wasteful marketing, an out-dated business model, safety and regulatory mishaps, and above all, the high prices of its products. While drug companies cite the substantial cost of making drugs in defense of their high prices, Wall Street further aggravates the issue by placing intense pressure on the industry to maintain stock prices and produce greater earnings.

Today, however, it is an industry undergoing a major transformation. While historically the industry rejuvenated itself by developing premium priced breakthrough therapies, it appears as though the “pipelines” of forthcoming drugs, on which its future health depends, have been drying up for some time (“Fixing the drugs pipeline” 2004; Saftlas and Diller 2006; “Is Merck’s medicine working?” 2007). The industry faces numerous additional challenges, which include patent expirations; market erosion by generics; pricing constraints; pressure to globally expand to cost effective geographies, such as Asia; improve the integrity of its supply chain; and the constant need to satisfy demands placed on the industry by regulatory agencies in America, Europe and Asia.

2.1.1. Industry Structure and Strategy

The pharmaceutical market is essentially divided into two segments: Over the counter (OTC) drugs and prescription medication (also known as ethical pharmaceuticals). The biggest rival to ethical pharmaceuticals is the industry’s generic sector³. The industry’s lack of new products and private third-party payers’ policies against price increases also is cutting into industry growth and profitability (Saftlas and Diller 2006). In the generic sector, success depends on being cheap

³ Between 2006 and 2010, at least 70 brand name drugs are expected to go off patent in the U.S., 19 of these are blockbusters Saftlas, H. and W. Diller (2006). Healthcare: Pharmaceuticals. Industry Surveys, Standard and Poor’s 50.. Further, \$30 billion in patents will elapse by the end of 2007, which creates a pool of potential for the generics industry.

enough to keep manufacturing and other costs down, big enough to dominate distribution channels to wholesalers, and fast enough to move in and out of markets as opportunity ebbs and flows ("Combination therapy" 2005). Ethical pharmaceutical companies are beginning to pursue one of two strategies for dealing with the incursion by generics: they either launch their own generic unit, or partner with an established generic firm (Saftlas and Diller 2006).

The industry is more affected by the health of the world population than by changes in the global economy.

The pharmaceutical industry is more closely tied to worldwide health trends than economic ones. As such, growth is expected to continue due to an aging population, lengthening average life expectancy, and the rising incidence of chronic diseases. A shift in the industry's principal therapeutic areas reflects a change in global medical needs: in the 1990s, the focus was on heart disease, hypertension, gastric ulcers and antidepressants, but that focus has shifted to diabetes, obesity, oncology, and age-related macular degeneration (Diller 2006).

Economic opportunities in pharmaceuticals is inextricably linked to the progress of science.

Tied to advances and discoveries in disciplines such as biology, chemistry and anatomy, pharmaceutical industry practices have shifted to focus on the exploitation of knowledge from the external environment as the starting point for R&D (DeLong and Fahey 2000). Over the past decade, the industry rapidly grew into a complex mix of private and public resources-- looking to universities, other pharmaceutical companies and biotechnology firms as potential organizations for accessing knowledge and skills located beyond their boundaries. Universities are particularly good resources for basic scientific research on biological or physiological mechanisms. Further, some academic institutions (especially in the US) are heavily involved in patenting, which led to a proliferation of negotiations and agreements among public and private scientists becoming a key feature of the industry over the past 10 years (Quere 2003).

With a rapid pace of knowledge advancement, biotechnology has the most to offer pharmaceuticals in terms of new knowledge and new technological platforms for drug discovery

and development (Powell 1998; Quere 2003). This means most pharmaceutical firms look to develop, with varying degrees of success, both in-house capacity in the new science and a portfolio of collaboration with dedicated biotechnology firms (DBFs) (Powell 1998). Alliances with biotech companies have revitalized many pharmaceutical R&D programs. Historically, very few DBFs managed to become vertically integrated producers of marketable drug products, relying on maintaining their roles as collaborators or suppliers to large pharmaceutical corporations in order to achieve product commercialization. In turn, pharma firms eagerly pursue licensing or acquisition deals with smaller companies if it involves access to new and upcoming products (Arnst, Barrett et al. 2004).

A branded ethical pharmaceutical company typically does not possess internally all the capabilities necessary to produce a new product.

In the past, most pharmaceutical firm's internal functional units handled the entire product lifecycle, from raw materials (ideas) to international marketing and distribution. Thus, companies focused on maintaining control at every level of their business which not only risks stifling innovation, but it also leaves the firms with a vertically integrated model that no longer fits the industry (Simons 2005). In doing so, pharmaceutical firms encountered the problem of many classically vertically integrated companies: firms try to do too many things and are not good enough at any of them. To solve this issue, many firms or industries form networks and collaborate with other firms for mutual success (Brannback 2003). Thus, within the last decade pharmaceuticals has moved toward becoming a networked industry (Brannback 2003).

The industry's pursuit of strategic alliances, cooperative agreements or collaborative partnerships with biotechnology firms, academic start-ups or university labs contrasts with earlier aggressive merge and acquire strategies. During the 1990s, mergers and acquisitions were an essential means of obtaining drug pipeline innovations and assuming control of any major technological changes for the industry's bigger players (Quere 2003). Expensive M&A demonstrated firms' willingness to purchase scientific or technological knowledge not available

in house that could extend the reach of the firm's capabilities or generate new intellectual capital (Quere 2003; McKenzie 2005). This is not to say, however, that the industry discontinued acquisitions.

The increase in collaborative relationships and alliances not only reflects the industry's low research productivity, but also the realization that the industry's rapid pace is such that recent advances are not fully absorbed before more discoveries come along; it is no longer possible for a single company to hold (internally) all the capabilities necessary to remain at the top of the industry. Companies that fell out of the top tier of drug companies (Bristol-Myers Squibb, Abbott, and Wyeth) quickly switched their efforts away from blockbusters⁴ and focused on innovative therapies for targeted disease areas (Arnst, Barrett et al. 2004). While pharmaceutical firms have not reduced their operations to specializing in providing a single function, most have narrowed their focus to smaller, strategically vital sets of capabilities that reduce capital assets and overhead while streamlining the organization (Gottfredson, Puryear et al. 2005).

2.2 Pharmaceutical Research and Development

The pharmaceutical industry is driven by the success of its research and development programs to create new products. As such, the industry has a long history of viewing R&D as "the ivory tower" and organizing accordingly (Becker and Lillemark 2006); R&D always has been the locus of control in pharma (Jassawlla and Sashittal 2000). Notably, the geographic center of the industry's R&D activities has shifted from Europe to the US. Efforts by many EU countries to aggressively cut pharmaceutical spending and encourage the use of OTC medicines⁵, also lowered the industry's incentive to spend on R&D there (Diller 2006). This underscores the argument that in parts of the world where the government controls prescription drug prices, both

⁴ Analysts suggest that pharmaceutical firms need a new business model, one that is not heavily reliant on blockbuster drugs. The blockbuster is defined as a drug that reaches \$1b in annual sales in its second year on the market. They accounted for 45% of industry sales in 2001. Blockbusters recover R&D (and other) costs fairly early "Big trouble for big pharma; the drugs industry." (2003). *The Economist* 369(8353): 67.

⁵ OTC medications are generally not paid for, or reimbursed by national health systems.

innovation and patient access to innovation suffer (PhRMA 2004). With a difficult European market, many companies focus their attention on the more profitable, biotech-friendly US market for their R&D activities (Diller 2006). Pharmaceutical product development comprises one of the most research-intensive sectors in the United States, with more pharmaceutical-related research conducted in universities and public institutions than in Europe (PhRMA 2004).

2.2.1 The Mechanics of Product Development⁶

The pharmaceutical industry is characterized by exceedingly long timelines, high attrition rates, and high degrees of uncertainty in product development.

An oft-quoted pharmaceutical industry statistic maintains that it takes, on average, 10-15 years and more than \$800 million to get a new medicine to patients; compare this with the cost of developing a new drug in 1975: \$138 million (PhRMA 2004). Further, only three of 10 marketed drugs produce revenues that match or exceed R&D costs. It is difficult to make a new drug: the industry spent a total of \$51.3 billion on R&D in 2006 (PhRMA 2006); this same year, only six new significant drugs were approved (Saftlas and Diller 2006)⁷. Considering the amount of time and money required to get a drug to market, it is not surprising that the industry mantra is “fail early, fail cheap” (“Fixing the drugs pipeline” 2004). Effective management of drug development means making correct decisions to cease development of failures and accelerate development of winners as early as possible: drug development is a knowledge-based decision-making process (Koretz and Lee 1998).

In developing new drugs, there are more failures in developing new chemical entities (NCEs) than successes (Cardinal 2001). Researchers must rely on a set of *potential* available scientific procedures and processes that may lead to a viable drug.⁸ However, firms cannot, from the outset

⁶ Each case company provided product development descriptions specific to their firm, and these will be discussed in a later chapter and appendices.

⁷ According to PhRMA, in 2007, the industry spent \$55.2 billion on R&D and had 29 drugs approved by the FDA.

⁸ By comparison, less innovative research, on incremental innovations of already existing pharmaceutical products, is focused on routine and narrow processes and procedures, which thus involves less ambiguity

of a drug project, identify the specific processes that will result in a radical innovation. Thus, a researcher is allowed to use his/her discretion in choosing processes that may result in a new drug. Drug discovery researchers must rely on the use of open-ended research strategies, ongoing trial and error, subjective judgement, and continual re-evaluation of existing knowledge in light of new information uncovered (Turner and Makhija 2006). Experiments, in particular, are a crucial source of the data and information - scientists learn from doing new things or doing old things in new ways (Fahey and Prusak 1998). Thus, it is difficult, if not impossible, to predict when a scientist's mind will conceive an idea beyond the limits of current knowledge (Sorescu, Chandy et al. 2003).

Once a potentially treatable disease is chosen, a target molecule, usually a protein, has to be identified and then modified to produce the desired effect. Next, chemical compounds are made and tested against this target. The most promising of the "hits" are selected and optimized to suit a profile of "drug-like" properties. These optimized hits become "leads" that are tested, first in animal models of human disease and then, if all goes well, in humans. Only one in 1,000 compounds tested makes it into human trials, and only one in five of those emerges as a drug ("Fixing the drugs pipeline" 2004).

The product development cycle breaks down as follows:

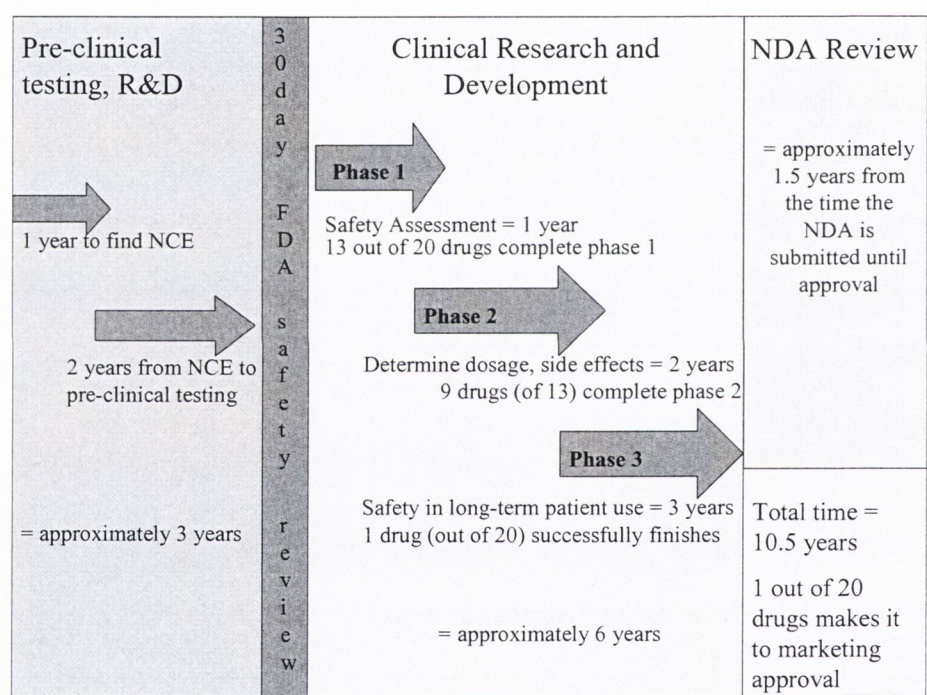
- Search for/discovery of new compound- 1 year to find an NCE
- NCE to pre-clinical testing (2yrs)
- Need approval from the FDA to proceed to clinical trials
- Phase I: Safety assessment (1year)
- Phase II: Assess effectiveness, dosage, side effects (2yrs)
- Phase III: Safety in long-term patient use (3yrs)
- Clinical trials end, FDA review (1.5yrs)
- When the clinical research on a drug is complete, companies submit a New Drug Application (NDA) to the FDA

and more certainty than when working with a new drug Cardinal, L. (2001). "Technological innovation in the pharmaceutical industry: The use of organizational control in managing research and development." Organization Science 12(1): 19-36..

Out of 20 drugs entering clinical testing, the FDA estimates that 13-14 drugs successfully complete Phase I. Of those, nine finish Phase II. Only one or two are likely to survive the rigors of Phase III. PhRMA (2006) reports that 50% of the drugs that reach phase III trials fail. In the end, only one in 20 is approved for marketing. When the FDA reviews a NDA, it looks to assess a product’s safety and effectiveness is demonstrated by well-controlled studies (PhRMA 2006).

Figure 1 (below) visually displays and summarizes the new product development cycle and indicates attrition rates during each phase.

Figure 2.1 New Drug Development



Adapted from www.fda.gov.

The industry was hoping to revolutionize the process of drug discovery by making the process more predictable and reliable through mapping the human genome. The initial sequencing of the human genome, however, failed to immediately live up to the industry’s expectations; more years of work and knowledge extending beyond the initial mapping phase would be needed (Lander March 9, 2007). Currently, the sequencing represents a “parts list” of genes whose connection with disease is still obscure. In order to profit from the human genome

project, the industry will need to combine old and new techniques, including a blend of physiology, pharmacology, and target-oriented chemistry on one hand, and genomics, molecular modeling and structural biology on the other ("Fixing the drugs pipeline" 2004).

The industry's existence depends upon patents.

Patents⁹ provide a major incentive for product development and innovation within the industry; without them, it would be difficult for the industry to survive. Weakening patents can stifle or slow innovation by making it hard to recoup the investments made to develop the product¹⁰ (PhRMA 2006). Patent extending techniques, termed "evergreening," include: introduction of new formulations (including fixed combinations), which are marketed heavily before the generic version of the drug is released; second-medical-use patents for drugs nearing the end of their basic patent life; repeated patent infringement suits, which trigger an automatic 24-30 month delay in processing of the generic product claims in Canada and the US; and collusion with generic manufacturers to keep products off the market ("An innovative challenge to the pharmaceutical industry" 2002; Henry 2002).

Pharmaceutical firms remain vigilant about the ticking time clock that overshadows the entire drug development process. Pharmaceutical companies receive patent protection for a newly discovered NCE for a period of 17-20 years from the NCE filing. In reality, however, the average effective patent life for a new drug is 11-12 years in the US, because significant portions of time pass before a drug is FDA approved (PhRMA 2006). The average effective patent life for most other (non-pharmaceutical industry) products is 18.5 years. Considering that a drug manufacturer's profitability depends upon how quickly a firm gets a drug to market, and that a

⁹ Two types of patents are issued for pharmaceuticals:

1. Process patent: patent is issued on the method of the drug's manufacture or synthesis
2. Use patent: lets patent holder manufacture and market the compound for a specific therapeutic purpose and prevents competitors from using the drug in the same way.

¹⁰ It is worth noting that on an international scale, the TRIPS (trade related aspects of intellectual property rights) agreement of the World Trade Organization (WTO) requires all members to adhere to minimum standards of intellectual property protection Subramanian, A. (2004). "Medicines, patents and TRIPS." *Finance and Development* 41(1): 22-25.. It establishes minimum international obligations for the protection of patented pharmaceutical products.

manufacturer can lose, on average, over \$1 million for each day's delay in gaining marketing approval from the FDA, it is important to satisfy regulatory requirements as soon as possible (Abraham 2002).

Pharmaceuticals is one of the most regulated industries in the world.

The industry has several masters from a regulatory standpoint: the US, Europe, and Japan. While the FDA monitors the industry in the US, the European Medicines Evaluation Agency (EMA) regulates the European industry, and the Ministry of Health, Labor, and Welfare supervises new drug approvals in Japan. The drug approval process moves much more slowly in Japan than in the US and Europe (Saftlas and Diller 2006). The regulatory environment in the EU has evolved in unifying the approval process so that the London-based EMA acts as a central clearing-house for drug applications; if approved, the EMA recommends the drug to the European Commission (EC), which grants European marketing authorization (Saftlas and Diller 2006). The EU drug approval procedures do not include refereeing drug cost. Drug costs are determined on a country-by-country basis and all EU countries employ some form of price regulation, determining price using therapeutic comparators or the price of products in other EU markets (Saftlas and Diller 2006).

Since receiving extensive public criticism for being too slow and too cautious in approving drugs, the FDA has streamlined its' drug approval system by reducing management, adopting new scientific techniques to improve the review process and adding a fast-track approval system for new drugs. However, in the wake of several drugs, such as Merck's Vioxx, being pulled from the market due to fatal side effects, the FDA was accused of being too hasty with drug approvals. In response, the FDA established the Office of Drug Safety in 2005 for the post-market surveillance of drugs (Saftlas and Diller 2006).¹¹ Notably, the EMA already had post-marketing

¹¹ Additionally, before the August 2007 recess, US Congress was drafting FDA legislation which would address long-term safety studies for approved drugs ("Transparency, strength at the FDA," Boston Globe, August 1, 2007.)

regulatory procedures in place, including a reauthorization process after five years on the market, and the power to demand additional studies in light of emerging safety or effectiveness concerns.

2.3 The Pharmaceutical Industry and Knowledge

The pharmaceutical industry is knowledge based, requiring integrated, specialized knowledge for R&D. The industry is a dynamic blend of both deep theoretical and practical knowledge; it essentially operates as a nexus between applied academic research, the health care sector, and the service sector. In its day-to-day activities, a pharmaceutical company acts as both a university and a hospital (Styhre, Ingelgard et al. 2001). Knowledge is the lifeblood of the pharmaceutical industry: drugs succeed or fail due to the success of the R&D process to turn knowledge into marketable products. Most profits in this industry are generated by two activities: developing new drugs and convincing doctors to prescribe them (Gadiesh and Gilbert 1998).

Innovative and technologically-oriented companies are governed by the rule that knowledge itself matters, and that knowing is a central task for everybody in the organization; knowledge is a resource that supports capabilities, activities and products (Helfat and Raubitschek 2000). The term “knowledge-intensive” applies to firms in which knowledge has more importance than other inputs (Swart and Kinnie 2003). Knowledge-intensive firms form the backbone of the pharmaceutical industry: most work is of an intellectual nature and well-educated, qualified employees form the major part of the workforce (Swart and Kinnie 2003). A key resource in knowledge-intensive firms is human capital or the intellectual material (i.e. knowledge, information, intellectual property and experience) that can be used to create wealth. New products are the manifestation of an organization’s knowledge, and its ability to combine knowledge from disparate areas such as marketing, R&D, and manufacturing (Dougherty, Barnard et al. 2004).

The beginning and ending of the drug development process relies upon the integration of functions between the start and finish points. The process depends upon a firm’s ability to

integrate knowledge from a variety of internal, external, local and global resources. In moving a drug to market, the integration of knowledge inside the firm- from R&D through to the supply chain- is critical. In making drugs, knowledge-intensive integrative practices and processes from a variety of specialized areas- biology, chemistry, physiology, and engineering- to name just a few, are involved.

2.3.1 The Knowledge-based View and Integration

Many argue that the essence of the firm, and the firm's organizational activities, depend upon its ability to create, transfer, assemble, integrate, and exploit knowledge assets (Cohen and Levinthal 1990; Grant 1996; Liebeskind 1996; Tsoukas 1996; Powell and Snellman 2004). Eisenhardt splits research on knowledge into four major streams: sourcing, internal transfer, external transfer and integration. The integration stream is most relevant to this dissertation. Grant posited that knowledge is the preeminent resource of the firm, and that the processes through which firms integrate knowledge are fundamental (Grant 1996).

The essence of organizations relies on their ability to integrate specialized knowledge (Eisenhardt and Santos 2002; Håkanson 2005). Firms are able to produce goods and services because they serve as an arena where knowledge is differentiated, intertwined, and reconfigured by multiple individuals possessing specialist knowledge (Grant 1996; Ingelgard, Roth et al. 2002). A firm must coordinate the efforts of many specialists so that specific, expert knowledge is integrated from multiple sources across disciplinary and functional boundaries. Organizational capabilities involve the integration of these multiple, and often specialized, knowledge bases (Grant 1996). The greater the scope of specialized knowledge integrated into a capability, the greater the difficulty faced by competitors in replicating that capability and the greater the competitive advantage (Grant 1996). Thus, knowledge integration, not knowledge itself, is the source of competitive advantage; resource and capability-based advantages are likely to derive from superior access to, and integration of, specialized knowledge (Grant 1996).

Innovation results from new combinations and configurations of specialized knowledge, or from extending a continuing core of capabilities across disciplinary and functional boundaries, more than from a constant creation of new capabilities (Schumpeter 1934; Grant 1996; Håkanson 2006). Organizations must develop mechanisms to apply integrated, specialized knowledge to new products and services (Eisenhardt and Santos 2002). Knowledge integration among organizational members is dependent upon the presence of common knowledge and language mechanisms to facilitate communication and understanding. Organizational culture (a form of common knowledge) also functions to facilitate knowledge integration within the company; common theories, beliefs and cognitive maps allow members of a community to transmit and receive codified knowledge as “information” (Håkanson 2006).

The challenge for product development teams is to access the breadth and depth of functional knowledge pertinent to the product and integrate that knowledge (Grant 1996). Internally, knowledge resources can be difficult to integrate because pharmaceutical firms have R&D centers and product-development teams scattered around the world. It is necessary to integrate knowledge from R&D centers in different locations so that centers do not remain confined to the thinking and technologies available in a single cluster. The probability of a successful innovation emerging from a group of people churning through the same existing cluster of knowledge is far less likely than that of an innovation being sparked when pieces of knowledge from diverse sources interact (Santos, Doz et al. 2004).

In the traditionally siloed pharmaceutical industry, the integration, expansion, or recombination of knowledge has been a struggle. Leading edge drug discovery requires the integration of knowledge across a wide range of complex and ever-changing disciplines and therapeutic classes that exist within firm boundaries, and the ability to access and integrate new knowledge from outside the organization (Henderson 1994; Henderson and Cockburn 1994). Organizations must disseminate knowledge to all parts of the firm involved in product innovation; ideally, the firm’s structure will maximize the movement of knowledge and allocation

of key knowledge resources through both formal and informal collaborative networks (Henderson and Cockburn 1994; Daghfous 2004).

Because pharmaceutical product development is information and knowledge-intensive work, firms that encourage and maintain an extensive flow of information across the boundaries between scientific disciplines and therapeutic classes within the firm will have significantly more productive drug discovery efforts (Henderson and Cockburn 1994). Furthermore, the nature of scientific knowledge in drug discovery means firms may develop unique disciplinary skills, or they might develop unique competences in particular disease areas (Henderson and Cockburn 1994). Thus, creating an environment or innovation chain within the firm which allows for internal and external knowledge spillovers across research projects that could positively impact productivity (Henderson and Cockburn 1994).

2.3.2 New Product Teams

Traditionally, the drug development process was split to accommodate different phases, from early screening phases to large multinational clinical trials, and each phase placed different demands on knowledge and competence (Ingelgard, Roth et al. 2002). This type of functional silo structure hinders communication, efficiency and the overall development process between the different stages and units that contribute to drug development (Koufteros, Vonderembse et al. 2001; Kirby 2003). To remedy this situation, product development teams integrate knowledge resources from different parts of the organization (Clark and Wheelwright 1992). Collaborations among various parts of the firm generate new and synergistic resource combinations because each source of expertise addresses a unique aspect of product development (Eisenhardt and Martin 2000).

Brown and Eisenhardt (1995) define cross-functional teams as those project groups with members from more than one functional area such as engineering, manufacturing or marketing. The benefits of a functionally diverse team revolve around the ability to increase the amount and variety of information available for product design (Brown and Eisenhardt 1995). Cross-

functional teams lead to an “integrated problem solving” approach, particularly because early involvement and increased information sharing means that different phases of product development can be worked on concurrently and downstream problems can be solved when they are still small and easy to fix (Brown and Eisenhardt 1995; Koufteros, Vonderembse et al. 2001). In addition, cross-functional teams permit the overlap of development phases, which can quicken the pace of product development; ultimately, a productive and efficient process means lower costs and thus, lower prices, which, in turn, should lead to greater product success (Brown and Eisenhardt 1995).

Cross-functional teams typically form the locus for effective product development routines which coordinate and overlap manufacturing, marketing, and design tasks during the course of the process (Eisenhardt and Martin 2000). Routines, or sequential patterns of interaction, also permit efficient integration of an individual’s specialized knowledge inputs for a particular project (Grant 1996). Routines, as well as a common language, create a system of signaling and responsiveness which develops between team members as a result of repetition and improvement (Grant 1996). Frequent and continuous communication among project members increases the information flow among team members, making it easier for team members to understand each other’s specialties and to coordinate project phases (Brown and Eisenhardt 1995).

Integrating knowledge can be particularly elusive in large, mature firms with strong functional groups, extensive specialization, large numbers of people, and multiple, ongoing operating pressures (Clark and Wheelwright 1992). In these organizations, product innovations can fail because all organizational members are not aware of the entire product development process. If people lack a consciousness regarding what they as a business, a function, or a firm can do and cannot do, they will fail to identify emerging needs (Dougherty, Barnard et al. 2004). This situation resonates with many firms in the pharmaceutical industry. A suggested remedy is heavy-weight project management: managers are senior in the organization, with primary influence over people in development efforts. The core team is dedicated and physically co-

located with the heavyweight project leader for the duration of the project (Clark and Wheelwright 1992).

While projects with dedicated teams are more successful (Bhuiyan, Thomson et al. 2006), sustaining teams is difficult in pharmaceuticals, as the development of medicine is a long process, taking sometimes up to ten years, which means that the same people rarely constitute a team throughout the life of a project. On a given project team, people are often the best source of expertise within a project team with stores of tacit knowledge, which is not as easy to generate, analyze and share as explicit knowledge (Ruggles 1998). Further complicating the team environment within pharmaceuticals is the creative, idea-generating R&D scientist or engineer who is innovative, technically well educated, and enjoys working on advanced problems, but as a “loner” (Roberts and Fusfeld 1981)- not exactly the most conducive profile for new product development teams.

The pharmaceutical industry, in most cases, has traditionally matched with Dougherty, Barnard and Dunne’s (2004) description of non-innovative firms, or Clark and Wheelwright’s (1992) functional team structure description¹². This leads to people having no sense of what others do, as responsibility is separate and handed off from one group to another, which reduces perspective, decreases the ability to see longer-term needs, and limits the extent of possible integration (Dougherty, Barnard et al. 2004). Since different parts of the innovation process happen at different times and in different places, knowledge recombinations remain within a function and do not permeate through the rest of the firm (Dougherty, Barnard et al. 2004). In contrast, and at the other end of the spectrum, are innovative organizations, which integrate, expand and recombine knowledge into new products, new product families, new abilities and processes, and new businesses. Innovation happens because the intersection of functions and

¹² People are grouped principally by discipline, each working under the direction of a specialized sub-function manager and senior functional manager.

knowledge systems are managed in terms of their contributions to innovation, not as “silos” or separate functions (Dougherty, Barnard et al. 2004).

2.4 The Pharmaceutical Supply Chain

Traditionally, the vertically integrated nature of the industry’s firms allowed pharmaceutical supply chains to remain virtually unchanged; firms have not had to continually assess and re-assess supply chain function and design. According to Shah (2004), a typical pharmaceutical supply chain consists of the following nodes:

- (i) Primary manufacturing (possibly including contractor sites): responsible for the production of the active ingredient (AI or API). Most complex pharmaceuticals are produced through multistage processes. Often multistage operations produce slow response times and are ultimately at fault for some of the poor supply chain metrics exhibited by this industry. Outsourcing to contract manufacturers for some of the active ingredient stages can also result in extended supply chain co-ordination problems.
- (ii) Secondary manufacturing (possibly including contractor sites): taking the active ingredient produced at the primary site and adding "excipient" inert materials along with further processing and packaging to produce the final products, usually in SKU form. The secondary manufacturing locations are often geographically separate from the primary manufacturing locations due to opportunities for tax and transfer price optimization within the enterprise. There are often many more secondary manufacturing sites than primary ones, serving local or regional markets.
- (iii) Market warehouses/distribution centres;
- (iv) Wholesalers; and
- (v) Retailers/hospitals.

The pharmaceutical industry possesses several traits which impact its supply chains: high levels of regulatory control; a knowledge-based industry in which raw materials are ideas; it does not have continuously changeable production lines; and the supply chain is integrally tied to knowledge-intensive drug discovery. These factors influence the supply chain, mainly in terms of superseding the traditional pressures that lead firms to develop their supply chains on operational, design and strategic levels (Connolly, Sullivan et al. 2005).

2.4.1 Operational-level Supply Chain Description

From an operations perspective, the most important metric for the industry to track and improve is overall supply chain cycle time. Poor supply chain metrics result from the multi-staged process that produces complex drugs (Shah 2004). Prioritizing improvements in manufacturing technology, which have not been considered a high priority to date, is one way of potentially shortening process cycle times (Shah 2004). Manufacturing methods for many drugs have not changed in decades, even though the benefits of improved manufacturing are well known: higher quality, higher compliance, improved operator safety, fewer lost batches, fewer deviations, shorter cycle times, and more data-driven decision making (Cini and Schneider 2004). The industry's reluctance to update manufacturing could be due to the fact that modernizing pharmaceutical manufacturing requires significant capital investment in new capabilities, expertise and equipment. This expense involves purchasing or updating not only production machinery, but also the accompanying information technology infrastructure to capture the data for analysis (Miller 2003).

There are significant regulatory costs involved with making changes in manufacturing processes, as every change must be authorized by the FDA. In addition to the time and financial costs, failure to get approval can lead to serious production delays and supply chain disruptions (Cini and Schneider 2004). The industry fears that the application of better manufacturing techniques will uncover problems with current processes that must be reported to the FDA, and subsequently resolved (Cini and Schneider 2004). Aware of industry concerns, the FDA has

attempted to alleviate the fear among manufacturers that introducing new manufacturing technologies will result in regulatory problems by encouraging and helping firms submit comparability protocols for manufacturing changes (Cini and Schneider 2004). Further, the FDA recognizes that outdated manufacturing systems and tools can block efforts to achieve high quality mass production of cutting-edge therapies (Wechsler 2004).

In an effort to better manage information flows, pharmaceutical firms adopted Manufacturing Execution Systems (MESs) to provide the interface between enterprise resource planning (ERP) systems and plant-floor control or distributed control systems (DCSs). ERP systems manage the business supply chain (i.e., demand forecasting and planning and strategic supply organizational planning) as well as the informational supply chain (facility management, control, and operational and materials planning), and match projected and actual orders (Russell 2004). The MES links the ERP system and DCS, to provide information to all parts of the pharmaceutical firm, which helps reduce compliance costs, improve overall product quality, and ensure that the correct processes are being followed (Russell 2004). It also helps to comply with FDA standards¹³ for guaranteeing the integrity of electronic records. MES eliminates paper, creates electronic batch records, and keeps all manufacturing process records on a database (Russell 2004).

2.4.2 Design-level Supply Chain Description

Some of the design-level issues plaguing the pharmaceutical industry's supply chain are tied to the long and arduous process of drug discovery. There is a limited ability to take advantage of a design for the supply chain approach, which synchronizes SCM decisions with product design decisions because of protracted and uncertain product development timelines. Firms find it difficult, if not impossible, to justify spending resources making downstream plans for a product that is not certain to receive marketing approval. Once there is a viable product from R&D, firms will do whatever it takes to get the product to market: the pharmaceutical supply chain is product driven. You cannot fit every drug into the same supply chain, like you can with computers,

¹³ FDA part 11.

which means that sometimes supply chains need to be created, or existing supply chains altered, in order to get a drug manufactured (NIBR 2005).

Another design-level issue, which also intersects with the operational and strategic levels, is designing a secure supply chain that guarantees the integrity of the industry's products. Pharmaceutical manufacturers are responsible for discovering or creating innovative methods to ensure the security of the drug supply (Schoneker 2005). Most current anti-counterfeiting measures involve packaging technologies such as holograms, inks, bar codes and RFID, but these are not guaranteed to protect the pharmaceutical supply chain. This is because drugs usually do not remain in original packaging; they are re-packaged in the pharmacy and elsewhere before reaching the final consumer (Schoneker 2005). The industry is currently considering the following technologies to prevent counterfeit drugs:

- Visual identification- unique colors, shapes, sizes and logos;
- Electronic identification- bar coding;
- Chemical identification- edible markers in the film coating; and
- Sensory identification- flavours or aromas with a unique profile (Schoneker 2005)

These solutions all provide on-tablet technologies that will make pills difficult to fake, but easy to identify; they are also cost-efficient and stay with the medication from the factory to the patient (Schoneker 2005).

2.4.3 Strategic-level Supply Chain Description

For the pharmaceutical industry, the strategic level of SCM is particularly relevant, as pharmaceutical firms regard minimizing a product's time to market and maximizing profit and return on investment in intellectual capital as a key organizational strategic objective (Malek and Breggar 2001). As with the design level, many of pharma's strategic level supply chain issues are linked to the R&D process because it significantly impacts downstream capacity and planning issues. For the most part, capacity issues often are not considered at the development stage,

because of the uncertainty drug companies face with FDA approvals, and as such, construction or re-purposing of manufacturing facilities (an expensive investment) begins late in the R&D phase (PhRMA 2006).

Adopting a perspective that manages the innovation and development processes through to capacity and production planning would help speed supply chain cycle times (Shah 2004). It may, however, be easier to do this with line extensions or “me-too” drugs, as opposed to completely new discoveries. Another strategic level idea includes replacing the separate functional units for each stage of the drug development process with a more decentralized organizational model based on discrete business units (Bain 2003). Furthermore, standard management practices, such as consolidating procurement, outsourcing personnel and finance functions, and automating transaction processing all compare poorly with other industries—pharma could stand to make some strategic gains here (“Big trouble for big pharma; the drugs industry” 2003).

In an effort to move towards a global supply chain management process that generates value for the customer and the shareholder, many pharmaceutical companies divested the excess capacity that was created by having many local manufacturing sites (Shah 2004). The next global trend may involve switching some production to low-cost countries (Scott 2004). For a long time, most Western companies felt that the lower prices in India and China (as much as 50% less) were not worth the reliability and quality problems or intellectual property violations. Attitudes seemed to shift after 2005, once India began enforcing all international patent protection laws, including pharmaceutical patents, under WTO regulations (Kripalani and Sager 2004). Now, big pharmaceutical firms (i.e. Pfizer, GSK, Novartis) have tapped into India’s research and manufacturing prowess to cut costs and speed development of new drugs (Scott 2004). Finally, firms may consider the value of contracting some of their manufacturing, as many firms still make pills in-house. In a similar vein, firms could improve the clinical trial process through

outsourcing their trials to Contract Research Organizations (CROs) or conducting e-trials which allow electronic monitoring and collection of data from trial participants (Scott 2004).

2.4.4 Strategic SC Design and Knowledge

From a SCM perspective, the strategic design of the pharmaceutical supply chain extends to pipeline and development management, which involves the selection of potential drugs to develop further, and planning development activities through introduction in pilot plants (Shah 2004). Due to the vertically integrated nature of the industry, this strategic design issue depends upon the firm's ability to manage the organizational knowledge surrounding drug development. Coordinated information flows and efficient knowledge exchanges between participants impact successful supply chain development (Ketchen and Guinipero 2004). The knowledge relationships involved in supply chain design continually experience disintegration and reintegration; this is reflected particularly in the shuffling of structural, technological, financial and human assets (Fine, Vardan et al. 2002). This shuffling process is most fluid in R&D, while in manufacturing, firms are locked into suppliers primarily because suppliers have received FDA approval and passed the firm's quality assessment¹⁴ (Pfizer 2005). In R&D, scientists frequently move to different teams, and projects are deemed failures as early as possible, to facilitate a reallocation of money and talent.

In pharmaceuticals, the flow of knowledge is most significant; although SCM is organized around technology and relationships, it is the application of knowledge across the supply chain that holds it all together (Connolly, Sullivan et al. 2005). This requires that the pharmaceutical organization know what information it has, where that information is, and what information it needs. In terms of knowledge flows, the pharmaceutical industry reoriented itself during the 1990s so that individual firms became more adept at generating knowledge based on external and internal resources and rapidly moved it across both inter and intra firm boundaries (Quere 2003).

¹⁴ Quality assessment can take up to six months.

Most firms, however, emphasized inter-organizational partnerships that support the acquisition of external knowledge for the drug development chain (Grant and Baden-Fuller 1995; Grant 1999). As new knowledge arises from the external, complex networks of cooperation and affiliation, the chain adjusts to exploit emerging knowledge bases that complement their current knowledge capabilities and generate new knowledge (Powell 1998; Quere 2003). Focusing on collecting and integrating external knowledge that fed into the drug pipeline (Argote, McEvily et al. 2003) was perhaps to the detriment of facilitating internal knowledge flows that would affect strategic supply chain design.

Because the pharmaceutical supply chain is inextricably tied to the drug discovery process that begins in R&D and is supported by knowledge, firms must possess the ability to bridge internal knowledge boundaries between organizational units (Argote, McEvily et al. 2003; Edwards and Kidd 2003). R&D and manufacturing conduct knowledge-based activities that impact multiple units involved in the drug development process. Effective and efficient interaction between R&D and production means improved knowledge flow among internal, cross-functional activities, such as between the drug discovery/development chain¹⁵ and the manufacturing chain (Daghfous 2004). While successful management of internal operations and supply chains is a key challenge to organizations (Daghfous 2004), to maximize product innovation it is imperative that knowledge-based activities located up and downstream work collaboratively, (not as silos, separate functions or within functional team structures) to communicate knowledge to all parts of the firm involved in creating the new product (Daghfous 2004).

Strategic supply chain design is an opportunity for a firm's internal pieces to interact efficiently and facilitate decision-making (Power 2005). This is particularly important given the current shape and speed of the pharmaceutical industry; the only constant factor in the industry at the moment is change. If firms fail to effectively manage the knowledge surrounding drug

¹⁵ This chain is coordinated by a firm's Research and Development (R&D) unit.

development, the drug is unable to leave the drug development chain, located primarily within R&D, and move to the drug production chain, housed in worldwide factories. Pharmaceutical strategic supply chain design plays a key role in moving a drug along this development path, and provides opportunities to cut product development cycle time by carrying out development tasks in less time, without sacrificing quality or eliminating steps (Hong, Doll et al. 2004). This is crucial in an industry in which time to market is one of the most important factors and where firms consistently and actively look for ways to reduce product development cycle time and maximize their R&D investments (Hong, Doll et al. 2004).

2.5 Summary

In considering the setting and context for this research, the branded ethical pharmaceutical industry shares a number of commonalities; this chapter identified and described six in particular, which are summarized in the list below:

- The industry is more affected by the health of the world population than by changes in the global economy.
- Economic opportunities in pharmaceuticals is inextricably linked to the progress of science.
- A branded ethical pharmaceutical company typically does not possess internally all the capabilities necessary to produce a new product.
- The pharmaceutical industry is characterized by exceedingly long timelines, high attrition rates, and high degrees of uncertainty in product development.
- The industry's existence depends upon patents.
- Pharmaceuticals is one of the most regulated industries in the world.

These insights are particularly relevant in light of the empirical research conducted at pharmaceutical firms and presented later in this dissertation. Not only are these characteristics apparent within the industry literature, but also they manifest themselves in practice, in the case descriptions in chapters 5-7.

In addition to explicating how the industry works, this chapter also established pharma's reliance upon knowledge. While the knowledge-intensive nature of pharmaceutical firms is not exclusive to this industry (i.e. software and biotechnology are examples of other knowledge-intensive industries), pharmaceutical firms require integrated and specialized R&D to maintain

their pipelines and produce new, innovative therapies. Because integrating knowledge in large, global and (traditionally) functionally siloed firms, is a significant challenge for pharma, the industry tends to rely on internal and external collaboration networks as well as cross-functional product development teams to combine knowledge resources.

Finally, the chapter explains that given the changing industry environment, it is becoming increasingly difficult for pharma firms to ignore their product-driven supply chains that are inextricably linked to, and dependent upon, upstream R&D activities. Remediating pharma's supply chain issues may involve mechanisms and strategies that differ from those employed by other industries or suggested within the management literature because of the nature of the industry's products, which relates to common industry characteristics outlined herein.

The following chapter will move the literature review forward with a more in-depth discussion of supply chain management, which adds to this chapter's discussion of SCM in the pharmaceutical industry.

Chapter 3: Supply Chain Management Literature Review

While the previous chapter gave an overview of an industry that traces its origins to the middle of the 19th century, this chapter focuses on a sections of management literature which have emerged only within the past 20 years (Cousins, Lawson et al. 2006). The field of supply chain management is relatively new and has been recently described as a “developing” discipline, lacking the coherence and depth to call SCM a discipline in its own right (Cousins, Lawson et al. 2006). The coverage of SCM in operations management, as well as in the broader management publications reveals SCM is connected to a “range of academic disciplines and diverse theoretical perspectives” (Cousins, Lawson et al. 2006). Understanding downstream activities and designing the downstream aspect of this study depended upon reviewing the body of supply chain management literature and the development of lean manufacturing practices.

3.2 Supply Chain Management

Much of the research regarding SCM has been confined, for the most part, to the operations and production area; the operations perspective is often characterized as an algorithm-oriented approach¹⁶ (Otto and Kotzab 2003). Operational and technological issues are well covered in production-oriented journals (business and research), particularly in terms of anecdotal profiles of high profile, well-known corporate examples (for example, Benetton, Dell, Wal-Mart), and related technologies, systems and processes used in SCM (such as EDI, intranets, ERP, e-business, etc.). To this end, firms have been operationally obsessed with creating more efficient supply chains that operate at rapid speeds. However, there has been significantly less theoretical exploration of SCM in terms of its strategic or design levels, in the management and strategic research journals; coincidentally, it is these two levels that hold the most promise for pharmaceuticals.

Generally, previous research looked at the different processes within manufacturing supply chains individually, but lately, there appeared an increased interest in the supply chain as a whole.

¹⁶ SCM has to configure a resource network and to program the flows within the configuration according to a specific objective function based on algorithms (Otto and Kotzab, 2003).

Although there are models for characterizing certain aspects of supply chains (i.e. (Voss, Tsikriktsis et al. 2002; Cigolini, Cozzi et al. 2004), there are no theoretical constructs or frameworks that place SCM in a 'wider context' that allows for the necessary links to a more general understanding (Mattsson 2003) or a 'coherent' evolution of the discipline (Croom, Romano et al. 2000). This lack of theoretical constructs and frameworks is important because it ensures that SCM remains an operational issue, which limits the potential for understanding how SCM interacts with other management and business phenomenon. In the meantime, research inquiries in the field of SCM, once an area considered only a minor concern to managers, forced SCM into a higher priority position within organizations, and moved it to the forefront of business planning (Mangan and Christopher 2005).

3.2.1 Defining the Supply Chain

In general, a supply chain can be defined as an integrated manufacturing process wherein raw materials are converted into final products, then delivered to customers (Beamon 1998). It can also be described as a complex, dynamic system or as a network of flows of information and goods (Simchi-Levy and Simchi-Levy 2003); the supply chain is normally characterized by a forward flow of materials and a backward flow of information (Beamon 1998). Supply chain management is supposed to connect value chain participants in an efficient network of relationships and transactions that can reduce costs, improve customer service, develop the organization's knowledge base, increase efficiency within the organization, and create barriers to entry for competing organizations (Fisher 1997; Simchi-Levy and Simchi-Levy 2003).

Whereas pre-SCM days discuss transfer, the essence of SCM is integration; SCM theory suggests the management of integration as a tenet (Mouritsen, Skjott-Larsen et al. 2003; Kotzab and Otto 2004). SCM requires that the organization be structured in such a way that information, material and financial flows are efficiently integrated into the operational units of the supply chain (Fisher 1997). Transfer, as opposed to integration, harks back to the days of silos and "over the wall" mindsets; a time in which conventional supply chains were developed from the factory

outwards (Aitken, Childerhouse et al. 2005). Silos or functional boundaries also signify a situation in which no one within the firm has complete knowledge of the process, including management (Thomas and Griffin 1996).

3.2.2 Framework for SCM¹⁷

To be successful, SCM needs to be integrated throughout all levels of an organization (Fine 1998; Deloitte 2003; Simchi-Levy and Simchi-Levy 2003; Deloitte 2005). Given that this is the case, one characterization of SCM accounts for three different aspects of SCM, which can be characterized as operational, design and strategy (Fisher 1997; Simchi-Levy and Simchi-Levy 2003; Vonderembse, Uppal et al. 2006). These three levels are differentiated as follows¹⁸:

- Operational: the integration of information, material and financial flows;
- Design: design of the interactions of the processes involved in creating the good or service from development to final destination; and
- Strategic: aligning the supply chain with the overarching objectives of the organization, reflecting both the dynamics of the organization's supply chain and the industry supply chain as a whole.

Many journal articles attest to the significance of the operational level, which includes the operational structures of the firm, paralleling the structures side of Fenton and Pettigrew's (2000) organization design model. It also includes production, aligning it with what Fine (1998: 202) refers to as "product competence... (being) ... sure that the final product works and performs adequately". Finally, it includes any planned activity that is intrinsic to the functioning of the organization, which is consistent with the management level of Denison's value-chain process model (Denison 1997). In practical terms, it covers the daily operations of the organization, including inventory management, production, planning and scheduling, as well as improved

¹⁷ From published work.

¹⁸ These levels have been variously characterized as Behavioural, Planning & Control, and Operational Closs, D. J. and D. A. Mollenkopf (2004). "A global supply chain framework." *Industrial Marketing Management* 33(1): 37.; Strategic, Tactical and Operational Narasimhan, R. and S. Mahapatra (2004). "Decision models in global supply chain management." *Industrial Marketing Management* 33: 21-27.; Strategic, Coordination and Operations Johnston, S. J. (2004). What Drives The Supply Chain? *HBS Working Knowledge*.; and Strategic, Design and Operational Huan, S. H., S. K. Sheoran, et al. (2004). "A review and analysis of the supply chain operations reference (SCOR) model." *Supply Chain Management* 9(1): 23-29.. This research stays with Huan's nomenclature, but draws on a range of the above and other writings to characterize the levels.

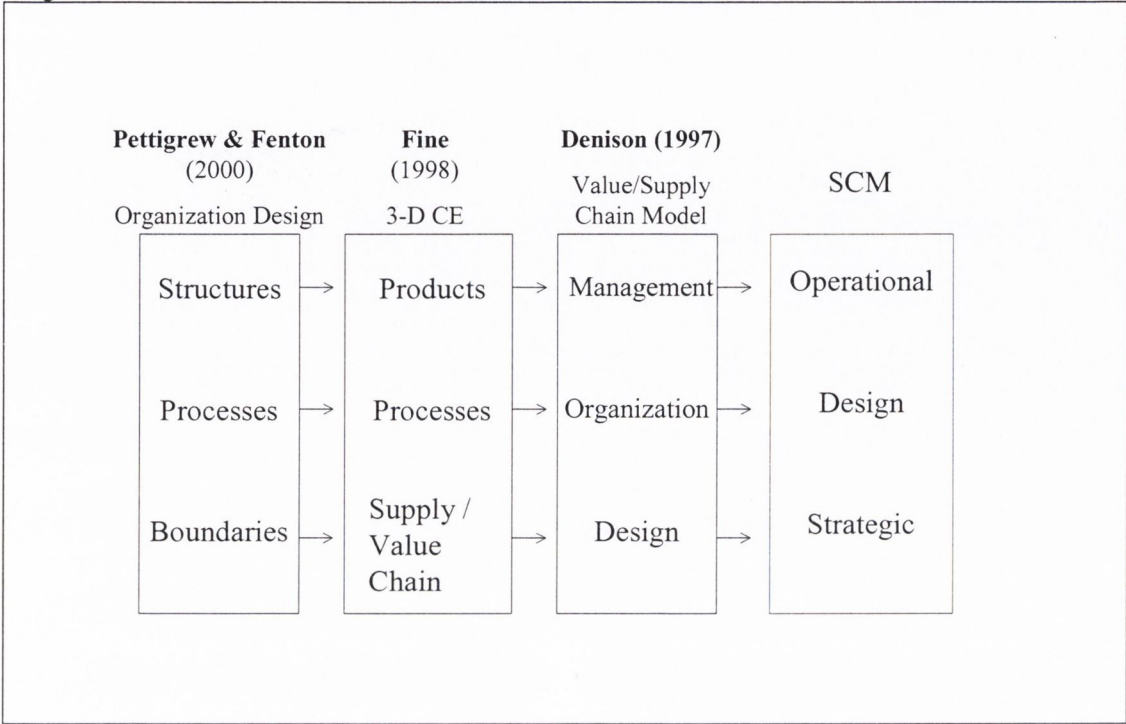
manufacturing methods (Huan, Sheoran et al. 2004). Bringing products to market and effective commercialization of products requires efficiencies at the operational level (Poh-Kam 2000).

The design level seeks to devise a supply chain that will balance and optimize an organization's strategic objectives with its operating realities. Thus, design includes the processes used by the organization to achieve its goals, and reflects "...a provider's execution capabilities and the design of its...processes" (Fine 1998). Fenton and Pettigrew (2000) also emphasize the importance of process in shaping the structures of the organization. Denison (1997) notes that the design of the value chain- the processes - is the manifestation of the organization's strategy. Synchronizing SCM decisions with product design decisions constitutes a "design for the supply chain" approach (Forza and Rungtusanatham 2005). The design aspect of SCM overlaps with, and can be difficult to isolate from, the operational and strategic aspects.

The strategic level addresses the overall planning used by an organization to identify and reach its objectives and thus focuses on the most fundamental aspects of a firm: who it is and what it does. As such, many SCM strategies will adapt to the characteristics of each business (Cigolini, Cozzi et al. 2004). Strategy encompasses the notion of boundaries (Fenton and Pettigrew 2000), as well as Fine (Fine 1998) and Denison's (Denison 1997) concept of supply / value chain design and management as the core competence of the firm. Devising an SCM strategy must consider the nature of demand for a company's products; other important aspects include product lifecycle, demand predictability, product variety and market standards for lead-time and service. A key strategic problem is the mismatch between product type and supply chain type ("Supply chain challenges: Building relationships" 2003).

Figure 3.1 summarizes and synthesizes the relationships between the above models and aspects of SCM. In addition to aligning with the Pettigrew and Fenton (2000), Fine (1998) and Denison (1997) models, this framework also aligns with the levels of fit between supply chain and strategic management (Cavinato 1999).

Figure 3.1 SCM Evaluative Framework



These levels are particularly relevant to considering the design and strategic levels of SCM in the pharmaceutical industry, and the lack of traditional pressures to excel at the operational level in this industry.

3.2.3 Leveraging Knowledge in SCM

Knowledge based theory (KBT) brings many useful concepts to the understanding of SCM, particularly when considering the three framework levels. Managing knowledge up and downstream within the supply chain supports operational-level manufacturing agility (Kidd 2003). Knowledge management and supply chain management are at a crossroads in many industries, as both provide strategies for reducing costs and cycle times (Desouza, Chattaraj et al. 2003; Burgess, Singh et al. 2006). Firms are struggling with using knowledge to reduce uncertainty and critical information delays at the design level (Mason-Jones and Towhill 1997).

Synergies exist between supply chains and knowledge management: in order to achieve supply chain optimization, all elements of the supply chain must be connected to enable the flow

of knowledge (Desouza, Chattaraj et al. 2003). The notion of knowledge flows suggests that knowledge is in constant flux and change. It is central to day-to-day activities. Individuals create it and it is largely self-generating. Moreover, it connects, binds, and involves individuals (Fahey and Prusak 1998). Knowledge flow networks wind through and across organizations; optimally structured flows between knowledge seekers and knowledge providers maximize the impact of knowledge (Holtshouse 1998), so that knowledge flows reach the right people at the right time (Pablos 2004). Treating the supply chain as a bundle of knowledge relationships makes it easier to determine which knowledge sets and knowledge gaps are critical to decisions affecting the flows of product and returns in the chain (Heron, Penny et al. 2001; Ketchen and Hult 2007).

A successful supply chain reflects coordinated information flows and efficient knowledge exchanges between participants (Ketchen and Guinipero 2004). Creating a balanced knowledge flow requires connectivity and communication (of knowledge), to allow all users in the supply chain to make business decisions that maximize customer value while reducing costs and cycle times. Facilitating knowledge flow also demands developing an environment with the social, cultural and technical processes that encourages the expansion, transfer and use of knowledge (Holtshouse 1998; Miles, Miles et al. 1998). In attempting to manage knowledge up and downstream in the supply chain, the organization must understand the need to share knowledge with others in the supply chain (Kidd 2003), because it is intellectual capital, or knowledge, that is the source of innovation (Warnock, Carpenter et al. 1998).

Inter-organizational relationships are particularly well suited to knowledge integration and transfer to support supply chains, especially when the necessary knowledge cannot be embedded within the product (Grant and Baden-Fuller 1995; Grant 1999). According to Lang (2001), the best companies formed industry-wide collaborative networks with their supply chain partners. In building collaborative supply chain networks, organizations must realize that two other key features of supply chains are competition and co-operation; each party must co-operate or the chain will not function, yet each is in competition with others to gain a greater share of the value

generated by the chain (Heron, Penny et al. 2001; Lang 2001). Thus, firms must remain aware of the tenuous balance of power within their supply chains.

To help maintain a balance within the supply chain, firms are often able to “lock-in” suppliers because they can help them “learn how to learn” (Bates and Slack 1998). Possessing knowledge or information can create dependence between firms within the supply chain. Successful knowledge exchange with large suppliers enriches and can improve technical or market knowledge. Technical knowledge exchange concerning manufacturing processes seems richer and likely more sustainable than market knowledge (Bates and Slack 1998). Enhanced technical or market knowledge within a small company can be instrumental in winning the business of a large supplier, particularly if this knowledge increases competitiveness (Bates and Slack 1998). Superior management of supply chain activities ultimately spills over to affect performance or quality of a company’s end product, thus improving profitability (Thompson, Strickland et al. 2004).

For firms to use the supply chain as a viable global resource positively impacting the firm’s bottom line and leading to strategic and competitive advantages, supply chains must become and remain dynamic (Rao 1999; Lancioni, Schau et al. 2003). Executives need to realize that their edge relies on more efficiently transferring knowledge across their organizations, thus creating value through internal knowledge transfers and changing the linear value chain (Warnock, Carpenter et al. 1998; Sveiby 2000). Potentially, this value chain can lower the costs of transferring tacit knowledge and problem solving abilities (Heiman and Nickerson 2002). These benefits- greater access to knowledge, at lower cost- makes pursuing SCM imperative for an industry experiencing significant changes (i.e., pharmaceuticals).

3.2.4 Creating Successful, Competitive Supply Chains (at the operational level)

With SCM becoming critically important to competitive positioning and the operational level of SCM taking precedence over the strategic and design levels, firms have often attempted to gain long-term competitive advantages through operational level strategies for improving their supply

chains (Tracey, Lim et al. 2005; Ketchen and Hult 2007). Many successful companies, like Wal-Mart, Dell and Toyota, have rewritten the rules of competition through the organization of their supply chains and achieved positive results ("Chain reaction: The logistics revolution" 2006). Firms are moving towards more coordinated, integrated design and control of all of their components in order to provide goods and services at low cost and high levels of service (Thomas and Griffin 1996).

Long supply chains can inhibit a firm's ability to respond quickly to consumer requirements and decrease competitiveness (Thomas and Griffin 1996). In many industries, product life cycles are very short, and long supply chains pose a high risk of inventory obsolescence. For this reason, supply chain models must consider life cycle constraints and costs (Thomas and Griffin 1996). Additionally, better coordination and control in SCM will accommodate shorter pipelines, reduce supply chain lead time, and keep production closer to the design and market bases (Cigolini, Cozzi et al. 2004). Here, qualitative performance measures include customer satisfaction, supplier performance, and the degree of information and material flow integration¹⁹ (Beamon 1998).

Successful supply chain characteristics include: communication within the organization; executive support for supply chain managers and processes; information systems for data collection, analysis and sharing; and measurement systems to assess total supply chain costs and performance (McKone-Sweet, Hamilton et al. 2005). For excellent firms, "doing it right the first time" is important, although service failures can provide valuable and easy sources of information to improve services, diagnose and resolve problems, and to avoid future problems (Morash 2001). The successful supply chain manager will draw from best practices in other sectors, possess an understanding of supply chain drivers, and engage in strategic thinking that influences the organization (McKone-Sweet, Hamilton et al. 2005). To achieve any measure of supply chain

¹⁹ The extent to which all functions within the supply chain communicate information and transport materials.

success, three critical elements- people, processes and technology- need to be balanced (Mangan and Christopher 2005).

While one school of thought believes the right software can replace people, another school believes worst practice is equating technology with the supply chain. The idea that “I buy technology, so I’ve got a great supply chain,” is nonsense. Innovation comes down to the people, the tools and what value senior management places on it (Kirby 2003). Information technology is, however, an important enabler for flexible and integrative supply chain practices (Morash 2001). Poor quality data will increase supply chain complexity (Thomas and Griffin 1996).

Within the literature, avoiding the consequences of long supply chains and ensuring competitive, successful supply chains, often means creating lean and/or agile supply chains. A lean supply chain employs continuous improvement efforts that focus on eliminating waste or non-value steps along the chain (Vonderembse, Uppal et al. 2006). An agile supply chain involves responding to rapidly changing, and continually fragmenting, global markets and moving information faster to make better decisions (Vonderembse, Uppal et al. 2006). In situations where demand cannot be forecasted with any degree of accuracy, agility is critical (Aitken, Childerhouse et al. 2005). In lean chains, operating costs and efficiency as well as quality and reliability are essential while agile chains focus more on innovation, speed, and flexibility. Lean supply chains continuously seek perfection and operational efficiencies (i.e. reduced cycle times) (Morash 2001). Quality and reliability remain significant in an agile setting, but operating cost and efficiency are overshadowed by customer demand for new, innovative, and application-specific solutions (Vonderembse, Uppal et al. 2006).

3.2.5 SCM and Firm Activities (at the design and strategic level)

It has been established that traditionally, management literature regarding SCM has been operationally focused, specifically on determining optimal input and output rates for inventory, production and distribution (Vachon and Klassen 2006). It is a mistake, however, for businesses to think that SCM is limited to inventory control, purchasing and order fulfillment (Horvath

2001); focusing only on these operational-level, or logistics issues, disregards other interfacing processes, or design and strategic level concerns, such as new product development (Cigolini, Cozzi et al. 2004) . Recent management literature has taken a more conceptual view in suggesting SCM should interact with a firm's upstream activities: the process of designing and developing products is linked to other areas of the business, such as manufacturing, marketing, and SCM (Singhal and Singhal 2002). SCM must include all processes from product generation through to end-of-life recycling and disposal; this includes product design, introduction, promotion, fulfillment, and product lifecycle management (Kopczak and Johnson 2003).

What is particularly relevant to this dissertation is the ability to think more generally about SCM and its relation to upstream activities. Even though the majority of SCM strategies concentrate on the operations side of the enterprise, with minimal participation and involvement in product development, the literature has established interdependencies between product development and SCM. Insight regarding how established design and manufacturing departments coordinate their activities is lacking however, which suggests the need to figure out how to manage the supply chain interface, and how actions taken in one area might affect the performance of the whole (Twigg 2002).

Some management and logistics literature suggested that that the nature of competition was changing so that supply chains were competing against each other (as opposed to companies) and that organizations should view an entire value chain as one competing entity (Lang 2001). This view shifted slightly to stipulate that companies need not just one supply chain solution, but many solutions. Further, companies should match the design of their supply chains to product and market characteristics, as designing and managing multiple pipelines will become a necessary competence in the search for competitive advantage (Aitken, Childerhouse et al. 2005).

Three-dimensional concurrent engineering (3D-CE) is the result of attempting to incorporate supply chain considerations with earlier upstream phases; it aims for the simultaneous and coordinated design of products, manufacturing processes, and supply chains (Koufteros,

Vonderembse et al. 2001; Forza and Rungtusanatham 2005). Fine described the “three-dimensional concurrent engineering challenge” as a company’s desire to create a new product, a new process to manufacture it, and a new supply chain to feed that process and distribute the product (Fine 2000). He argues that firms cannot achieve improved manufacturing performance solely, or even primarily, by concentrating on the factory; they must also focus on concurrently designing the product and the manufacturing process (Fine 2000). Further, he is convinced that the strategic nature of supply chain design compels its integration with product and process development (Fine 2000). The three processes interact with one another to produce an integrated supply chain that works as a unit to meet the required performance objectives (Beamon 1998).

Upstream processes are as critical as downstream ones in creating benefits for the entire chain; this includes reduced costs and conceiving of processes and flows on a larger scale, as opposed to being confined to a mentality that focuses on specific functions (Balasubramanian 2001; Mangan and Christopher 2005; Tracey, Lim et al. 2005). The basis of integration is about managing integrated chains of processes, not individual functional processes (Power 2005). Silo structures can threaten the survival of the entire chain; the whole must become more than the sum of its parts (Min and Overby 2001; Power 2005). Identifying and managing internal functional relationships and coordinating product design activities to speed up business processes make up key components of the interface between product development and SCM (Hult 2003). As firms learn to co-develop products and processes more frequently, they begin to avoid costly mistakes in both time and quality (Koufteros, Vonderembse et al. 2001).

Relationship management, including directing transitions and creating alliances between internal silos, is important to achieving internal integration ("Supply chain challenges: Building relationships" 2003). Increasingly, innovators must integrate a number of interdependencies among product development decisions, concurrently addressing customer needs/values, product technical specifications, and supply chain capabilities (Swink 2006). SCM is based on the

concept that integration across business operations is essential to customer satisfaction, value creation, and exceptional returns (Tracey, Lim et al. 2005).

Collaboration on product development projects should begin early in development phases and reach deep into each function that holds a stake in the success of the project (Swink 2006). This inherently involves recognizing the interdependent nature of product and process design specifications and making it a high priority. Early collaborations between logistics and design positively impact manufacturing enterprises (Vonderembse, Uppal et al. 2006). Collaborative new product process development includes representatives from important parts of the supply chain as full partners on design-build-support teams. A team approach during product development results in better planning, a faster response to unanticipated changes from suppliers, and fewer costly late-stage changes (Vonderembse, Uppal et al. 2006).

Organizationally, this team approach coincides with a shift in business practice from a vertical to a horizontal orientation. Collaborative efforts reach across disciplines, functions, product generations and other product families within the enterprise to consolidate expert knowledge regarding product and process technologies (Swink 2006). The horizontal shift centered on manufacturing, driven by the desire to shed assets, reduce costs, and improve flexibility (Downey, Greenberg et al. 2003). Consequently, vertically integrated supply chains have become increasingly rare. In the horizontal organization, leaders must provide a common process focus, direct different functional skills, and communicate across functions to coordinate SCM; this aligns the interests of functional groups and multiple partners so that projects move forward in unison (Kirby 2003; Mangan and Christopher 2005).

Haque proposes that the solution to some problems hinges on considering supply chain issues at a very early stage of the design, so that all parties are aware of the requirements and constraints. Designers need to recognize the impact of their decisions on the management and design of the supply chain (Haque 2003). Integrated strategies help companies tackle upstream R&D problems such as insufficient speed, inadequate yield, waste and rapidly shifting markets

(Downey, Greenberg et al. 2003). Proponents of lean and agile supply chains discuss the benefits of integrating suppliers by involving them in product design, and in some cases making them responsible for the design of components and systems that decrease product development time (Vonderembse, Uppal et al. 2006). Tasking selected suppliers to meet technical and business performance objectives as part of new product process development provides an opportunity to align decisions across product design, the manufacturing process, and the supply chain (Forza, Rungtusanatham et al. 2005).

3.3 Summary

This chapter reviews some of the relevant literature on supply chain management. It considers the definition of SCM and synthesizes multiple SCM models to produce one framework for thinking about SCM on an organizational basis, as opposed to from a purely (and more traditional) operations perspective. The chapter also addresses how knowledge connects to SCM as well as how SCM relates to firm activities, both of which are potentially significant factors in considering how R&D works with SCM. Thus far, the literature review chapters have endeavored to establish how the pharmaceutical industry operates and what the management literature has to offer the industry in terms of knowledge theory and supply chain management. The next chapter discusses the methodology employed to examine R&D and SCM within the pharmaceutical industry.

Chapter 4: Methodology

The development of the qualitative case research for this study was iterative progression or evolution. The literature review, detailed in chapters 2 and 3, supported the design of a qualitative investigation of SCM in several pharmaceutical firms. Further, the gap between SCM theory and practice (discussed in chapter 3) also supported using case study methodology to collect data in this relatively unexplored area of management research (Storey, Emberson et al. 2006). While the initial case study iteration explored underdeveloped SCM in two pharma firms, it also produced discoveries and observations that slightly changed the qualitative research in two subsequent case study iterations. The case studies following the first iteration, in consultation with the literature and collected data, expanded to consider investigating the relationship between upstream processes (mainly R&D) and downstream processes (primarily SCM). These completed case study iterations preceded the construction of a final analysis and synthesis with the literature (in chapters 8 and 9).

This chapter aims to explain the evolution of the three case study iterations, beginning with the research philosophy and methodology that supported this research. It then outlines the design and implementation of each case study iteration. Finally, it reviews the presentation of findings (in chapters 5-7), the decisions made regarding case study analysis, the limitations of case study research and ethical considerations.

4.1 Philosophical Paradigms Used in Research

The research conducted during this project was empirical in nature. Empirical research is based on, or guided by, the results of real-world observation or experiment (Remenyi, Williams et al. 1998). Empirical research is frequently associated with a positivist view, which requires that the subject under analysis should be measured through objective methods in order to derive law-like generalizations. These generalizations are similar to those produced by the physical and natural scientists, with an emphasis on quantifiable observations that lend themselves to statistical analysis (Remenyi, Williams et al. 1998; Adam and Healy 2000; Amaratunga and Baldry 2001).

Realism²⁰ contrasts with positivism and more closely fits the paradigm for the case research conducted with the pharmaceutical firms in this study. These pharmaceutical organizations are real: they have form, structures, boundaries, goals, resources, and members whose behaviors result from structured relations among them (Dubin 1982). The realist tries to understand and explain a phenomenon, such as underdeveloped SCM in the pharmaceutical industry, rather than search for an external cause or fundamental laws (Remenyi, Williams et al. 1998; Amaratunga and Baldry 2001). Further, illuminating the issues in this qualitative study presented a descriptive, rather than prescriptive, task, which also corresponds with the realist paradigm.

With realism, each situation is seen as unique and its meaning is a function of the circumstances and the individuals involved (Remenyi, Williams et al. 1998). Following from that, analysis and understanding is rooted in the researcher's frame of reference and in the context of the research, in this case the pharmaceutical industry, and thus cannot be independent of the research entity (Adam and Healy 2000). As such, this type of research is not readily conducive to generalizations, other than the type that state that as the phenomenon has been shown to exist or occur at least once, it is probable that it will exist or occur again (Remenyi, Williams et al. 1998).

4.2 Methodological Approach

The nature of this research project was largely exploratory, with very limited available work regarding how SCM functioned in the branded ethical pharmaceutical industry and to what extent new product R&D considered SCM. These topics lacked a mature literature base within this particular industry, with only one notable paper (Shah 2004) that discussed SCM in pharma. SCM coalesced as a management discipline in its own right within the past twenty years (Cousins, Lawson et al. 2006; Harland, Lamming et al. 2006; Storey, Emberson et al. 2006), and lacked the maturity of other management disciplines, such as strategy. This combined with little previous research or formal theorizing regarding branded ethical pharmaceutical SCM, indicated

²⁰ Also known as interpretative or phenomenological.

that the proposed doctoral research corresponded with Edmondson and McManus' (2007) nascent archetype of methodological fit in field research.

The nascent theory area, that was the focus of this research, was explored qualitatively, which agrees with the archetypes set forth in Edmondson and McManus (2007). These authors identify three levels of prior work- nascent, mature, and intermediate- that correspond to three methodological approaches: qualitative, quantitative, and hybrid, respectively (These three archetypes are outlined in detail in Table 4.1). With nascent theory, researchers do not initially know what the key processes and constructs are, as they could if mature theory on their topic were available (Edmondson and McManus 2007). Thus, the nascent archetype is conducive to inductive theory development²¹. In fact, nascent theory work should conclude with a suggestive theory of the phenomenon that forms a basis for further inquiry (Edmondson and McManus 2007).

The research questions for this study addressed how a phenomenon (how SCM works with R&D in branded ethical pharma) unfolds and aimed to develop insight on the topic, which also fits well with working in an area of nascent theory (Edmondson and McManus 2007). Further corresponding with the nascent archetype was the impetus for this research, which stemmed from identifying and addressing gaps in existing literature, research and theory.

²¹ Inductivists prefer to first go out into the field to generate a theory while deductive methods work within a framework of a given theory (Simon, Sohal et al. 1996).

Table 4.1 Three Archetypes of Methodological Fit in Field Research

State of prior theory and research	<u>Nascent</u>	<u>Intermediate</u>	<u>Mature</u>
Research questions	Open-ended inquiry about a phenomenon of interest	Proposing relationships between new and established constructs	Focused questions and/or hypotheses relating existing constructs
Type of data collected	Qualitative, initially open-ended data that need to be interpreted for meaning	Hybrid (both qualitative and quantitative)	Quantitative data, focused measures where extent or amount are meaningful
Illustrative methods for collecting data	Interviews; observations; obtaining documents or other material from field sites relevant to the phenomena of interest	Interviews; observations; surveys; obtaining material from field sites relevant to the phenomena of interest	Surveys; interviews or observation designed to be systematically coded and quantified; obtaining data from field sites that measure the extent or amount of salient constructs
Constructs and measures	Typically new constructs, few formal measures	Typically one or more new constructs and/or new measures	Typically relies heavily on existing constructs and measures
Goal of data analyses	Pattern identification	Preliminary or exploratory testing of new propositions and/or new constructs	Formal hypothesis testing
Data analysis methods	Thematic content analysis coding for evidence of constructs	Content analysis, exploratory statistics, and preliminary tests	Statistical inference, standard statistical analyses
Theoretical contribution	A suggestive theory, often an invitation for further work on the issue or set of issues opened up by the study	A provisional theory, often one that integrates previously separate bodies of work	A supported theory, that may add specificity, new mechanisms, or new boundaries to existing theories

Source: Adapted from Edmondson and McManus, 2007.

4.2.1 Justification of Case Study Methodology

Nascent research aims to collect qualitative, open-ended data that needs to be interpreted for meaning. It relies on collecting this data through interviews, observations or documents from the field sites. Further, it particularly advocates using open-ended research questions to gather qualitative data. Together, these specifications support the use of case studies in areas of nascent research.

A case study is an empirical inquiry which investigates and describes a complex business or management phenomenon in a holistic way to develop a level of understanding so that future hypotheses and applications will evolve (Yin 1994; Stake 1995; Finch 1999; Remenyi, Money et al. 2002); cases can act as precursors to more elaborate, large sample hypothesis testing (Humphrey and Scapens 1996). Case studies are typically organized around a small number of issues or research questions which seek out “compelling uniqueness,” as opposed to gathering data to validate hypotheses (Stake 2000). Thus, the research problems addressed via this approach are more descriptive than prescriptive; the case studies for this research aimed to describe the extent to which branded ethical pharmaceutical new product development considers SCM.

According to Remenyi, Money et al. (2002), the term “case study” is amongst the most abused in the lexicon of the business and management studies researcher. These authors point out that the case study is not an all-purpose catchall name for “other” research methods. Case study research refers to quite a particular approach to research, one that is not only underpinned by a specific philosophical orientation, but also by a set of qualifying guidelines (Remenyi, Money et al. 2002). Cases are useful in the following situations: where the phenomena is broad and complex, where the existing body of knowledge is insufficient to permit the posing of casual questions, and when a phenomenon cannot be studied outside the context in which it naturally occurs (Bonoma 1985; Yin 1994). Case studies provide a way of looking at the world around us, without needing to control or replicate a phenomenon in a laboratory or experimental setting in order to better understand it (Yin 1994; Amaratunga and Baldry 2001). Thus, part of the benefit

of qualitative methods is that they allow researchers to learn about people, groups and experiences in ways not possible with other research approaches (Simon, Sohal et al. 1996).

Like other qualitative methods, cases rely heavily on verbal reports (personal interviews) and unobtrusive observation as primary data sources (Yin 1994; Simon, Sohal et al. 1996). Important advantages for case studies include a detailed understanding of the phenomena under study, and the ability to devote attention to complexities in observation, reconstruction, and analysis of the cases in such a way that it incorporates the views of the case study “actors” (Amaratunga and Baldry 2001). Simon, Sohal et. al (1996) outlined the key benefits to case study research as follows:

- Case studies provide a wealth of examples.
- Cases permit multiple sources of information and materials.
- One or several cases can lead to a range of further research needs being identified.
- The style of writing is often more readable than quantitative research.
- The use of interviews allows insights into issues that are normally not amenable to questionnaires. Unstructured interviews or parts of interviews enable people to tell “real” stories, and observation, particularly of team meetings and presentations. This permits the researcher to see, analyze and interpret real activities.
- Enables varying perspectives from a range of organizational personnel²².

Case studies are preferable to other available methodological approaches (i.e. surveys) for new research areas in which existing theory seems inadequate (Eisenhardt 1989; Finch 1999; Rowley 2002; Edmondson and McManus 2007). Because case research remains unconstrained by the boundaries of questionnaires and models, it can lead to new and creative insights, development of new theory, and identification of emerging practices (Voss, Tsikriktsis et al. 2002). The nature of exploratory research means that as long as the purpose of the research is defined, it is acceptable if sometimes research questions are not formulated or remain open-ended (Rowley 2002; Edmondson and McManus 2006; Edmondson and McManus 2007). While exploratory research can begin with only a broad definition of the research problem, the problem

²² As opposed to questionnaires usually reach only one person, whereas an extensive case study program can involve many interviews with a cross-section of people.

can be refined through consulting the literature and making links with the wider theoretical debates which exist therein (Pettigrew 1990).

Case studies are particularly good for theory building: the likelihood of valid theory resulting from case based research is high because the theory-building process is closely connected with evidence, making it consistent with empirical observation. While quantitative research provides evidence to support or disconfirm an emergent theory, it is qualitative research that initially generates theories (Amaratunga and Baldry 2001). Theory building requires rich description, richness comes from anecdote and thus, it is anecdotal data that enables theory building (Mintzberg 1979). Theory building which simply replicates past theory is a modest contribution (Eisenhardt 1989). However, this is not to say the relevance of past theory should be discarded. “It is impossible to go theory-free into any study... Both (prior theory and theory emerging from the data) are always involved, often simultaneously,” (Perry 1998). Linking results or emergent theory to the existing literature is necessary to enhance internal validity, generalizability, and the theoretical level of theory building from case study research (Remenyi, Williams et al. 1998; Rowley 2002).

4.2.2 Using Case Studies in an Area of Nascent Theory

The qualitative case research for this study went through several iterations, which will be explained in the next section. The iterative progression or evolution of this research was supported by Edmondson and McManus’ 2007 article. Here, they argued that the inductive nature of nascent research means that researchers must remain aware of emergent themes and issues in their data, with an evolving research design to account for the difference between the ideal version of the project and the version that was both feasible and viable (Edmondson and McManus 2007). Hence, the qualitative research design for this research evolved through a process of reviewing the literature, adjusting the case study design, collecting data and data analysis; this was an ongoing back and forth during the case study iterations. The three cases for

this study were not conducted simultaneously, but were added and augmented based on site availability and observation during the data collection and analysis phases of each case.

Edmondson (2005, 2007) describes a combination of research-before-theory and theory-before-research models, characterized by a spiraling, as opposed to linear, progression. With every two steps forward, you take a step or two backward before proceeding any further. What results is no longer a linear progression in a single, forward direction, but a spiral forward, never actually leaving any stage behind completely. What Edmondson (2005) describes is an iterative process, which is why the term “iteration” is used in tracing the evolution of the case studies developed for this research.

4.3 Case Study Iteration 1

The first case study iteration was part of a larger project, *The design and evolution of global supply chains: The organization of international flows* at Trinity College’s Institute for International Integration Studies (IIIS). This two-year project investigated the unexplored evolution of global supply chains in the pharmaceutical and medical device industries over a 30-year period. Thus, the early determination of two key areas of research, supply chains and pharmaceuticals, inevitably influenced the future course of this doctoral research. This first phase produced discoveries and observations about pharmaceutical supply chains that, coupled with ideas from the management literature, made examining upstream activities in pharmaceuticals a compelling idea for later phases of this project. As such, an additional, complementary phase that aimed to examine the relationship between upstream processes (mainly R&D) and downstream processes (primarily SCM) was designed for iterations 2 and 3.

4.3.1 Initial Industry and Methodology Selection

A number of selection criteria were used to evaluate which industries to choose for the study, including trying to balance different types of industries (for example, fast cycle versus slow cycle), while keeping enough commonality to be able to make meaningful comparisons (i.e., level of regulation, selling paths). When writing the initial grant proposal for this project, the principal

investigators chose pharmaceuticals as the leading contender to serve as the classic industry. The classic industry needed to have a well-developed industry structure, been exposed to, and succeeded in, weathering changes in the internal and external operating environments, and it needed to continue to meet the challenges of evolving business environments. Finally, to create a balance between the two selected industries, one industry needed strong supply chain management capabilities, while ideally, the other industry would be the opposite, and not strongly affected by SCM's rapid evolution. The pharmaceutical industry clearly was the latter, and became my responsibility.

Once industries were selected and evaluated, several methodological approaches appropriate for management research were evaluated. Case study methodology provided a way of examining pharmaceutical companies in detail to assess the previously unexplored issue of SCM in relation to R&D in branded ethical pharmaceuticals. After consideration of the purposes and goals of case studies, case studies were chosen to examine the evolution of SCM in pharma during the initial iteration in this research (this methodology was confirmed later as the correct choice for the subsequent case study iterations). The limited available work regarding pharmaceutical SCM made this close to the 'ideal' of beginning a case study with "...a research problem and...some potentially important variables, with some reference to extant literature" (Eisenhardt 1989). Case study methodology also allowed for exploring how supply chain management worked and had (or had not) evolved within the pharmaceutical industry. Moreover, the descriptions and understanding achieved through the initial case studies would be linked to the existing literature and used to develop other cases.

4.3.2 Criteria for Case Selection

The case study literature avoids specifying the exact number of cases or sample size for a qualitative research project, leaving this decision to the researcher (Perry 1998). Looking at the literature in the aggregate, the widest accepted range seems to fall between two to four cases as the minimum, and 12 or 15 as the maximum (Perry 1998). While the number of units in a case

study is much less than in a survey, the extent of detail available for each case should be greater (Rowley 2002). Case selection is significant because the population from which the research cases are drawn is a defining factor which helps control variation and define the limits for generalizing the findings (Eisenhardt 1989).

The issue of whether to use a single case study or multiple case studies is often debated within the methodology literature. A single case is a specific, unique, bounded system (Stake 2000). Single case studies are appropriate when the case is special (in relation to established theory) for some reason (Rowley 2002). Researchers can view the use of multiple case studies as the equivalent to multiple scientific experiments, meaning that the more cases that either establish or refute a theory, the stronger, more compelling, and more robust the research results (Amaratunga and Baldry 2001; Rowley 2002). Multiple cases have the benefit of deepening understanding and explanation processes because outcomes and patterns are observable across many cases (Miles and Huberman 1984; Eisenhardt 1991). Multiple cases permit replication²³ and extension²⁴ among individual cases (Eisenhardt 1989; Eisenhardt 1991). Researchers can stop adding cases at the point of theoretical saturation, where incremental learning is minimal because the researchers are observing phenomena seen before; Lincoln and Guba refer to this as the point of redundancy (Lincoln and Guba 2000).

Perhaps the most valid guidance, particularly in the case of doctoral research, is Edmondson's notion that no one gets to complete their ideal project, so by extension, no one gets to work with their ideal set of case companies: research projects manage complex relationships with sites, cope with constraints on sample selection and timing of data collection (Edmondson and McManus

²³ If two or more cases are shown to support the same theory, replication can be claimed Rowley, J. (2002). "Using case studies in research." *Management Research News* 25(1): 16.. If the predicted results do occur in a number of carefully selected cases (i.e. literal replication), or if the contrary results are produced but for predictable reasons (i.e., theoretical replication), then the case study method can play a significant role, transcending the local boundaries of the cases researched Tsoukas, H. (1989). "The Validity Of Idiographic Research Explanations." *Academy of Management. The Academy of Management Review* 14(4): 551..

²⁴ Extension refers to the use of multiple cases to develop more elaborate theory.

2007). In doctoral research (and this research project was no exception) case selection is often contingent upon the limits of time, funding and accessibility (Pettigrew 1990; Perry 1998; Rowley 2002). Thus, case selection often becomes a compromise involving discretion and judgment in selecting sites which fit the components of a research project and at the same time are willing to provide the level of access necessary for rigorous research (Burgess, Pole et al. 1994; Amaratunga and Baldry 2001). As will be explained shortly, time and access constraints dictated the number of cases included in the qualitative data collection in this research.

4.3.3 Candidate Identification and Selection- Iteration 1

To deepen understanding and create an explanation of global supply chain management, iteration 1 started with two in-depth, highly detailed, exploratory case studies on supply chain management per industry (pharma and medical devices). Initially, two top 10 ethical pharmaceutical firms were desired for this iteration. In identifying the leading pharmaceutical firms, a list was derived from Hoover's Pharmaceutical Industry Report, Standard and Poor's Industry Survey: Pharmaceuticals, and from Pharma Exec's list of the top 50 pharmaceutical firms for 2003. According to Standard and Poor's, the top 10 firms accounted for 50% of pharmaceutical industry sales. The firms were ordered by volume of pharmaceutical sales/revenue (see Table 4.2) In total, there were 12 firms that appeared on the three lists (Hoover's, S & P, Pharma Exec). Two firms were excluded (Johnson & Johnson, Abbott Labs) because their pharmaceutical units were small portions of a much larger operation and findings in either of these firms could be distorted by the influence of other industries in which the firm operates. Of the remaining ten firms, one firm was excluded because it was undergoing a re-organization due to a merger (Sanofi-Aventis). This left a list of the top nine firms to target for this research.

Table 4.2 Top Pharmaceutical Firms

FIRM	TURN OVER (\$B, 2004)	S&P TOP 10	HOOVERS RANK	PHARMA EXEC RANK	OUR RANK	REASON TO EXCLUDE
Pfizer	47.08	1	4	1	1	
GSK	30.78	2	3	2	2	
Merck	22.58	3	1	3	3	
Johnson & Johnson	22.18	4	2	4	-	Mixed
Sanofi- Aventis	17.02	7	6	5	-	Current Merger
AstraZeneca	19.21	6	9	6	4	
Novartis	20.25	5	5	7	5	
BMS	15.69	8	8	8	6	
Wyeth	15.9			9	7	
Eli Lilly	12.58			10	8	
Abbott Labs	13.27	10	10	11	-	Mixed
Roche	15.23	9	7	12	9	

In the first iteration of this research, in which the focus was strictly limited to SCM, one pharmaceutical firm belonging to the top ten pharmaceutical firm echelon (Sellers 2004) was chosen to act as a proxy for the industry, or control case study. The top three firms, Pfizer, GlaxoSmithKline (GSK) and Merck were selected as target control case-study firms. At the time, these firms were the top three players in the industry (respectively); all three companies had pursued a combination of competitive strategies to expand their firm capabilities, grow their companies, and, by extension, their supply chains. Given that the selection criteria involved choosing an industry leader as the control firm, Pfizer Ireland, *the* industry leader, was selected as the top choice firm for the control case study.

When the research team did not have much success gaining access to a second top-ten participant for this phase, the selection strategy changed²⁵. Instead of choosing two field cases because of their ability to produce similar results (literal replication), we chose cases that would produce contrasting results but for predictable reasons (theoretical replication) (Rowley 2002).

²⁵ Given the iterative nature of qualitative research, in situations where a sufficient number or type of cases cannot be collected, a researcher can change the research questions, selection criteria, or analysis scheme to address these limitations Larsson, R. (1993). "Case survey methodology: Quantitative analysis of patterns across case studies." *Academy of Management Journal* 36(6): 1515-1547..

Thus, a smaller top-25 firm was identified for a contrasting study. In choosing a contrasting firm, the leading pharmaceutical firm list²⁶ was once again consulted, and Fujisawa Ireland (now Astellas) was suggested as a potential candidate for the contrasting study. A further driving factor in selecting Pfizer Ireland and Fujisawa Ireland was relatively easy access to these firms via the School of Business Studies faculty.

4.3.4 Case Study Interviews- Iteration I

When case studies are used for descriptive and explanatory studies, research questions should be translated into propositions or organized into a descriptive framework (Rowley 2002).

Developing propositions that speculate about the research results based on the literature and early evidence is not necessarily possible with nascent theory, so a number of potential questions for qualitative data collection were brainstormed, to help with thinking through the type of information needed from SCM informants. Then the questions were organized according to themes and evidence found within the literature (Rowley 2002). This produced four important categories were addressed in semi-structured interviews with case study informants²⁷; interviews aimed to capture information in the following categories:

- The interviewee's role and background;
- How the organization is structured;
- How the supply chain operates within the firm;
- Important considerations for supply chain strategy and design.

4.3.5 Conclusion to Iteration 1

Iteration 1 concluded at the same time as the larger design and evolution of global supply chain project came to a close. At this time, the inclusion of one of the pharma case study firms, Fujisawa, had to be reconsidered. Fujisawa faced an upcoming merger with Yamanouchi Pharmaceuticals that was not evident at the time of candidate identification and selection. Thus,

²⁶ Same as previously referenced list derived from Hoover's Pharmaceutical Industry Report, Standard and Poor's Industry Survey: Pharmaceuticals, and from Pharma Exec's list of the top 50 pharmaceutical firms for 2003.

²⁷ There would be two pharma case studies and two medical device case studies as part of the larger, global supply chain evolution project.

Fujisawa became a pilot case²⁸ for this research. With a merger drastically altering the company landscape, interviews with Fujisawa were most valuable for making revisions to the interview protocol and data collection procedures to reflect a better understanding of the industry setting (Miles and Huberman 1994; Perry 1998; Remenyi, Williams et al. 1998).

4.4 Case Study Iterations 2 and 3

After conducting a series of semi-structured interviews with supply chain and manufacturing managers at Pfizer Ireland and Fujisawa Ireland as part of iteration 1, the focus and nature of this research was reconsidered using the data collected from this set of initial case studies. The primary realization during this initial phase was that supply chains extended beyond the boundaries of the manufacturing/supply chain units. Considering the R&D organization, which develops the product for the manufacturing side of the company, could result in a unique research contribution. Thus, iteration 2 added an exploration of the upstream activities within pharmaceutical firms, with an emphasis on upstream's connection to the downstream SCM function. Therefore, the study moved forward with two types of interviews, one for SCM (developed during iteration 1) and one for R&D (developed during iteration 2).

4.4.1 Case Study Iteration 2

Iteration 2 began by modifying the research objectives and research design based on the applicable literature and the emergence of a more relevant, unexplored and interesting area of questioning (Remenyi, Williams et al. 1998; Amaratunga and Baldry 2001). This iteration would continue to use case studies as the primary means of exploration, and ideally, wanted to recruit and investigate R&D and SCM activities in four of the top nine ethical pharmaceutical firms. However, gaining access to four top firms proved a major obstacle during a time when the industry had been heavily criticized in the press and was extremely wary of outsiders. Pfizer

²⁸ A pilot case study is often conducted on the grounds of convenience, access and geographic proximity Remenyi, D., B. Williams, et al. (1998). Doing research in business and management: An introduction to process and method. London, Sage..

Ireland agreed to make their R&D team in the U.S. available for additional R&D research; thus, Pfizer would make one complete case study. In finding other case study firms, the list of top nine pharmaceutical firms (compiled during iteration 1) was consulted. Contacting each of the nine firms failed to elicit a positive response from any of the nine firms, except Novartis. Thus, at this time, iteration 2 progressed, adding Pfizer R&D as well as Novartis R&D and Novartis SCM to the study. Also, at the time, it appeared that only two complete, detailed case studies in top 10 pharmaceutical firms would be available to this research.

4.4.2 Case Study Iteration 3

Later, and unexpectedly, during the data collection in Iteration 2, a third opportunity emerged at Novo Nordisk, with a high level of access. Although Novo Nordisk was outside of the top 10 pharmaceutical firm echelon, it was within the top 25, and it presented a chance to explore or test ideas observed during the other two case studies.²⁹ Thus, a total of three case study iterations took place to collect all the relevant data for this research; each iteration relied upon, and improved upon, its predecessor. In the end, three complete case studies were developed to support this doctoral research (see chapters 6-8). Table 4.3 summarizes this process below.

Table 4.3 Summary of Case Study Iterations

Company	Iteration 1 (SCM focused data collection)	Iteration 2 (Adds R&D to data collection)	Iteration 3 (Unexpected opportunity develops)	Final Result
Fujisawa	SCM	-	-	PILOT
Pfizer	SCM (Ireland)	R&D (U.S.A.)	-	COMPLETE
Novartis	-	Both SCM and R&D	-	COMPLETE
Novo Nordisk	-	-	Both SCM and R&D	COMPLETE

²⁹ This is in accordance with the iterative, nonlinear process of conducting field research Eisenhardt, K. (1989). "Building theories from case study research." *The Academy of Management Review* 14(4): 532-550, Edmondson, A. and S. McManus (2006). "Methodological fit in management field research." *Academy of Management Review*..

The three case study firms displayed both similarities and differences in terms of organizational characteristics. The case study methodology literature alleviated the need to be overly concerned that firms varied in terms of organizational size, type, or national origin because fundamentally, the research's emphasis was on abstract principles (SCM and integration). Most important was the "level" of R&D and SCM practice, the intention was to understand and compare the practices within these organizations via three in-depth, highly detailed, robust case studies (Amaratunga and Baldry 2001; Rowley 2002).

4.4.3 Case Study Interviews- Iterations 2 and 3

During iterations 2 and 3, the SCM/manufacturing units at Novartis and Novo Nordisk had to be interviewed, and for these interviews, questions were asked which addressed the four categories developed during iteration 1; during iterations 2 and 3, there was an added emphasis on how SCM worked with R&D. Starting with iteration 2, R&D activities were added to the study, and an additional set of interview categories, specific to R&D, were designed. Thus, questions focused on the functions, processes and potential links between R&D and SCM. The R&D-focused interviews concentrated on achieving an in-depth understanding of the nuances of each firm's R&D process; an extensive discussion was often triggered by asking interviewees to provide an overview of the drug development process or explain how a drug gets from the research phase to the launch phase. Since the knowledge theory group seemed particularly relevant with respect to R&D, some questions were asked with a view towards understanding how knowledge operated within this environment, particularly knowledge needed to move a drug through development stages. Overall, the themes explored during the interviews were as follows:

- Interviewee's role and responsibilities.
- How the interviewee's department fit into the drug development or supply chain process.
- Overview of organization's research, development or manufacturing process.
- Other units the department worked with- locally, regionally, internationally.
- How transitions between units were managed/how a drug moved through development phases.
- View of knowledge in everyday work.
- Collection and storage of knowledge in various development phases.
- Sources of expertise about a new drug.

4.5 Case Study Procedures

The data collection for this research stemmed from semi-structured interviews, observation and examination of documentary material (Eisenhardt 1989; Rowley 2002). Semi-structured interviews with R&D and SCM/manufacturing team members helped determine the relationship between R&D and SCM in ethical branded pharmaceuticals (Yin 1994; Cooper and Schindler 1998; Naumes 1999). The principal informant within each company was sent an overview of the research project and a list of topics the interview would cover (based on the developed interview themes for the SCM and R&D interviews). Typically, the principal informant forwarded the project description and questions to potential interviewees and interviews were scheduled at the convenience of willing participants. Principal informants and interviewees often provided additional internal documentary data; external documentary information was collected and reviewed before the case interviews.

Interviews were conducted with mid-level to senior level managers involved in the R&D, new product development, supply chain or manufacturing unit of the organization. Each interview lasted 60-90 minutes. Depending on company policy, interviews were either audio/video recorded and then transcribed³⁰. Field notes were written if a company or interviewee preferred that recording equipment not be used. Interviewees had the option to review transcripts or notes, and the principal informant at each company approved the final case

³⁰ A brief note on recording data: While there is a strong foundation for documentation of the evidence gathered in case research, there are very divided views on whether tape-recorders should be used in interviews. Recording equipment certainly provides an accurate representation of what is said. Where exactness of what people have said is important, then taping will benefit. If interviews are more focused on objective data, as is often the case in operations management research, then the benefits of taping are reduced. On the negative side, transcribing tapes is very time consuming and may inhibit interviewees Voss, C., N. Tsikriktsis, et al. (2002). "Case research in operations management." International Journal of Operations & Production Management **22**(2): 195-219..

report included in this dissertation. Feedback from the firm added to the study's construct validity (Remenyi, Williams et al. 1998).

Semi-structured interviews were conducted with each informant. As the interviewer, I had to bear in mind the interview theme list that was developed for the type of informant (SCM or R&D), and ensure that each theme was touched upon, in some way, during the course of the interview. Using a semi-structured interview framework was different from a questionnaire framework, where detailed questions would have been formulated ahead of time. Instead, the semi-structured interviews started with a more general question or topic (i.e. How long have you worked in R&D at this company?) and allowed a conversation to develop; if one word were to describe the interviews, it would be "conversational". Instead of pre-designing and phrasing questions before the interviews, follow-up questions were created and asked during the interview, which allowed flexibility to probe, discuss, or clarify emergent concepts and issues (Eisenhardt 1989). A semi-structured format also allowed interviewees to remain more engaged and able to digress or discuss issues and events that were relevant or meaningful to them (Mason 1994; Simon, Sohal et al. 1996).

4.6 Case Study Analysis

Each phase of qualitative research has implications for other phases. The choice of research questions and research site selection have implications for data collection, what data is available for analysis, and the topics and themes of data analysis (Burgess, Pole et al. 1994). It falls to each researcher to decide how to analyze the evidence collected, and then how to synthesize the results of the analysis to produce a contribution to the body of knowledge (Remenyi, Money et al. 2002). Unfortunately, analysis methods for qualitative data are not well defined. Further, under-researched topics require methods that allow data collected in the field to strongly shape an understanding of the phenomenon (Edmondson and McManus 2007).

After completing interviews at case firms, interviews which were recorded were transcribed; interviews that required field notes were organized and written-up. The raw interview data was then reviewed and a list of eight categories was developed (based on commonalities which emerged from reviewing the raw data): company background, Research activities, Development processes, R&D improvements/challenges, SCM operations, SCM strategy, SCM improvements/challenges and project (or drug)-specific stories. Then, on a company basis, the interview transcripts were coded by the set of categories, and all the data corresponding to a specific category was aggregated into one document; for example, all the interview data on Research activities at Pfizer was collected in one document. Thus, each case company ended up with a set of eight documents- one document per category. By organizing the raw data this way, the eight documents were used to create complete case narratives about each case company.

The next step involved creating extensive case write-ups with an emphasis on developing descriptive, narrative accounts³¹, which were central to gaining familiarity with the cases as well as uncovering new insights (Eisenhardt 1989; Amaratunga and Baldry 2001). Constructing the descriptive cases were particularly helpful in sorting through the volume of data collected during site visits/interviews (Eisenhardt 1989) and provided a method for organizing and understanding the qualitative data (Bryman and Burgess 1994; Stake 1995). Constructing detailed descriptions could potentially reveal the dynamics of the phenomena under consideration and allow analyses to emerge over time (Dyer, Wilkins et al. 1991; Remenyi, Money et al. 2002).

With fieldwork and single case write-ups completed, data from individual sites was available to interpret the particular circumstances of each case. A single case analysis was then written on

³¹ Eisenhardt (1991) argues that an essential first step in case study analysis is developing a story; stories are often more effective than statistical displays of ideas and claims because they demonstrate a greater depth of inquiry than other methods (i.e. surveys) Dyer, W. G., Jr., A. L. Wilkins, et al. (1991). "Better Stories, Not Better Constructs, to Generate Better Theory: A Rejoinder to Eisenhardt; Better Stories and Better Constructs: The Case for Rigor and Comparative Logic." Academy of Management. The Academy of Management Review 16(3): 613, Remenyi, D., B. Williams, et al. (1998). Doing research in business and management: An introduction to process and method. London, Sage, Remenyi, D. and A. Money (2002). "When is a doctorate dissertation ready for submission?" Irish Journal of Management 23(2): 111..

each firm, after each case narrative was re-examined to answer a set of questions, which were inspired by being immersed in creating the case narratives and thinking back on the relevant literature:

- What is unique or striking about the way this firm operates?
- Does R&D work with SCM? Yes or no? Why or why not?
- What themes or concepts from the literature review are echoed by this case?
- Is there something (a practice or process) that this firm seems especially committed to or proud of?
- How does this firm compare to the other two firms? What is similar? What is different?

This process of thinking about each case singularly, and then with respect to the other cases, was an iterative, open process that took months to complete and allowed observations and insights to emerge inductively from the data set. The cases were considered together, as one set, in developing the final conclusions related to theory and the extant literature (Pettigrew 1990; Perry 1998). Linking results to the literature was particularly crucial in this exploratory project because the findings relied on a limited number of cases; thus, any further corroboration of internal validity or generalizability was important (Eisenhardt 1989; Weerd-Nederhof 2001).

Regarding the replication and reliability of these case studies, Humphrey and Scapens (1996) report that with case studies, no researcher can provide an objective assessment of events; all case studies involve a degree of interpretation by the researcher. A different researcher may obtain a different set of findings, but this would not be the same case study, for the researcher is not a neutral observer, but an active participant in the construction of the case study (Humphrey and Scapens 1996). This relates to the phenomenologist argument that all situations and organizations are different and therefore the same results cannot ever be obtained again. Consequently, reliability is not a central issue (Remenyi, Williams et al. 1998).

4.6.1 Triangulation

Part of the analysis phase included methodological triangulation³², often defined within the literature as combining qualitative and quantitative methods to study the same phenomenon, so that formal relationships between constructs can be identified and a more complete account of social reality can be developed (Jick 1979; Simon, Sohal et al. 1996; Amaratunga and Baldry 2001). Data source triangulation is useful to corroborate findings as well as achieve data validity, reliability, and generalizability (Bonoma 1985; Yin 1994; Stake 1995). Because these case studies were descriptions of management situations, they leveraged multiple data sources and used documentary material as a means of triangulation and a way to view a fuller picture of the business unit under study (Bonoma 1985). Both internal and external documentary data (i.e. annual reports and articles) about the case study firms was reviewed to provide some degree of triangulation (Rowley 2002). Because multiple perceptions clarify meaning and verify the repeatability of an observation or interpretation, having more than one interviewee in a single organization also served as a form of triangulation (Perry 1998; Stake 2000).

4.7 Limitations of Case Study Research

The case study approach is not without its limitations: “All research strategies have flaws...” (Bonoma 1985). Researchers desire high levels of both data integrity and results currency, but not a single research method minimizes threats to either. When researchers make methods choices, it is somewhat inevitable that there are tradeoffs in choosing one research methodology over another (Bonoma 1985).

³² The complexity of reality and the limitations of a researcher’s mental capacity increases the significance of data triangulation (Perry 1998). With this approach, the researcher is not simply gathering facts or measuring the occurrence of patterns. Instead, the researcher aims to appreciate the different constructions and meanings people place upon their own experiences and the reasons for these differences (Amaratunga and Baldry 2001).

A major concern with case study research is low external validity, that the small number of organizations studied makes it impossible to create global generalizations or conclusions (Mintzberg 1979; Miles and Huberman 1984). It is difficult to generalize findings to different settings as phenomenon and context are necessarily dependent and unique, thereby creating a limited basis for traditional “scientific generalization” (Amaratunga and Baldry 2001). Because cases capture the experience of an organization only at a particular period in time, changes will take place that make conclusions reached in a case outdated. However, this does not detract from the importance of the case study method for exploratory research, which aims to understand and articulate patterns and linkages of theoretical importance (Amaratunga and Baldry 2001).

Another challenge with case study research is communicating the wealth of information and understanding acquired in an unbiased way (Humphrey and Scapens 1996). To address this concern within this research, the case study results were initially compiled as concisely written, descriptive cases independent from discussion and analysis sections (Simon, Sohal et al. 1996). To reduce bias in this project, findings (i.e. the descriptive case write-ups) and interpretations were presented to participants for feedback (Humphrey and Scapens 1996).

Finally, a limitation in choosing the case study approach includes the constraints that impact on case selection: accessibility, resources, and time available (Rowley 2002). Identifying pharmaceutical firms willing to provide convenient access was a significant challenge in this study. The nature of the industry meant contending with a reluctance to share information and allow an outsider into the organization. Furthermore, I had to be sensitive to interviewee’s time, keeping interviews to 60 minutes and in most cases, limiting contact with each participant to one meeting, and then subsequently sending him or her a transcript or notes from the meeting with ample time to review, so as be as unobtrusive as possible.

4.8 Ethical Considerations

Case study research must be conscious of adhering to practices that protect research participants as well as confidential company and individual data. This project incorporated the following considerations during the case study research phases:

- **Informed Consent.** Individuals and companies who participated in this research did so voluntarily. All participants received an explanation of the research project, an overview of the interview in which he or she would participate, and information regarding how interview material would be used.
- **Confidentiality.** Participants were advised about the confidentiality of his or her interview. Information about companies and individual research participants was kept confidential, unless appropriate permission was given for its release. Case study data was stored in secure locations that were protected from unauthorized access.
- **Permission to Quote.** If any research material was intended for use outside of this dissertation, i.e. quotes from a particular individual, s/he would be asked for permission for the quote and identifiable information.
- **Permission for Recording.** Permission for the electronic recording (audiotape or videotape) of case interviews was obtained verbally from the participants at the start of the interview, before turning on recording devices. Participants were advised that, if at any time s/he did not feel comfortable, the recording device could be switched off. Participants were advised that recordings were for research use only and were not intended for public viewing at any time.
- **Company Permission.** All case reports were sent to the organization (usually the principal informant, who was also a high-level organizational representative) for review before they were included in this dissertation. This provided each firm with an opportunity to correct errors of fact and to ensure commercially sensitive information was not divulged inadvertently. Additionally, each participant was provided with a copy of his/her interview transcript/notes to review and comment on before the final case report was drafted.

4.9 Summary

Overall, this project aspired to choose interesting research issues; to use and interpret evidence that was varied, accessible, and reliable; to report findings in clear, detailed case descriptions; and to seek out other explanations and examples from the literature that would either contradict or confirm case study results. The methodological approach pursued to answer this study's central research question involved developing qualitative case studies to explore a small slice of the how things work in the ethical branded pharmaceutical industry. By looking carefully at living, breathing firms this research aimed to develop a full picture of pharmaceutical SCM and how new product R&D worked with SCM (Remenyi, Williams et al. 1998). In this way, the case

study work aimed to bridge the gap between academia and industry, particularly given that SCM has been qualified as an emerging discipline (Cousins, Lawson et al. 2006; Harland, Lamming et al. 2006; Storey, Emberson et al. 2006).

The research methodology employed involved a process of reviewing literature, adjusting case study design, collecting data at pharma firms, and data analysis. Moving forward from here, the following three chapters provide case descriptions from each of the three pharmaceutical firms: Pfizer, Novartis and Novo Nordisk. Arguably, these narratives represent findings in that they each add something of value to the body of knowledge and provide an explanation of the observed phenomena (Remenyi, Williams et al. 1998). Based on the fact that the case research did not proceed sequentially, and involved cycles of iteration with the literature, study design and data collection, the cases are presented individually, as opposed to from a common platform. Imposing a common platform, retrospectively, on these narratives would damage the uniqueness captured in each case and betray the nature of nascent research as well as the iterative principles discussed throughout this chapter.

Chapter 5: Case Description- Pfizer, Inc.

With the literature review and explanation of the project's methodology detailed in the preceding chapters (2 and 3), this chapter is the first of three providing case descriptions of the companies that participated in this doctoral research. As Pfizer was the first organization that joined the study, the results of the case research conducted there are presented first.

In 2005, Pfizer spent \$7.4 billion on R&D. Pfizer's pharmaceutical R&D organization, Pfizer Global Research and Development (PGRD), employed more than 12,500 scientists and researchers worldwide. Pfizer Global Research and Development was headquartered in New London, Connecticut and had major research campuses in Ann Arbor, Michigan; Groton, Connecticut; La Jolla, California; Nagoya, Japan; and Sandwich, England³³. Additionally, PGRD formed over 250 partnerships in both academia and industry to gain access to the latest scientific knowledge, data and tools. Pfizer reported that their medicines library included about 3 million druggable compounds, a pipeline with 140 new molecular entities, 80 enhancement programs for marketed products ("me too" drugs) in development, and 400 compounds in discovery research in multiple therapeutic areas³⁴.

5.1 Co-development Teams: R&D to the New Products Group

Two managers who worked at the interface of PGRD and Pfizer Global Manufacturing provided an understanding about the bridge between these two units: Dr. Tim Hagen, Vice President, Science and Technology and Kevin Nepveux, VP of New Product Development. Organizationally, Hagen was located under the PGRD umbrella, while Nepveux belonged to PGM. PGM and PGRD worked together through a process called co-development to develop

³³ 2005 is the time of this case. Updated company information reports that Pfizer spent \$7.6 billion on R&D in 2006. Furthermore, the firm streamlined PGRD into four major campuses: Groton, St. Louis, La Jolla and Sandwich. Pfizer reported that as of January 2007 their pipeline included 177 NMEs, 72 product line extensions, and promised to deliver four new medicines a year as of 2011.

³⁴ From Pfizer company information.

new products. This case description intentionally separates the co-development perspectives provided by each interviewee, to maintain the authenticity of the interviews.

5.1.1 PGRD: PharmSci

Dr. Tim Hagen³⁵ was based at Pfizer's Groton, Connecticut research campus. This campus focused only on research, with two million square feet of laboratory space and more than 4,000 highly skilled research scientists, technicians, clinicians, and other professionals. Research was conducted on a range of diseases, including central nervous system disorders, inflammatory diseases, immunological disorders, cancer, diabetes, obesity, osteoporosis, and infectious disorders. The New London, Connecticut site was home to the 2,000 members of global drug development.

Hagen explained Pfizer's relatively complex organizational structure in order to understand where his unit, Pharmaceutical Sciences (PharmSci), fit into the organizational picture. PGRD and PGM were two large divisions within Pfizer. Research and Development were separate zones within PGRD. Within the Research zone, there were six subunits divided by platform sciences (see Figure 5.1, Pfizer Organizational Chart A).

Pharmaceutical Sciences was one of the platform sciences headquartered in Sandwich, UK and Groton, CT with over 2,700 members worldwide and a budget of \$1 billion³⁶. A potential drug comes to PharmaSci from the disease area/discovery/marketing team with a set of specifications; for example, the drug must be oral control release, must be low cost, and needs to be made in a number of dosage strengths. Then, the PharmSci project team needed to work to achieve these specifications, or in other words, find the science to give disease area/discovery/marketing team what they wanted. It was imperative when Discovery believed that

³⁵ Brief biographical information: Hagen earned a Ph.D in Pharmaceutical Chemistry and joined Pfizer in 1979 after working as a pharmacist in hospitals and drugstores. Hagen explained that he worked his way up the ladder at Pfizer on the drug product side of the organization.

³⁶ PharmSci made a few investments outside the organization, but this only accounted for 5% of their total budget. They spent maybe \$80 million on outside strategic alliances and some contract manufacturing.

they had a viable drug, that PharmSci got the chemical synthesis correct to get molecule into a product.

PharmSci broke into five workstreams:

- Regulatory Chemistry, Manufacturing and Control (CMC): essentially regulatory
- Portfolio Strategy Operations (PSO): project management
- Supply Chain: manufacturing capabilities within PharmSci
- Science and Technology
- Biologics

PharmSci functioned in project teams with the necessary representatives assigned to them based on the nature of the drug project. Usually, the PSO person on the project served as the full-time PharmSci team leader for the project team. Teams always had representatives from the API, Drug Product and Regulatory CMC divisions. Project team members fit into the overall organization as follows:

Each project team member has a “home” in the line organization. In the line organization the individual is responsible for ensuring scientific and organizational expertise and ideas that will improve the business of the line their “home” is in. Individuals construct two goal statements: one for their line discipline, one for his or her project (Hagen).

Hagen explained project teams further:

Project teams also bring cross-disciplines together. This can break down organizational silos if the project teams are good. This, in turn, can address the issue of how to capture knowledge created by one team and transfer it to another team so you’re not always reinventing the wheel.

Project team members ranged in educational backgrounds from bachelor’s through Ph.D. degrees. While Hagen felt that the organization needs M.S. and Ph.D. scientists to ensure competitiveness, enable growth, and develop skill sets to push projects forward, those with lesser education, or bachelors degrees were important to the organization too: “Pfizer values strong leadership because of all the work in teams. Some higher educated people cannot work in teams. As such, some leaders don’t have PhDs.”

Science and Technology and Biologics were similar workstreams in that they were staffed by scientists who made drugs for commercial markets, but Science and Technology focused on small molecules. Science and Technology further divided into four separate divisions (see Figure 5.2).

Hagen managed the 560 Science and Technology employees in Groton. Science and Technology was the largest group within PharmSci, with 1,300 members on a global scale, of which 1,000 were dedicated to products heading to market and the remaining 300 worked in development/discovery. Supply chain was the next largest group in PharmSci after Science and Technology. Biologics and Science and Technology created drug products and interfaced with PGM.

PharmSci Science and Technology was situated between Discovery and PGM. “Everywhere there are discovery scientists within Pfizer, there is a PharmSci Technology presence to work with the chemical synthesis of the drug product that is destined for market and PGM.” This made Hagen one of the key people involved in the interface between PGRD and PGM. He explained that this was a divisional interface that came under the Human Health Leadership group reporting structure. Those that interacted at this particular interface “are fairly high up” in the organization.

Hagen explained that the relationship between PharmSci and PGM was rather unique. The research division of the organization was distinctive in its people-oriented culture, primarily because people were producing molecules. In contrast, PharmSci looked more like PGM because of its engineering focus, efficiency and efficacy goals, and need to capture information. The organization had often considered moving PharmSci to manufacturing:

We often discuss if PharmSci should move to Manufacturing. There is a huge overlap between PharmSci and PGM. There’s more overlap with PGM than with Discovery molecular biologists who develop the lead compounds. PharmSci has GMP capabilities which makes them look more like PGM. Pilot plants are within the PharmSci domain. They [PharmSci] produce API and Drug Product (Hagen).

The PharmSci pilot plant facilities were very similar to small manufacturing facilities. PharmSci maintained these manufacturing capabilities because “not all programs make it all the way and we need technically experienced people that can try new manufacturing strategies to keep projects from dying.” Once a drug successfully made it to PGM, the view was more long term: “this is a product that will be made for 20 years, so it has to be done as best as we can.” Thus, a different mindset and skill set was necessary in the PharmSci pilot plants than in PGM.

5.2 Co-Development System

Pfizer used the term “co-development” to describe the process by which PGRD, and more specifically, PharmSci, engaged with New Product Development (NPD) in PGM. On a global scale, PharmSci and NPD came together to enable product development, ensure manufacturing processes that maintain the safety and efficacy of a product, and meet standards for worker safety and environmental impact³⁷. The Co-development Leadership Team (CDLT), chaired by Hagen and Nepveux, supervised the co-development system. Ten team members with the resources and responsibilities that affected co-development sat on the CDLT team. They were responsible for processes; responding to new challenges that may occur because of regulatory, environmental, and business concerns (i.e. to make something cheaper); and overall long range strategies.

5.2.1 Co-development from the PharmSci Perspective

For each NCE that moved into PGM, a co-development team was assembled which included PharmSci, plant and NPD people as members of the team. The team tailored activities for the transfer of the drug from PharmSci to PGM. Most of the time, sub-teams were designated for API and drug product because usually, these two were made in different locations. For example, most API went to Ireland and drug products were sent to Fryeburg, Germany.

Co-development was not considered for a product until its bond forming and chemical attributes had been determined (or, in other words, when Analytical and Chemical R&D finished). The co-development process began when the PharmSci team leader issued a co-development alert notice for the API and the drug product, which effectively gave PGM a “heads-up” that a product was headed their way. This co-development alert was sent to the standing co-development management teams, which evaluated each alert on a case-by-case basis because “nothing is ever the same.” The major, and final, co-development plan which “lives” and was owned by PharmSci and New Product Development team leaders was constructed and finalized

³⁷ Plans to guarantee worker safety and detail environmental impact were built into the product profile.

six months before Phase III kicked off; this plan detailed the transfer to PGM, and included a validation plan, and batch specifics. Phase III was a significant milestone, according to Hagen:

The big picture was that about 45 products come out of Discovery and go to Development. At a steady state of attrition, 4 products must come out each year. Attrition occurs early on in the process, much of it happens in Phase II. Only 10% of products make it to phase III and the goal is for 28% to make it to Phase III. From phase III there is only a 50/50 shot that the product makes it to market.

Given the high attrition rate in the drug development process, there were certain capabilities that worked to facilitate the success of co-development. Hagen explained that there was a recently created “right the first time” office for co-development. This office aimed to “consolidate and direct a single means of product development.” Right the first time looked at how to define key parameters for the process, assess risk, decide on how much risk to accept, and how much knowledge was needed for a successful transfer. “This office is as close as it gets to having a knowledge management system,” said Hagen.

The formation of the right the first time office was also driven by the sheer size of Pfizer in combination with the need to successfully transfer knowledge in such a large firm. “Knowledge transfer is absolutely critical. You need to enable a common language for transfer to occur.” Part of the get it right the first time initiative was to create language and standards within PGM to prevent barriers relating to transfer that have occurred in the past. Hagen said:

When Pfizer was a small organization, knowledge transfer was not a problem because there were only three or four of us that had to worry about this issue. All three or four of us used the same language, understood how to transfer, and understood the level of risk. This was much easier with four people. Now, there are 300-400 people on the PGM receiving end, and 1,000 researchers on the PharmSci side.

As Hagen saw it, on an organization level, “size is a problem”. In a smaller company, there were only two or three projects going on at the same time, and everyone knew about all of them.

“With Pfizer, you have to carve [the organization] into silos because it is such a big, global firm. You want to allow a network driven by scientific expertise and knowledge sharing to occur by discipline.” When Pfizer was smaller, there were time periods in which no products were transferred for one or two years. So the team became “rusty” in terms of practices because these

practices were only retained within the individuals and not anywhere on paper. This highlighted the fact that Pfizer was a very oral culture: “We convey and transmit knowledge through people on the phone or in face-to-face meetings. Therefore, it is much harder to retain knowledge as an organization.”

With a larger organization, there were more members, and thus, more knowledge that needed to be captured and retained via a standard knowledge capture and application process. This was a process Hagen believed Pfizer should have to improve overall development efficiency. The extent of capture and sharing was exemplified by collecting project reports in a centralized Global Document Management System built in a searchable and retrievable database, similar to an online library. In the past 18 months (months preceding March 2006 interview), Pfizer installed an electronic brainstorming system so that all the organization’s chemists could see problems, work on problems, and make suggestions. “This was a big step,” according to Hagen, but long overdue, as units such as Discovery, PharmSci and PGM all had a substantial number of synthetic organic chemists.

5.2.2 Co-development from the PGM perspective: New Products Group

Kevin Nepveux³⁸ was the VP of New Product Development, which belonged under the umbrella of PGM and linked into the co-development process. Following proof-of-concept trials, Nepveux’s New Product Group began to pay attention to a new drug; prior to this, it was possible the team has not even heard of the product. Three or four years before filing with the FDA, PGM selected a site for product manufacture. This site selection was determined by the following factors:

- The existing technologies at a site (i.e. capsules or tablets) determines the first cut of possibilities;
- A site’s role in the network: was the site suitable for making a product for a global launch or did it have a more regional capacity;

³⁸ Nepveux was a chemical engineer who has been with Pfizer for over 25 years; 15 of those years were spent in new product development.

- The site's overall volume capacity: was there a need to add additional capacity at a site? Will the site work for the first 4-5 years of making the product? (initial site choice was for the first 4-5 years of making a product);and
- Overhead and labor costs at a site under consideration; were there any tax benefits of the site under consideration?

After considering these factors, a recommendation was made to Pfizer management. Nepveux thought that as far as manufacturing was concerned, the high technology steps (i.e. the last steps of making an API) were critical, and would probably stay within the U.S. or Europe. Anything that was less critical or characterized by stable technology, would eventually move to low cost locations; low cost locations were suitable for simple processes or intermediates. Perhaps over time, according to Nepveux, Pfizer would increasingly use low cost countries.

At the time a site was selected for product manufacture, the co-development team was also selected. A technical project manager from Nepveux's new products group would lead the co-development team. Typically, if the product involved making an API, a chemical engineer led the development team, serving as technical project manager. If it involved a tablet or a capsule technology, a pharmacist led the team as technical project manager. All technical project managers leading co-development had prior experience in manufacturing or R&D, which meant that prior to becoming a technical project manager, he or she had experience developing and transferring technology.

The co-development team was responsible for: planning/executing technologies, supplying clinical trial demand, generating data for commercial manufacture, conducting any research related to a technology, qualifying a manufacturing site, and creating a launch plan (which covers product validation through launch). Different types of technological co-development teams were assembled based on what the product needed. An API team was always part of co-development. This team focused on blending, filling, and identifying critical parameters of an API as well as performing stability profiling of the API. The other two main types of technological competencies/teams necessary were:

- Formulation team: specialized in capsules, tablets, etc.
- Chemical synthesis team: focused on technology, the processes and safety issues surrounding a technology (i.e. explosivity; transition energies) and the ability to produce the correct physical properties.

Technical project managers assisted in evaluating new drug delivery technologies (i.e. technology for extended release tablets), keeping in mind if the technology under consideration would require Pfizer to contract, partner, or invest internally, as this choice effected the overall management of the project. Pfizer would develop new drug delivery capabilities if the technology was going to be used for several other projects in the future. As a rule, the firm preferred drug delivery technology platforms that would be used over and over, and were not once-off technologies. While the development division chose the technology platform used for a new drug, it was the co-development team's responsibility to follow through and implement that choice. Good communication was key so that a technology was not only efficient, but also safe within a commercial facility. Commercial efficiency, or making the best use of commercial equipment, was important to Pfizer, particularly in maintaining low cost. According to Nepveux, most of Pfizer's partnerships formed because of technology; particularly in the case of acquired products, which joined the Pfizer portfolio with pre-existing relationships and contracts.

The co-development team remained together through the product launch. Getting to product launch was a process that required coordination from a number of angles. Most planning and coordinating could be done electronically, "everything is virtual" says Nepveux, citing teleconferences, video conferences, e-mail, and net meeting as virtual communication methods used within Pfizer. All planning activities were organized using Microsoft project, and could be accessed by all members of a team (from development through manufacturing) via a database on the company Intranet. Any activities and plans involving regulatory tended to be more controlled and presented in formal documents that were strictly monitored in terms of version control.

Nepveux believed that leadership on co-development teams directly impacted a product's success: "good leaders have successful teams. They're able to motivate their team and interact

with development and manufacturing, essentially bridging these two areas.” Co-development teams typically had a separate manufacturing leader with significant experience (classified as 10 years or more) within manufacturing or new products. Prior to launch, teams were in a situation in which no one had experience with the new product, there could be surprises. These surprises were manageable because of good leadership and Pfizer’s policy of keeping new drug products at sites with experience launching new drugs, mainly Ireland and Puerto Rico. “Launches will most likely always occur from Pfizer facilities. After a successful launch, manufacturing can move elsewhere. Pfizer will aim to keep more complex products within their control and probably at their original manufacturing sites,” reported Nepveux.

Figure 5.1 Pfizer Organizational Chart A

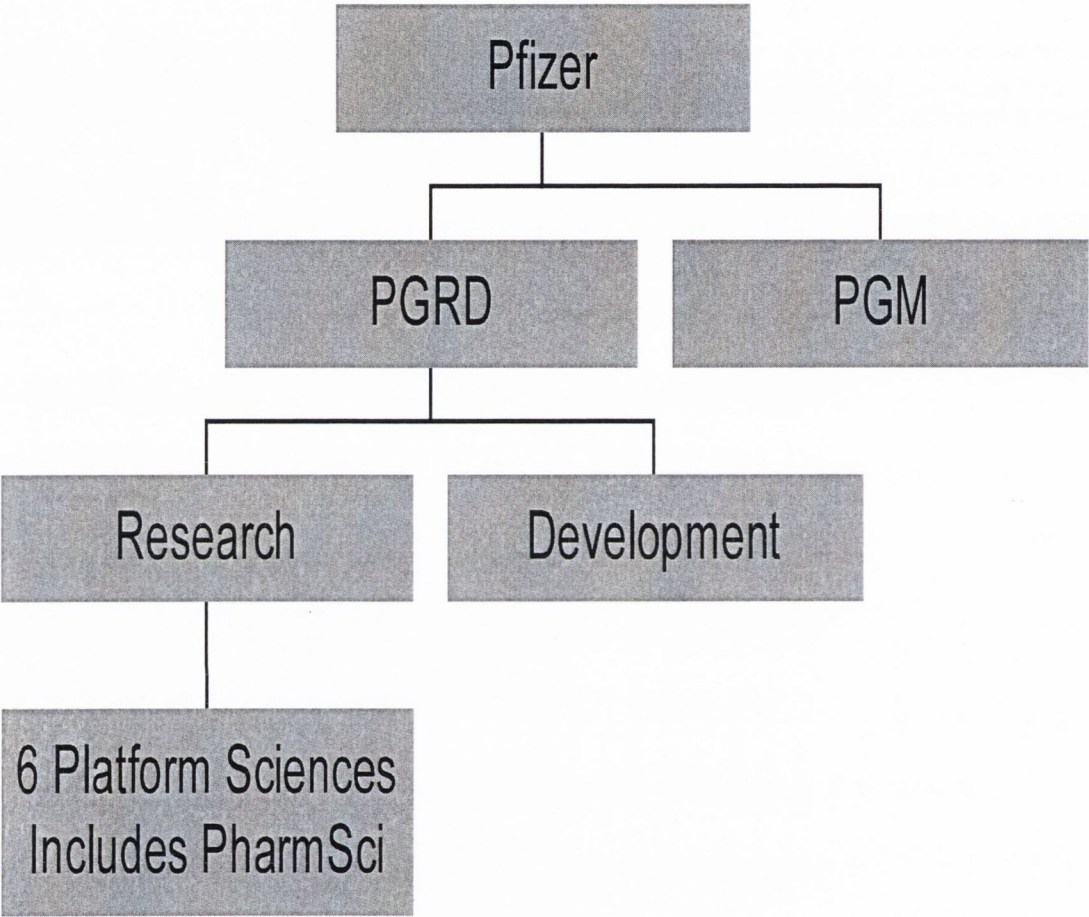
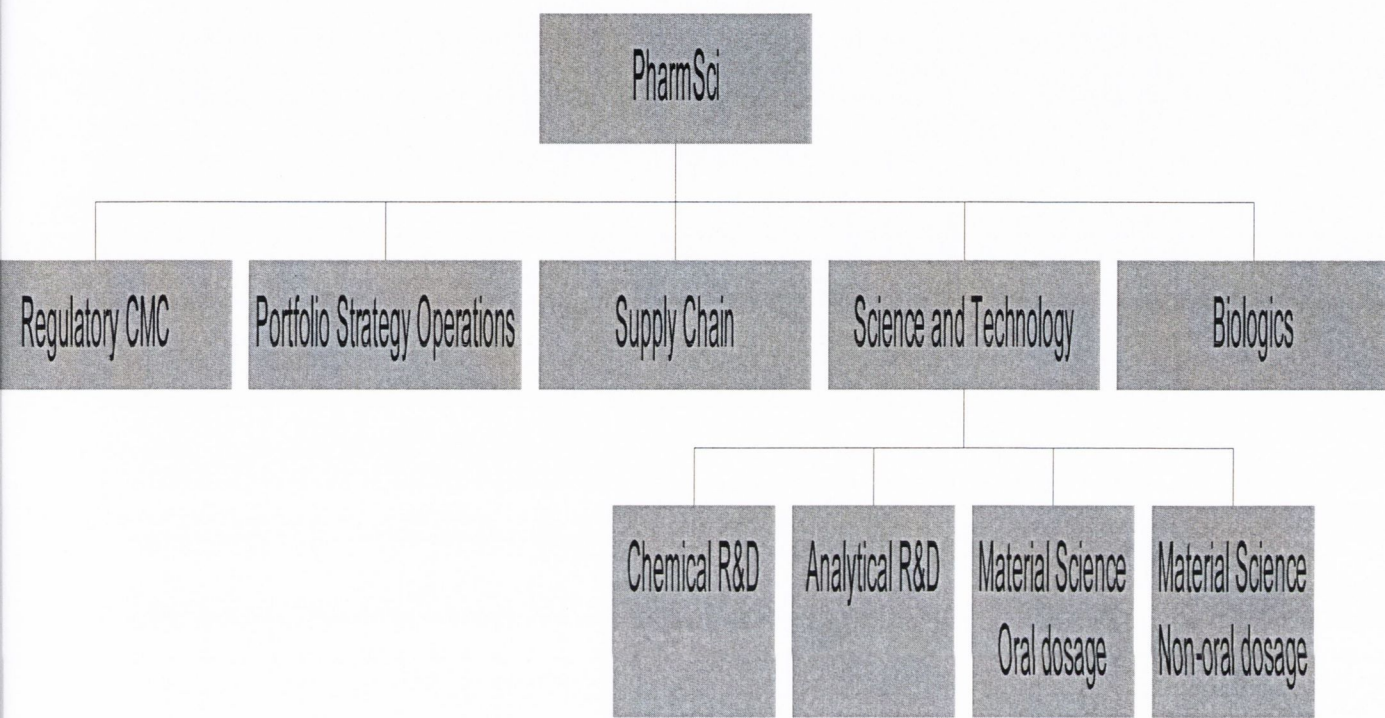


Figure 5.2 Pfizer Organizational Chart B



Description of Science and Technology sub-units

- Chemical R&D: Involved with bond forming for synthesis, scale-up and transfer to PGM. There were two focuses within chemical R&D: design and optimization for PGM.
- Analytical R&D: The glue that held it all together in terms of reproducibility of the product. Developed mechanisms to assess key parameters that must be controlled to ensure the safety and efficacy of drug products.
- 2 centers of emphasis: material science (oral dosage) and parenteral development (i.e. drug products that were not oral, i.e. injectables or inhalables).

5.3 Supply Chain Management at Pfizer Ireland facilities³⁹

Pfizer Global Manufacturing (PGM) operated worldwide, supporting the firm's major markets. PGM aimed to meet the demand for Pfizer products and to act as a strategic resource in launching new products once regulatory approval was obtained. Supply chain management was part of PGM and acted as the link between Pfizer's customers' needs and operations. Its goal was to ensure Pfizer met customer needs and expectations 100% of the time, which included assuring that Pfizer products were always available to customers.

5.3.1 Evolution of Pfizer Ireland

In Ireland, Pfizer's 2000 acquisition of Warner Lambert added four plants; acquiring Pharmacia in 2003, brought the overall portfolio to six plants. Five of the six plants were located in the Cork area, and one was in Dun Laoghaire (County Dublin). Four of the six plants were Active Pharmaceutical Ingredient (API) facilities, and the other two were drug product facilities. One of the drug product facilities (Dun Laoghaire) was a sterile plant. The other drug product plant in Loughbeg, Co. Cork was a tableting facility that made Lipitor tablets.

Ireland was part of a global network of Pfizer plants. The expectation was that by the end of 2006 there would be a total of 71 worldwide Pfizer plants. The legacy Pfizer plants added together with plants acquired from Warner Lambert and Pharmacia, totaled 93 plants in the network. By June 2005, 12 of those plants had been shut for synergy reasons. Another 10 were in the process of being shut or divested. According to John Cronin, Director of Customer Service at the Ringaskiddy plant "one partial requirement of our network is in justifying the continuation of some of the plants, and indeed, as you would expect, there is some duplication of activity that would prompt the need for consolidation and synergy".

5.3.1.1 *Little Island API*

Little Island had 16 different API insured or legacy insured products and was in the midst of introducing three new products. All Little Island products contained active pharmaceutical

³⁹ For biographical information on subjects interviewed for this section, see Appendix I.

ingredients. The customer base for this plant was mainly 15 other Pfizer drug product plants. The customer base for this plant was about average for an API plant. By comparison, a drug product plant had about 100 customers and interacted with a myriad of countries. However, API factories only dealt with drug product sites. The APIs (from Little Island) went to drug product plants, the main customers were located in Sweden, Italy, and Belgium; then a number of APIs were distributed from Italy to other countries, such as Australia, Mexico, Korea, Japan, but Little Island API maintained the responsibility for managing those relationships.

Little Island began manufacturing Gabapentin, the drug substance for Neurontin, in 1994 and Lipitor in 1995. In 1997, Lipitor was launched and because of its phenomenal success, a large expansion program began at both the Little Island and Loughbeg sites. The expansion program took 4 years to complete. All drug substance for Lipitor was supplied from the Little Island site with intermediates from Little Island and Loughbeg.

On June 7, 2005, Pfizer announced that the Little Island site (a Warner Lambert legacy site) would combine with the Inchera site (a Pharmacia legacy site), and be called Little Island API.

5.3.1.2 *Ringaskiddy API Plant*

Pfizer set up its first production facility in Ringaskiddy in 1969 to produce food chemicals, including citric acid and gluconate products. In 1972 another production plant, Organic Synthesis Plant 1 (OSP1), was constructed to produce bulk pharmaceutical products. A second Organic Synthesis Plant (OSP2) was completed in 1984, effectively doubling production capacity to meet the increasing demand for pharmaceuticals and a widening range of products. In 1990, Pfizer sold its worldwide citric acid business to Archer Daniels Midland. In 1995, a third plant, OSP3, began production, once again doubling production capacity at Ringaskiddy. In 2001, OSP4 was successfully completed to meet growing production demands by increasing overall capacity on the site by a further 40 percent. These four plants were all multipurpose, manufacturing APIs. Ringaskiddy had 14 APIs for in-line products. In the new product portfolio, the site usually had would between three and five APIs, at any given time.

Pfizer at Ringaskiddy exported bulk pharmaceuticals, which were shipped from Ringaskiddy to Pfizer plants across the world for finishing and packaging. This plant also scaled up new products in cooperation with Pfizer Global Research & Development (PGRD) to ensure timely approval and launch of these new products. The supply chain group at Ringaskiddy was responsible for four functions:

- Planning, production planning, associative demand management;
- Customer service: supplying product to customers and associated responsibilities;
- Procurement: everything Pfizer purchased for the products they made, chemicals they used or office supplies;
- Facilities management, warehousing and storage: several facilities on site at Ringaskiddy.

5.3.1.3 *Loughbeg Drug Product Plant*

Lipitor's success made it necessary to build a new state-of-the-art tableting facility at the southern tip of the Loughbeg peninsula in Co. Cork. This location was chosen because of the availability of a highly educated and skilled workforce and the close proximity to the existing bulk chemical site that would supply its drug substance.

At its peak, 1,200 people worked on the construction of the 380,000 sq. ft facility, which commenced in December 1997. An extensive recruitment campaign attracted some 1,600 CVs and the first colleagues moved into the new plant in November 1999. Regulatory approval to produce commercial batches was granted by the Irish Medicine's Board and the Food and Drug Administration within an unprecedented two and a half years of breaking ground.

The Loughbeg Drug Product Plant was one of Pfizer's legacy plants, it belonged to Warner Lambert until May 2000. As such, unlike the Little Island and Ringaskiddy plants, Loughbeg supported two third-party customers, one in Italy and one in Spain, who had contracts with Warner Lambert before Pfizer took over. These two third-party customers comprised about 2-3% of the Loughbeg plant's business.

Additionally, this plant was different from Little Island and Ringaskiddy in that it was a tableting plant, not an API plant (for organizational differences, see appendix II). The Loughbeg plant took the API made by Ringaskiddy and combined it with other ingredients (i.e. binders,

fillers, and disintegrants). Essentially, these ingredients were put together in a big bin, more liquid was added, and it was placed into a big dryer. As for the remainder of the tableting process, Kieran Ruddy, Supply Chain Team Leader at Loughbeg Drug Product Plant, said:

Once we have a gram of it, it's as good as a tablet... the machine, compacts powder together with force. This machine is double-sided, probably 80 punches on either side, revolves around at about 60 revolutions per second, so every second you'd get about 160 tablets off... And this thing is running 24 hours a day, so we manufacture for Pfizer about a billion tablets a year.

Loughbeg's mission was clear: to make tablets, and to make them in very high volume. The whole plant was designed for one product: Lipitor; the plant layout was also geared toward high volume, low complexity, and took advantage of scale. Loughbeg made three strengths of Lipitor. The fourth strength was made in Puerto Rico. At one stage, the plant packaged the product, when the plant was smaller, but that stopped when Pfizer executed the merger (packaging is now done in Fryeburg, Germany).

At the moment, Loughbeg was in the process of qualifying a second and a third product, with production slated to begin in 2006.

5.3.2 Global Scope

Ireland was a key location for the company. Locations in Cork and Dublin maintained close working relationships, especially since some contributed to the same product. Furthermore, the product profile in Ireland was important: "... a very key one would be our Lipitor product. We have a lot of products that are very key, so as a region I believe that Ireland would be seen as a very important location," said Teresa Chambers, Supply Chain Team Leader at Little Island API.

The global nature of Pfizer's supply chain was most apparent with the Lipitor product. A Pfizer customer in Fryeburg, Germany took more than 80% of Loughbeg's Lipitor drug product and packaged it for the U.S. (the biggest market for Lipitor). Fryeburg also packaged for the local area markets of Germany, Belgium and Holland. And, it packaged for Turkey, and the Middle East. All total, Fryeburg probably supported about 100 of the Lipitor markets. However, Loughbeg sent drug product to the U.K. for packaging in the U.K.

The Fryeburg location was also responsible for managing the complexity that went with packing the drug product. This meant keeping track of how many markets were supported, language and regulatory issues, and the numbers of strengths of tablets. According to Ruddy, all of these configurations “just blow up into a thousand different SKUs.” Fryeburg managed complexities in terms of leaflets, cartons, the packaging literature, etc.; this site’s job was to take this high volume product, turn it over quickly, and get it out the market via wholesalers and distributors.

5.3.2.1 *Ireland and Singapore*

Within the Pfizer Global Manufacturing division, Pfizer was organized across five operating areas, each directed by a division president. Those operating areas were as follows:

- The U.S.- including Puerto Rico;
- Latin America and Canada, which obviously includes South America and Mexico;
- Asia, Africa and the Middle East;
- Europe, *not* including Ireland; and
- Ireland and Singapore.

Geographically, the pairing of Ireland and Singapore did not make sense. However, the two were paired together because Pfizer recently built a plant and commissioned a major API facility in Singapore. This meant that outside of the U.S., all the APIs for Pfizer were manufactured either in Ireland and/or Singapore. Ireland traditionally was its own area, separate from Europe, because of critical mass reasons: there were about 2,000 people in Pfizer in Ireland, spread across six plants; Ireland produced a significant amount of product for Pfizer, which was sent to the major plants across the world; from Ireland, product was used in approximately 80 countries and transported to 130 markets around the world. Management targets Irish plants for new products, to manufacture them until they got to a mid-range level in the product’s lifecycle. Some of these products would become blockbusters (for details of a product lifecycle see appendix III). In that case, Ireland would be responsible for the scale-up of the product and then would transfer production to Singapore (where manufacturing was cheaper).

5.3.2.2 *Taxes and Low Cost Countries*

“Manufacture in Ireland. Make no bones about it. The education system is very good, smart work force, but it is taxes.” –Kieran Ruddy

According to Kieran Ruddy, the tax regime in Ireland was what made the pharmaceutical industry so successful here. For example, the Lipitor patent “is very tied up in the whole Ireland area. They’ve manufactured in Ireland for a long time. The tax benefits of doing it here outweigh many other possible locations”. Lipitor was made in Ireland because it was an ideal tax location; manufacturing in the U.S., with tax rates near 40%, would not have been nearly as profitable.

However, tax rules were slated to change in 2010 and move from 10% to 12.5%. Thus, manufacturing here could become less lucrative. Ruddy thought this could lead to a situation in which Pfizer scaled up and perfected new drug products, while taking advantage of tax benefits in Ireland, and then moved the drug to a lower-cost location such as Singapore. However, Ruddy said when you compared Ireland to other locations, it was not attractive at all:

Ireland is an expensive place to do business. People are expensive here, capital and investment is extremely expensive... costs are higher over here, for example waste disposal costs... But, there is technical expertise here as well, which you may not have in less-established markets. However, once you have a presence in less-established markets, it opens up a whole new market for you as well.

While Ruddy envisioned many companies moving to low-cost locations, he did not think it would mean a major problem for Ireland’s pharmaceutical business. Moving to low-cost locations entailed many challenges. For example, there were not many FDA-approved facilities in China. A company like Pfizer could not risk sending a product to a low-cost location for manufacture if potentially it would be illegally copied two weeks later. If a product was competing with generics then it could become imperative to do something in a low-cost location for the sake of staying competitive.

5.3.3 Relationships

Teresa Chambers explained that most relationships with outside parties were developed through procurement; most relationships, once established, turned into long-term relationships.

According to Chambers, “I think that would tend to define the pharmaceutical industry more than other industries: the movement toward long-term and being in the long-term... a lot of relationships [in the pharmaceutical industry] are over a 20 year period, whereas other companies may be more 3-5 years.”

Chambers insisted that developing long-term relationships was an integral part of the industry, partially because of regulatory requirements. The regulatory aspects involved with making a change within the supply chain required long-term relationships; as soon as a drug company patented a drug, they must establish long-term relationships with reliable suppliers to maximize the patent life of a product. Through relationship maintenance with suppliers, Chambers believed Pfizer could “ensure that we get the best as Pfizer... and leverage ourselves so we get the best performance from our supplier.”

Ensuring the stability of the supply chain required having two suppliers for every component Pfizer sources from outside the company. Then, if something went wrong with one supplier, the company already had another supplier that could replace or increase capacity of the supply so that drug production would not fluctuate.

5.3.4 Regulation

A constant issue within the industry had to do with regulators, particularly the FDA, EMEA and Japan. Over the past few years, Pfizer focused on how it could work best with regulators, and how to get regulations to work best for them. Staying aware of regulations in different countries was not an easy task. Chambers said:

The FDA has autonomy over what is done in the US, and the IMB [Irish Medicines Board] has autonomy over what we manufacture⁴⁰. It’s actually a very significant point. It’s a group we work very closely with. But our overall quality group is working really with all of the regulatory groups to really come up with the best ways and to work toward a model of being more flexible... I suppose part of the complexity is the number of regulatory bodies you’re dealing with. You mentioned the EMEA and within that you’ve got all the European countries, you’ve got Japan, you’ve got Canada, Australia, a full range of them there.

⁴⁰ The IMB issues Little Island API with their manufacturing license.

Chambers continued to explain that further complexity usually stemmed from smaller countries:

...And sometimes it's the smaller ones that you get caught with. They [small countries] may have just one, a different test or a different specification or something that's a little bit different. What you're trying to do in that case is really harmonize as much as you can. You're working to harmonize one specification or two, or possibly three. But in general your focus is on doing that because if you don't and you want to maintain it, it is more complicated as you move forward.

Making changes to a product, within the supply chain or manufacturing was a serious decision at Pfizer. Changes that would have an adverse effect on the patient or the product were not allowed. Further, the value of making minor changes for the sake of increasing profitability had to be carefully considered:

...it varies by context really, you've got for any of our products they're marketed in over 100 countries. So in terms of making a change you're looking at over 100 countries to make a change in. Some are very simple, some are very clear, and some are less simple and less clear. In fact, where you have the clarity that's what really makes things easier. At least if you know, for example, exactly what to do and how to get your approval, it's very clear... In cases where it's not that clear, it can be difficult... You may have plans to make a change, but you have to be really clear about what's going to happen, how you're going to bring it through (Chambers).

Changes were implemented sector by sector because firms must notify sector regulators about the change, and approval needed to happen then, in each market, before a new product was shipped out to the market. Furthermore, some markets approved faster than others⁴¹, meaning a firm would be making a different series of products for different markets, and this seriously complicated the supply chain. From the supply chain perspective, products cannot ship to a market that did not have approval for a variation or change; this needed to be controlled through the supply chain, and in particular through the packaging locations.

Oftentimes, the easiest point at which to deal with regulators was when starting a new product. At this stage, a firm could report to authorities what the product was and how it would

⁴¹ Approvals could take two years, three years, or five years, while some markets approvals were made within thirty days. Ruddy said that there were markets, "like Taiwan who don't want to hear about any changes, or Russia, Poland or Ukraine. " By the time you got approval for a two year old change, firms could very well have made a number of other changes that were waiting to be approved.

be manufactured. It was difficult to envision how a product was going to evolve and what the evolution of a product would mean for regulatory obligations; thus, Pfizer's product model considered product evolution.

Chambers and Cronin were fairly positive about the existence of regulatory bodies, even though they added complexity and constant monitoring of updates and changes to regulations. Kieran Ruddy at Loughbeg, however, was more measured about the role of regulation: simply put, regulators "increase the length of the supply chain... It increases the inventory of the whole." According to Ruddy, regulation was a checks and balances system that ensures that the product going out to the customer had the correct efficacy. However, this meant that pharmaceutical firms cannot operate in isolation: whatever Pfizer puts out on the market they must take responsibility for, even if they did not supply all the components of the product themselves.

Ruddy considered the FDA the most up to speed on what was happening within the industry and what other regulatory bodies were attempting or implementing. Pfizer left much of the interface with regulators to their global group in New York, called Global Manufacturing and Compliance. While overall regulatory coordination happened in New York, there was a person in each of Pfizer's markets who was responsible for interactions with the authority for that market. In the case of making changes to drugs, this "on the ground" agent needed to take the changes and put through the appropriate documentation. In some cases there was a language issue, which led to a protracted time frame, and difficulties in making certain changes in certain markets. The size of a product's customer base could also influence regulatory authorities, for example, "Lipitor's a big product and it might get more air time, whereas if you're making a less big product in that market, and you've got all your competitors making changes at the same time, you're sort of feeding all into one funnel, maybe feeding faster into the funnel than approvals are coming out" (Ruddy). According to Ruddy, no matter which way you looked at regulatory issues, "it must be a lot of paperwork and a lot of cost."

5.4 Supply Chain Operations

The basic day-to-day supply chain operation was similar between the three Irish plants. The supply chain teams in each plant were responsible for working to assure the reliable supply of everything needed to manufacture products; controlling the dispensation of materials for immediate dates of manufacture; and making sure that the products get to customers in the appropriate condition and at the appropriate time based upon their needs and requirements. Achieving those three goals involved a huge amount of detail. In addition to those goals, each plant, from a procurement perspective, had a fundamental objective to improve the quality and cost of Pfizer products; to buy quality goods and services at the best possible competitive market prices.

In Ringaskiddy, the supply chain group was comprised of 38 people in the following teams:

- 24 staff in warehouse activity who controlled all materials;
- 5 staff in stores- material management for the stores (which means engineering spares, replacement items for the plant, the physical plant, laboratory equipment, etc.)
- 9 staff managing all supply chain activities, including procurement, planning and customer service.

Loughbeg had a slight variation on this structure, Ruddy organized in terms of four blocks:

- Procurement
- Purchasing
- Planning
- Customer Service

Procurement and purchasing were interlinked because of the requisitioning system between the two, while planning and customer service worked together to meet customer demand.

5.4.1 New Product Introduction

When Pfizer Global R&D (PGRD) developed a new product, early in the product's life cycle, a Pfizer Co-Development team began to analyze which plant was the best fit. The best manufacturing site for a product was often determined by a number of factors, including equipment availability; product and local knowledge; the ability for technology transfer; plant capacity; timing and the ability to get the product to launch quickly. The co-development team

aimed to maximize the product mix for the manufacturing site. This team would also closely look at the product mix, cost and quality within Ireland. For both old and new products, Pfizer focused on getting and maintaining the best pricing from their suppliers; pricing was particularly important for newer products because the firm always wanted to “achieve the lowest cost of production early on and carry it through the life cycle of the product” (Chambers).

Ireland, and more specifically, the Ringaskiddy API plant, had a key role in the scale-up of new products. Making a new product, just out of PGRD, was a considerable challenge. This was primarily because there were many new issues associated with new materials, and/or new technologies. New materials and new products often required evaluations that were best left in the hands of a mature manufacturing site, according to Cronin. By comparison, “Singapore is a very young site. It would not have the experience in new product introduction along the lines of what Pfizer Ireland would have” (Cronin). Furthermore, “Pfizer Ireland is regarded generally as a scale-up area within Pfizer, for reasons that we have a whole series of capabilities and experience that goes back 30 years” (Cronin).

Kieran Ruddy anticipated that Loughbeg would produce TCP, short for Torcetrapib⁴², because it was related to Lipitor. TCP was combined with Lipitor to reduce bad cholesterol and increase good cholesterol. TCP would be one of the two new products Loughbeg added to its portfolio; it made sense to produce it at Loughbeg because this drug had the same supply chain and the same tablet mold as Lipitor. Ruddy said that “anything to do with Lipitor, we probably would try to make it” and he believed Pfizer management would consider the Irish plants first for a new Lipitor-related drug.

Two years ago, the Loughbeg site began qualifying a second product for the plant, Norvasc, for hypertension and blood pressure. But, Norvasc was going off patent in 2006, and Pfizer could lose approximately 5 or 6 billion dollars. According to Ruddy, “without a patent your business

⁴² In 2006, Pfizer halted late-stage development of torcetrapib after a trial showed it was associated with an increased risk of death. Torcetrapib's failure was a huge disappointment that contributed to a decline in Pfizer shares.

goes off the cliffs. Gone. So Pfizer will be looking to extend the patent or protect the patent by combining two products together” (Ruddy).

5.4.1.1 *SC Design*

The supply chain at Little Island API could accommodate a large range of products. The site’s profile included 16 APIs, but about 10-12 product campaigns could occur simultaneously. Some products were produced by tons, some in hundreds of kilos, some in tens of kilos and some in kilos, according to Chambers.

Supply chain design was driven by supply chain network design. A network driven supply chain often related to tax drivers. According to Ruddy,

We’re [Pfizer Ireland] competing with Puerto Rico and Singapore. They’re tax locations, we’re competing with some of the locations. So initially as you uncover a new product, a new API, you bring it to, probably Ringaskiddy... to optimize the process, and then probably move it on somewhere else.

In other cases, the product determined the supply chain design. If, for example, an API was classified as high containment, the compound was hazardous, potent and expensive to make, as in the case of some oncology drugs, the product needed go to a high containment facility. Thus, oncology products were often grouped in terms of supply chain and disease area; Little Island, for example, was an oncology drug production site.

Also factored into supply chain design was the cost of creating supply chains. High containment and tableting plants were very expensive to build and maintain. Tableting facilities were especially unique because of the technology involved, and Pfizer had only a few tableting plants around the world. The supply chain at Loughbeg, for example, was focused around tablets and had an added degree of specialization because Loughbeg only made drugs in the cardiovascular disease area.

5.4.2 Tools

Kieran Ruddy seemed to be the resident Pfizer expert on supply chain management technology, and predicted that Pfizer’s tools for SCM would further evolve over the next few

years. The tools used to manage the supply chain essentially revolved around the MPS, or mass production schedule. The MPS dictated which product the plant made, when it was made and how much of it was made. The MPS was loaded into a (Loughbeg) site-wide ERP system, called MAPS, which was able to run the MRP (materials requirements planning) program and told the organization what needed to be bought, when, and how much.

The supply chain team did not need to manually do anything in order to determine production and planning schedules. Logic was built into the ERP system, to figure out what materials were needed. Ruddy explained, “So as your MPS changes based on demand, you’d need a bit more or less of different products that you have to use. You run MRP and it tells you how much you need to either expedite in case you’re not going to have enough of this specific component or de-expedite it, look we’ve got so much of it.”

The ultimate goal, as far as Ruddy was concerned, was to inter-link the MAPS systems on a global basis. In 2005, each plant had its own MAPS system. “So there’s a MAPS in Loughbeg, and Little Island, Ringaskiddy, and our customers have MAPS framework. But they wouldn’t have these systems hooked up [to ours] (Ruddy).” Pfizer wanted the plants and the markets to coordinate through MAPS systems. Ruddy explained that there were two systems within MAPS that could work together when, and if, the system was globally integrated:

MAPS would be like a retention system. There’s two systems. One is a forecast, the second would be replenishing. So we operate two supply chain processes. One is to take the order, the other is replenishing. So orderers, it’s like, the customer says ‘I want 10 pounds of one tablet on the fifth of January, and here’s a PO number, a purchase order. For replenishment, what we do is you agree with your customer to certain parameters, a minimum and a maximum of inventory. So I want 10 pounds, the maximum is 15 pounds. So it’s up to the plant to make sure the inventory is replenished in the market, anywhere between those two numbers. So we don’t care, you know, one purchase order would cover 8, maybe 12 months, we only take it out when we need it, so you need to have system that can monitor it on the industry level and figure orders automatically... So based on the market inventory, an order is figured back to the plant automatically, a drug product plant and that’ll pack another order for Taiwan, and create an order in the system, process planning, and execute that plan and pack it off.

Loughbeg was an anomaly with access to the MAPS system of Fryeburg, its biggest customer. Loughbeg was able to log into Fryeburg’s planning system every day, see what inventory they

had, and see what the packaging schedule was for the next 18 months. Loughbeg could take raw data from Fryeburg's system and put it into MAPS via the MPS and get an MRP schedule created automatically.

Ideally, increased visibility between plants and customers would be highly beneficial. If Loughbeg were hooked into the API plants they received product from, they could see when they were going to receive API to make the drug product. Ultimately, this would lead to a total transparency of demand, inventory and supply; a more efficient supply chain.

5.4.3 Best-in-class/Benchmarking

In terms of benchmarking and introducing products and practices that were best-in-class, over the past several years, Pfizer had created a "get it right the first time" group. This group was responsible for focusing on areas and processes that would ensure that any new products or changes to existing products were manufactured correctly the first time. Chambers said that this "get it right the first time" group actually covered a huge variety of areas within the company and was continuing to refine their contributions and responsibilities. Perhaps this group would take some initiative in constructing benchmarking practices for Pfizer, as benchmarking manufacturing practice was something that Pfizer needed to start doing.

According to Ruddy, the biggest measurement area with the Pfizer, and industry supply chain, was inventory. "Inventory has become a big focus with Pfizer, typically the industry, or Eli Lilly or Schering-Plough, hold months and months of inventory" (Ruddy). Inventory was higher in this industry because pharmaceutical companies wanted to make sure that a customer never runs out of product (according to Ruddy). If Lipitor was not available, then perhaps the patient would switch to a competing product, like Crestor. Ruddy explained:

We're looking more closely at inventory. Inventory will be a focus moving forward- particularly in terms of manufacturing cycle times, testing cycle times. How long it takes the laboratory to test a batch of the product, and then once the test is done there's a release date as well so there's a lot of documentation that needs to be reviewed. That whole release, how long it takes to make a batch, release the batch and then get it to these guys- that is going to be a focus. We need to minimize the number of tablets tied up in the chain.

5.4.4 Scaling Up

Pfizer Ireland, and more particularly the Ringaskiddy API plant, were particularly adept at handling new products and serving as a temporary home for products as they were scaled up before moving to more permanent manufacturing locations. To support new product manufacturing, Pfizer Ireland was strengthening their organization by creating a new product introduction and team leader position in Ireland to support all of the plants. The need for such a specific position stemmed from the fact that scaling up was a complex process.

A plant was normally asked to scale a product when it was phased through clinical trials. The plant then focused meeting several scale-up objectives:

1. To prove that the process works;
2. To produce quality products in accordance with our specifications and methods; and
3. To provide data to input into our regulatory findings, and to qualify the site as a location of manufacture.

Accomplishing those objectives normally took from the time the product facility was proposed to the time a plant was able to complete a Pfizer Approval for Work (AFW) campaign. Cronin explained:

The AFW, or Approval for Work, system is a very basic trial. An AFW campaign would take, from start to finish, from 12 to 18 months to complete the product and have it tested. Then we move on to the next phase of activity, provided that the product is successfully making its way through clinical trials. We may have what's called, and this is optional, we may have a reload campaign. A reload campaign is to provide more material into the supply chain for the purposes of clinical activity, studies and research and so forth. So that may be required if the product demands it, and then again it may not. Then the third activity, which is if the product is successful and reaches what we call its filing mark, to be filed with the regulator for approval. Around about that time we start to manufacture what we call the launch quantity. So, we make the API and that API is supplied to the various drug product plants, to provide them with the materials available to the supply chain network. More globally, the materials that we would use to launch the product commercially.

5.4.5 Key supply chain characteristics

Each Pfizer interviewee was asked the question, “In your opinion, what are the most important characteristics for your supply chain to have?” Answers varied depending on the interviewee and, the product mix/portfolio of each site. Discussion was organized by interviewee/site in this section and quotations used to maintain accuracy and authenticity of the responses.

5.4.5.1 Chambers (Little Island API)

I suppose you’d look at it in terms of strongest contribution. I think about how I can make the strongest contribution here. I think you’ve got to have flexibility and agility, and I think that’s becoming much more apparent in the industry. I think maybe in the past that’s one thing that hasn’t been as strong.

That’s your absolute goal [making a patient better]. So you do have to keep that end in mind at all times. It’s kind of complex, because you’ve got the agility, but you also have to be able to deal with things on a very immediate day-to-day basis, but keeping the very long-term goal in mind, looking toward the long term. I think that maybe what makes supply chain different from some of the other areas is that supply chain goals must consider how the chain will look in 3 years time or 5 years time. It’s almost that longer term combined with what I’m doing right now, what is it actually going to deliver in a couple of years time? That can have quite a difference on your thinking.

I think though, because it’s a very knowledge based industry as well, on that basis you need quite a bit of stability in that [referring to knowledge]. The more knowledge you have and that you can keep with your people [is important], it isn’t something that you can pick up very quickly. There is a lot that you need to learn when you come into the industry. It is kind of different, and I guess a number of people in my supply chain team came from different industries. They were aware that it would be a very steep learning curve and to be ready for that and to really go for it, that it would be very different from the collective industries they had been in. They brought a lot of different things with them, and I came from a different industry background as

well. It is that different. Sometimes when you look at it, it looks to be almost stagnant from the outside, but it's running hard on the inside. It's about understanding the complexities from inside, and how do you actually get from something that looks to be stagnant or not to be moving very quickly...

[it doesn't look to be moving because] Sometimes it takes 12 or 36 months to complete a project, when in another industry a similar thing might take six months. To really say that you have the stamina to go after it and that you really will stick with it. Resilience. Resilience is a word that I would focus on in the industry. It takes resilience to go after something and say that I'm going to complete it in a 3 year time frame. Because it is going to be worth it, it is really going to be worth it and it is going to deliver.

It depends on having the right employees... there is quite a bit of learning in it [this industry], and I wouldn't underestimate that. It's probably less immediately transferable, there's a lot to learn about the pharmaceutical industry that may not be as clear in other areas... but, for example, the principles of dealing with vendors and the principles of procurement would be very similar across other industries, that aspect wouldn't be as specific to the [pharmaceutical] industry.

5.4.5.2 *Cronin (Ringaskiddy API)*

First of all, we need to understand the life cycle of a product, from a basic understanding of its progress, from discovery, through development, through clinical trials, to launch, and obviously supplying for the marketplace. So we need to have an understanding of that, first of all. Then, there are dozens, if not hundreds, of specific aspects that we need to understand from a supply chain perspective: everything stretching from the commercial side of it, how much will the product cost, how can we put it into our plant, what technology is required, where will it fit, what's the timeframe its needed in? All the way to: how capable is our supply base, what are the regulatory or special considerations that we need to put into place to ensure that we have a robust supply chain into the product. Then we have to manage it through our system, and then we have to manage it out of the system again, to the customers.

First time activities for new products requires a lot of establishment of basics, like codes, logistical requirements, any special packaging and transportation issues that there may be... I've tried to give you a snapshot there, kind of a broad overview, but it's a huge undertaking. You'd almost regard it as, producing a product is almost like the birth of a child. You've a long journey to go before you achieve it.

... What we want to do is get to a situation where the visibility of products, from the time we commence a production order here at Ringaskiddy, all the way through to its final destination in the distribution network, is visible. That's what we want to see. We have some people who would regard this as conflicting priorities, but we have challenges to balance currently: the needs of having a shipped product available for people to arrive in the right form and in the right place and in the right quality and so forth [right product, right place, right time], but the other thing we have to balance with that is our management of cash and cash flow, and ensuring that the inventory side of it is appropriate for the needs of our business. Pfizer, like any other business, needs to manage its affairs reasonably well, to ensure that we are getting the right return on investment for the company, and that we have the most effective and efficient organization.

So we're very heavily focused on ensuring that we have the two elements of improving our efficiency and improving our effectiveness. Both of those principles are being underlined by an initiative currently within Pfizer called Adapting to Scale, A-T-S... Pfizer is essentially saying through the work of all the stakeholders, and there's over 100,000 of those, that we will improve the efficiency and effectiveness of our operation, such that by 2008 we will have annual savings based on today's baseline of cost of 4 billion dollars.

5.4.5.3 *Ruddy (Loughbeg Drug Product Plant)*

Complete visibility across the chain: from the API through to end customer. Visibility in terms of how much is needed, what is needed, who wants it, when they want it, and why they want it... It's enough to figure out who wants what and when they want it. In the past, some of those systems have been manually, you know, maybe forecasting every month, and then typically,

depending on whether they get it or not, sometimes you might say 'I wanted two tons of that one, I only got one ton, so now I need four tons, not two'. Replacing demand, where it's just going to be total transparency to know the extractions of the ERP systems. They'll extract data automatically into a system called Manugistics. We need total transparency for everyone so you get data much quicker and [ERP systems] take all of the analysis out of it.

Everyone needs to be able to sit at their desk and know what is going on in other locations in terms of inventory, materials, shipments, etc. That's the big thing in terms of the supply chain. This will happen, in the next year or two. A global IT group will come in and coordinate this. We've actually got some people [global IT] here, we've been running a pilot here for the last, probably, year. We set up a pilot project on atorvastatin so we set up the whole system, we captured all of those things [data capture]. We reviewed it more than once, so we get together with people from Fryburg, Loughbeg here, Little Island, people in New York and Germany, we look into the system and we see what they're doing, if all the numbers are there. So next it needs to be put out on a bigger scale.

5.5 Manager Reflections

Each Pfizer interviewee also offered his or her perspective on the state of the industry, current industry challenges and what the future of the industry may look like.

5.5.1 Challenges = leaner and fitter

Chambers, Cronin and Ruddy all agreed that a significant amount of company change coincided with industry changes. Pfizer progressed through a series of mergers since 2000, and needed to make the best of its scale. Chambers said that to do this, the company must be leaner and fitter; the right-first-time group was part of a leaner mentality. Furthermore, even with the regulatory restrictions, which made it easy for processes to become stagnant, Pfizer still had to try and do things better or find another way of doing things. This would entail interacting with

Pfizer's regulatory group and quality control, to determine how to work with certain supply chain complexities.

5.5.2 Product withdrawals = good for nobody

According to Cronin, the industry was going through a very tough time, partially because of drug safety and efficacy issues, which had received attention because of the COX-2 inhibitors and Vioxx situations. Vioxx triggered attacks on the FDA and a renewed interest in drug safety and efficacy. Additionally, because Vioxx was withdrawn from the market, there were follow-on judgments made about Bextra, which was a Pfizer product.

This adverse event was bad for an entire industry. In fact, according to Cronin, "We take no measure of comfort at all that one of our competitor's products ran into trouble. In fact, we consider it to be a disaster." This was because of the large number of people around the world with arthritic complaints using products as powerful as Vioxx, Bextra, and Celebrex. The products helped arthritic sufferers manage pain, and the failure of one product within this disease area had a knock-on effect.

Cronin believed that the current debate about drug safety and efficacy stemmed from a misunderstanding on the part of consumers that taking prescription medicine was risk-free. This perception was a very difficult one for Pfizer to manage. He said:

Taking prescription drugs is not risk-free, that is why they are on prescription. That's why doctors prescribe them, and that is why they are carefully administered to people in a very controlled environment. However, that message does not appear to sit well with the community at large. People do not expect to take prescription medicine and have any risk at all. They expect that it will be risk-free and there will be no complications whatsoever, no difficulties.

5.5.3 High Cost Criticism

The industry continued to suffer from public criticism regarding the high cost of its products. Cronin, for one, believed the cost was justified:

The reality is that companies like Pfizer are funding a huge research program. We will spend approximately 8 billion dollars this year on research and development. That is a lot of research and development. You could ask yourself, ‘what government in the world is spending 8 billion dollars on researching new chemical entities for meeting an unmet medical need?’ The answer is, none. So it has to be paid for, and the way we pay for it is by seeking to charge what we believe to be fair and appropriate prices for our product.

Again, Cronin argued that the public was suffering from yet another misperception: that drugs were the most expensive part of healthcare and therapy. The industry posited that drugs keep people out of hospitals and surgery- both of which were more expensive than the cost of drugs. In particular, Lipitor was providing protection against adverse cardiac events with serious consequences, for millions of people. Lipitor was likely saving healthcare authorities and governments billions of dollars a year.

Furthermore, Cronin thought the industry would benefit from working on its public relations strategy, trying to provide a better explanation of the industry’s activities. This could correct the public feeling that Pfizer was not a very open organization, or that the pharmaceutical industry was not very open. Cronin insisted that in reality, Pfizer was very open: “We share our data with everybody who has, first of all, a right to know, a need to know, and basically, who would request information. We do that in the spirit of our mission elements, which are very clearly defined... we are a values-driven organization.”

5.5.4 Supply Chain Skills

With respect to supply chain abilities, Ruddy, a former electronics engineering in the computer industry, said unequivocally and without hesitation that pharmaceuticals was “catching up” to most industries and it would take a couple of years to catch up to other industries. The computer industry was much better at recognizing problems with huge amounts of inventory, and subsequently found ways to reduce that inventory and related costs, said Ruddy. At Apple, inventory was taken each day and if components were needed for the day, they were brought in

that morning. In contrast, Pfizer received inventory in months in advance, partly because of the need to evaluate and test materials before they were made into drugs.

Ruddy went on to explain that companies such as Dell were quick to recognize the value of IT and the Internet in processing orders and getting computers out to customers as quickly as possible. Ruddy suggested that perhaps in the future, customers would be able to order prescriptions direct from Pfizer via the Internet. However, to achieve a system like that Pfizer would need a logistics partner to facilitate that process. Ordering direct from the pharmaceutical company would, without a doubt, revolutionize the industry because it would eliminate pharmacies, middle men, as well as costs, lead times and inventory.

5.5.5 Global Sourcing and Cost Reduction

Consistent throughout all the interviews was the fact that Pfizer was honing in on how it spent money and how it could reduce costs. The number of products slated to come off patent in the next two to three years, in which Pfizer would lose at least 14 billion dollars from the bottom line of their profit, was driving these efforts. Ruddy said,

Drugs losing patent protection include three blockbusters: Zithromax, Zoloft, and Neurontin. It's forcing us to look at different ways of doing business than we did in the past... And its come across pretty strong that a bit of research savings is involved in this as well. By 2008, Pfizer said it will take four billion off our costs. So we've got to figure out how to do that.

Ruddy went on to discuss another situation from the electronics industry that the pharmaceutical industry could learn from: electronics sourced and built things more cheaply in places like Taiwan, Korea, and China. When Ruddy worked for Apple, they made products in Taiwan, then shipped them to Europe. Once upon a time, Apple used to make the majority of products in Cork, including high-end systems, low-end systems and laptops. Now, however, Apple in Cork made only the high-end systems. Cork did not have any logic boards because that was outsourced to Singapore and laptop manufacturing took place in Taiwan, for example. He considered this “the ultimate supply chain... they really are slick in the way they use their global IT systems and those systems are linked in with their logistics department and shipping agencies like DHL.” This type

of organization allowed computer companies to get customers their product as quickly as possible, but at low prices.

5.5.6 Autonomy and Decision-making

As part of Pfizer's global organization, each Irish plant was ultimately responsible to management at Pfizer's global headquarters in New York City. There was a supply chain organization within the New York offices, which was headed by a vice president for the supply chain. But, this formed just one area of coordination or masterminding, as each plant was expected to handle day-to-day operations and decision-making on their own. Each supply chain manager consulted with New York to decide their overall budget, volume and structure. Changes or deviations made from the broad parameters set in these yearly plans must be discussed with headquarters. However, flexibility existed within these parameters, particularly in the area of cost savings. Chambers explained:

We interact quite a bit with New York. I think it's important to Pfizer that you do that. Day to day decisions would tend to be quite local. You're authorized to use your discretion. If you're going to have a major impact or farther impact with what you're doing, you've got to keep them informed and keep them in the loop. There's quite a bit of interaction with New York. And that's part of being part of Pfizer, a very large company... one of the complexities of a large company is that you have sufficient communication without overpowering... You've got to have enough, you've got to keep the right people in the loop.

Cronin said that within the organization, "all stakeholders have a part to play." Elaborating on this, he said that in terms of local supply chain operations at Ringaskiddy, the engineering group, environmental health and safety, quality operations and technical services all contributed to ensuring that the chain was capable and robust. Outside of those groups that directly impacted the day-to-day supply chain in Ringaskiddy, Cronin kept in contact with headquarters in New York:

We talk to New York and we talk to the network all the time. Obviously, our primary responsibility here is to run this plant and to run the business in an appropriate manner, to meet the needs of supply of product, quality, safely and cost-effectively. So fundamentally, we have decision-making powers around what we do here operationally. However, obviously there are many decisions we have to take in, I wouldn't say in a confrontational way, but in an agreeable way. For example, supply chain in New York would provide us with a volume

indication on needs. That's how we generate the demand line on the analysis of what product is going to be needed. You first of all have to have a need. Then you determine based on that need, the profile of that need, what your manufacturing requirements are. Particularly in relation to new products, it's very, very important that we make sufficient [amounts] to meet the needs of the establishment of the product, but at the same time that we manage Pfizer's grid. The risks associated with a new product's research and development are huge. There are many candidates that fall by the wayside, and that's after many, many millions of dollars have been spent. So the investments that are necessary, this is not a low risk business. This is a high-risk business, and we have to fund that in an appropriate way, of course. And we do that... In terms of autonomy and in terms of decision-making power we have the ability to appropriately question and challenge, and we're expected to. If something that doesn't look sensible to us coming from the center, that tells us we're going to need to make, for argument's sake, 10 kilos of something when we know we're going to need 40. We would say 'are you sure about this', let's dig deeper. We have that kind of relationship. I would say that we have a very vibrant communication process going on. Indeed, we're always looking for ways to improve that. There's nothing more constant in our industry today than change. Change is absolutely with us. The key element to proper change management is communication, communication and then more communication. That's crucial. If we don't get that right, then we are likely to find ourselves in, shall we say, all kinds of unplanned states.

Ruddy also stressed the connection with headquarters in New York in terms of volume indications and long range planning issues:

We would consult them and, at the same time, we would feed them information in terms of long-range forecasts, timeframes and capacity... Equipment lead times and commission of equipment can take a lot of time, it can take a year to 18 months.

However, Ruddy pointed out that accurate information leads to more autonomy and an increased ability for his plant to do things quickly:

Collapsing the planning time cycle and supporting it with available, accurate information gives the plants more autonomy. In the past, if your information was disbursed, it was an effort to coordinate it. The data in the system must be correct and everyone must have total access for things to run quickly and smoothly.

5.5.7 Knowledge

Chambers, Ruddy and Cronin also explained that knowledge was an integral part of the industry and in managing their teams. Chambers explained that there was a certain tension between tacit knowledge and codification of procedures:

A lot of what we do has to be proceduralized, it's a requirement. Again, it's part of the industry, which is very proceduralized. But a lot of dealing with outsiders has to be kind of learned on the job and isn't part of any prior knowledge you would have. So it's a combination: a certain amount is proceduralized, written down and is clearly there, and certain amount has to be learned as you work with people. As your knowledge evolves, you

learn. There's a lot in your head, though, and you need to consider the appropriate way of ensuring that knowledge is available to other people.

On the other hand, Cronin thought knowledge was expressed in terms of talent and IT:

Knowledge is critical. Two things, in fact, around knowledge: knowledge, and I would say talent management, talent development, people development are critical to any successful organization. On the knowledge front, what we have done is made some very significant investments from an information technology perspective, on improving our systems. We have internally some core systems that we use, which are currently being rolled out, as we speak actually, to some of the legacy pharmacies and plants, including the one in Little Island, called MAPS... We also have other systems that we are using in our network to help us understand product flow and demand through the supply chain.

Finally, Ruddy believed the team structure at Loughbeg was the locus for knowledge and thought IT could support the team's knowledge base:

Knowledge is everything. Teams are designed so that everyone has the same sort of knowledge base. You don't really have, one person that knows more than another. People share knowledge as well. It's part of the learning organization, that you don't keep it to yourself. Some of the challenge is to have everyone know everything about everything. We believe people need access to information to do the job... in terms of the future, the future of IT systems is in automation. So you can access information. So systems provide information on the process or the particular routes of the product you're making, and you can get information very quickly through those systems.

5.6 Summary

The data collection at Pfizer spanned case study iterations 1 and 2. Pfizer was critically important to this study not only because it served as a "jumping off point" for the empirical research, but because, at the time of the study, it was *the* biggest, most profitable global pharmaceutical firm. During iteration 1, it served as a proxy for SCM within the pharmaceutical industry, thereby offering a better picture of SCM capabilities within the industry and providing substantial knowledge on the subject as the study branched out into two other pharmaceutical firms. In iteration 2, as PGRD was explored, the benefits and consequences of Pfizer's size and global scope, which were present in PGM, became more apparent and perhaps more significant in the context of PGRD.

Chapter 6: Case description- Novartis

The second case description presented here coincides with the second firm to join the qualitative data collection and provide access to both their R&D and SCM units: Novartis. As such, this chapter recounts the findings from investigations conducted at Novartis' Institutes for Biological Research (NIBR) and with Novartis' commercial supply chain unit. Additionally, the last part of the chapter summarizes Novartis' most notable drug development story (Gleevec) in order to understand the contributing success factors.

Formed January 1, 1997, Novartis (from the Latin, *Novae artis* meaning "new skills") resulted from the mega-merger of Swiss pharmaceutical companies Ciba and Sandoz. At the time, both Ciba and Sandoz were plodding, risk-averse and assiduously Swiss firms that often got trounced by faster, fiercer U.S. rivals (Langreth 2001). The President of the Sandoz board instigated the merger, in order to strengthen Sandoz' core business through a mega merger with a competitor (Ruhli and Sachs 1999). Ciba was stuck with an unsuccessful portfolio and unable to make changes to correct this situation (Ruhli and Sachs 1999). Sandoz' more successful patterns of organizational and strategic developments before the merger dominated Novartis' strategy and structure: Sandoz was structured as a holding company, giving a high degree of operational autonomy and freedom of leadership to the core-business divisions (Ruhli and Sachs 1999). Novartis became a holding company, unifying a few, but strong world-class small business units (Ruhli and Sachs 1999).

The merger's success depended upon the strong Sandoz product pipeline, Ciba's broad presence in the marketplace, and Ciba's high level of R&D (Ruhli and Sachs 1999). Perhaps CEO Daniel Vasella, M.D., however, deserves most of the credit for the merger's success. Vasella became CEO in 1996 when the Novartis deal closed.⁴³ He inherited two underachieving drug companies, which gave him the excuse he needed to dramatically change the business

⁴³ After a brief career as a physician, Vasella joined Sandoz in 1988 and went to the U.S. to manage Sandostatin sales. He returned to Sandoz headquarters in Basel in 1992, and began running the Sandoz pharmaceutical unit in 1995.

(Langreth 2001). Influenced by his years in the U.S., Vasella introduced American-style capitalism to the company: “I learned everything in America. From my perspective the basic tenets of being successful are in line with the American capitalist style” (Vasella in Langreth 2001). Vasella expanded the bonus pool, created a stock-option plan, and persuaded Swiss unions to accept performance-based incentives. After the merger, he quickly replaced complacent managers and cut 12,500 jobs in two years (Langreth 2001). Vasella transformed Novartis by taking risks, speeding up machinery and rewarding those who deliver; mediocrity was not tolerated (Langreth 2001).

Vasella’s management style delivered impressive results:

- Novartis was (in 2005) the fifth largest drug company in the world, with net sales of \$28.2 billion in 2004.⁴⁴
- Drug pipeline: 75 projects in clinical development, of which 52 are in Phase II, Phase III or registration.⁴⁵
- Industry leader with 13 regulatory approvals in the U.S. since 2000.⁴⁶
- R&D budget: \$4.8 billion in 2005.⁴⁷
- It won seven drug approvals in major markets in 2004, and was on track to deliver seven promising new drugs by 2008 (Novartis 2004).

Furthermore, in 2004, Novartis extended its capabilities with the \$8.3 billion purchase of Hexal, a German generics firm, and its sister company in America (Eon labs). At the time, this created the world leader in generic medicines with annual global sales of over \$5 billion and a pipeline that contained virtually all drugs due to lose patent protection between now and 2009 (Griggs 2005).

6.1 Novartis Institutes for BioMedical Research: Background

The Novartis Institutes for Biomedical Research (NIBR) had five global locations that function as a single scientific institute: Basel, Switzerland; Horsham, UK; Vienna, Austria; Tsukuba, Japan; and Cambridge, Massachusetts, U.S.A. In 2002, Novartis founded new Research headquarters in

⁴⁴ \$37 billion in 2006.

⁴⁵ As of 2006: 138 projects in clinical development, of which 94 are in Phase II, Phase III or registration. Of these 138, 50 are NMEs and 88 are lifecycle management projects involving new indications or formulations.

⁴⁶ Compared with nine by the next nearest two rivals, Sanofi-Aventis and Pfizer.

⁴⁷ \$5.4 billion in 2006.

Cambridge, Massachusetts. This effectively shifted the Research operations center from well-established facilities in Basel, Switzerland, where Ciba and Sandoz had legacy operations. Transferring Research operations to the U.S. could not have been an easy decision with Switzerland's reserve of scientific expertise; Swiss drugs research papers receive more citations than U.S. papers (Gapper 2005). Novartis' decision to move Research headquarters to the U.S. coincided with other European pharmaceutical firms making similar choices. The industry's R&D shift from Europe to the U.S. was motivated by European governments failing to match the extraordinary investments in biology and biotechnology made by the U.S. government and venture capitalists (Lawler 2002).

Novartis was drawn to Cambridge's "interwoven environment" where the traditional lines between industry and academia were growing increasingly blurred (Lawler 2002). Cambridge, along with San Diego and Seattle, earned a reputation as a research community in which many health care industry firms chose to locate labs near or adjacent to major academic and biotech facilities (Hall 2003). Pharmaceutical firms actively pursued mergers, forged collaborations with academic groups, struck deals with biotechnology companies, and established outposts near hotbeds of university research. Drug companies were geographically positioning themselves to take full advantage of the flow of information revolutionizing biology and medicine (Hall 2003).

Novartis chose Cambridge, made a multi-billion dollar investment, and set out on a major overhaul to improve the drug discovery process (Hall 2003). The firm changed everything from corporate culture to the nature of their collaborations with university researchers. This reflected an industry trend combining academic biological research with entrepreneurial character of biotechnology companies, coupled with the economic strength of major corporations (Hall 2003).

A project as large as the Cambridge NIBR center, with a multi-billion dollar price tag, plans to house 1,000 scientists, and comprise one-third of Novartis' global research team, would help elevate Novartis to great pharma giant status (Capell 2003). The firm opened two state-of-the-art buildings adjacent to Massachusetts Institute of Technology (MIT) in Cambridge. The first

opened in March 2003 in Technology Square. The second building, opened in April 2004, won a number of architectural awards for its renovation of the New England Confectionary Company (“Necco”)⁴⁸ building (Studt 2005). The interior of the old candy factory was re-designed to encourage, foster, and facilitate collaboration and the exchange of ideas among the resident scientists:

An open, transparent lab environment was created by the design team to reinforce the mission of changing the way the researchers do science by stimulating collegiality among them... To reinforce the sense of openness and transparency, all offices have at least one glass wall, allowing visual contact between researchers and fostering collaboration... Connectivity between clusters of labs, offices and workstations is achieved by incorporating full-height glass partitions between areas that were traditionally separated (Studt 2005). The building’s design was unique among scientific research buildings, with a light and airy affect. The geometric angles of hallways and labs were more in the tradition of Picasso than Mondrian (Hall 2003). The architectural detail was intended to inspire innovation and bring people together from different departments and disciplines.

6.1.1 Mission: “Develop new medicines based on good science”⁴⁹

NIBR’s core strategic elements included innovation, a focus on patients and a strong commitment to external collaboration and strategic partnerships. Novartis did not rely on marketing blockbuster pills, like Merck and Pfizer. Its drug portfolio focused on oncology and cardiovascular disease⁵⁰, but NIBR’s development portfolio, especially in infectious disease, was focused on products that could meet significant unmet medical needs. (See Table 6.1: Selected drugs currently in development).

⁴⁸ Necco was a famous New England candy company that produced a variety of candies for over 78 years in Cambridge.

⁴⁹ From interview with Jason Ravenel, Ph.D., Associate Director of Program Office at NIBR (11/1/05).

⁵⁰ Novartis’ heart drugs Diovan and Lotrel, as well as cancer drug Gleevac, have strong sales figures.

The culture of drug discovery at Novartis began to change in 2002, when the company hired Dr. Mark Fishman to lead Research. Fishman immediately promoted a more academic-style understanding of biological processes and pathways that could speed up the drug discovery process (Hall 2003).

The greatest opportunities in science today, its very frontier, lie in the discovery of new medicines. Using the words revealed through modern genetics and chemistry, we can today begin to write the new grammar for drug discovery.

-Dr. Mark Fishman (Novartis 2004)

The lack of integration between research and development teams in the traditional R&D model made it difficult to improve the drug discovery process. Pharmaceutical research teams discovered promising compounds and transferred them to development teams. This transfer created a discontinuity and breakdown in communication between research and development, in which the research team often never knew if a compound given to the development team proved effective in humans; once a compound moved to development, the research team continued with other projects. The drug's effectiveness was determined after the development team extensively tested the compound in humans (Truelove 2005).

Fishman revolutionized NIBR's research strategy by focusing on genetics, taking advantage of advances in science, implementing proof-of-concept trials and redesigning the chemistry aspect of the organization. Part of this reorganization was driven by the disappointing human genome mapping results, which failed to provide a myriad of contributions to the drug development pipeline. NIBR also decided to explore new discovery platforms, including a focus on gene families; although genome mapping did not live up to the hype, Dr. Fishman still believed genetics remained valuable to understanding disease (Truelove 2005).

Dr. Fishman emphasized changing traditional pharmaceutical research by incorporating cutting-edge scientific advances. For example, traditional discovery efforts focused on single drug targets (single proteins), but NIBR expanded this "single-target approach" and leveraged insights gained from advances in pathway biology. At NIBR, new targets were identified and

validated in the context of cellular networks. Using this approach, a disease target did not need to be identical with the protein that malfunctioned in disease, but rather belonged to the same disease pathway as the abnormal protein. As such, disease targets represented “drugable nodes” in the disease-causing pathway.

Moreover, pathway biology revealed that a disruption in the normal functioning of a signal pathway could result in multiple diseases, which could present in the clinic as different entities, (for example, different types of tumors) but could be closely related at the level of the molecular pathway. Thus, understanding disease-causing pathways and key network nodes could lead to treatments for several seemingly unrelated diseases.⁵¹

Novartis’ cancer drug Gleevec was an example of how researchers used information on targeted molecules and pathways to develop a highly successful drug. Gleevec targeted the molecule that produced chronic myeloid leukemia. Gleevec worked on a signaling pathway to block the cancer-causing molecule and fix the malfunction within the pathway. Originally designed to treat chronic myeloid leukemia, a niche disease, Novartis executives decided that Gleevec’s potential as a major cancer advance outweighed the downside of its small market⁵² (Vasella and Slater 2003). Through understanding Gleevec’s mechanism of action, Novartis extended the drug’s treatment area to patients with gastrointestinal stromal tumors (GIST) (Truelove 2005); chronic myeloid leukemia and GIST share the same pathway. This expansion of effective cancer treatments radically increased the oncology market’s value for Novartis (Gapper 2005).

While at Massachusetts General Hospital’s Cardiovascular Research Center, Dr. Fishman used proof-of-concept trials, which were small clinical trials that aimed to discover new, innovative therapies. He transplanted proof-of-concept trials to NIBR to change how clinical trials were designed (Truelove 2005). The key to successfully using proof-of-concept trials was

⁵¹ This paragraph written in consultation with Novartis.com and Kaitlyn Sullivan, M.Sc. Cell Biology.

⁵² Note: Gleevec treatment costs \$28,000 per year (Gapper 2005).

testing drugs on niche diseases with mechanisms of action that were present in other, more common diseases (Truelove 2005). By looking at niche diseases, and examining these diseases in proof-of-concept trials, scientists focused on the population that was likely to best respond to the trial drug. If the proof-of-concept trial drug did not work in a specially chosen patient population, then investigators could discard the drug. The reason for this was that if the drug failed in the target population that should best respond to the drug, researchers were confident that the drug would not work in anyone else with a disease that shared similar biomarkers to the niche disease. If the drug did work, however, the next step was to determine how to extend the product into different populations (Truelove 2005). Novartis also created an exploratory clinical development team comprised of clinical experts that examined projects from very early discovery to decide which patients might benefit most, how the new medicines might be safely tested in the clinic, and how to expeditiously perform early clinical trials (Novartis 2004). These efforts were intended to rapidly assess a compound's efficacy in humans to provide a foundation for early decisions to advance or terminate projects. This shifted the compound's failure rates to earlier stages of the drug development process, thus, saving money and time (Truelove 2005).

In redesigning the research process, NIBR created a global discovery chemistry group, an aspect of drug discovery that many companies in the industry outsourced (Truelove 2005). This group was unique in its involvement in the early phases of drug discovery, including designing chemical probes and chemical IDs to find drugs. The success of the global chemistry group was attributed to its ability to explore a multiple compounds, about five or six at the same time, and advance those with superior promise to the next phase of drug discovery (Truelove 2005).

Finally, NIBR recognized the value of scientific advances made by partners and aimed to source the best technologies and early stage compounds, a task made slightly easier by establishing roots in a city with significant biotechnology activity. NIBR aspired to adopt those biotechnologies that would boost the pipeline and drug discovery process (Hall 2003). In 2004 alone, NIBR established 150 collaborations, including 50 with biotechnology companies, to

complement internal research activities (Truelove 2005). On a global scale, NIBR was working with the Shanghai Institute of Materia Medica (SIMM), a leader in the study of traditional Chinese medicine. NIBR was interested in extracting single active ingredients from SIMM's store of traditional remedies and analyzing them for possible development as modern drugs. The effort yielded more than 1,800 compounds with the potential to treat cancer, diabetes and other diseases (Stipp 2005).

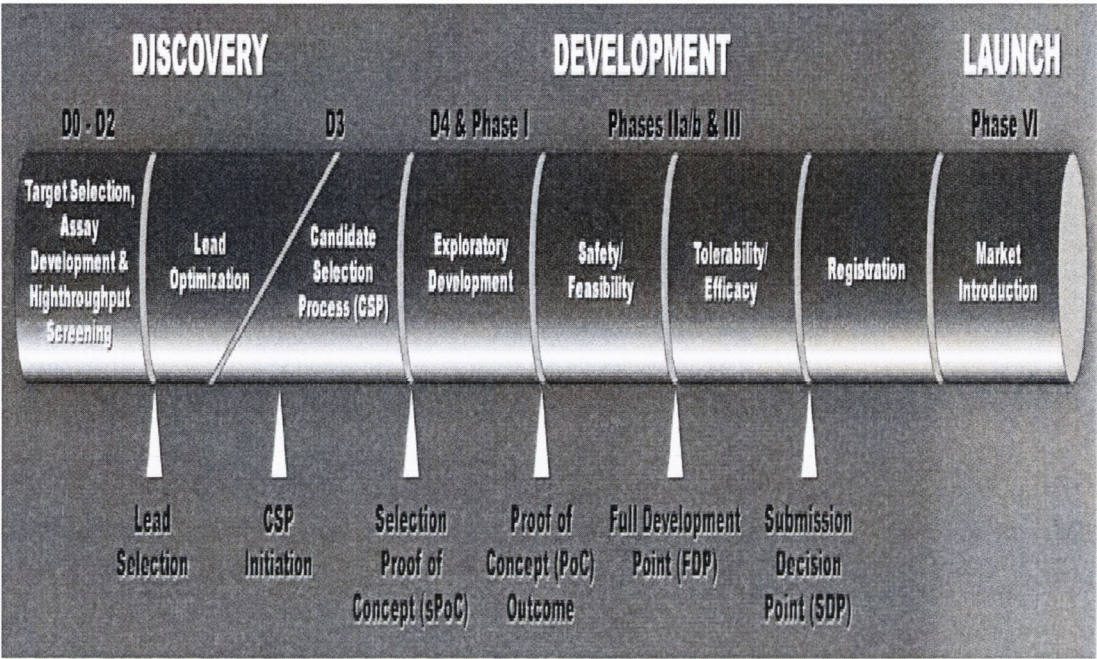
NIBR's commitment to incorporate cutting-edge science into its research and development process reduced the time it took to bring a drug from clinic to market by nearly two years. The addition of Mark Fishman, M.D., as Director of Research marked a sea change in drug discovery strategy: he led an overhaul and restructuring of the drug design process at NIBR (see Figure 6.1 NIBR's revised R&D process). In keeping with the accelerating pace of drug discovery and incursion by the biotech culture and entrepreneurial underpinnings, NIBR reoriented its organizational culture partly by locating in a densely academic and biotech area, and by making concerted efforts to encourage collaboration and innovation across all areas of the firm.

Table 6.1 Selected drugs in development at the end of 2005

Name	Indication	Comments	Phase
Indacaterol QAB149	Asthma/COPD*	Taken once daily, supplies full 24-hour symptom control.	Phase II/III
Femara	Breast Cancer	Significant advance in treating postmenopausal women with early breast cancer immediately following surgery. Sept. 2005- FDA granted priority review.	Approved
Telbivudine	Hepatitis B	Developed with Idenix; plan to file with FDA by the end of 2005 for marketing approval for treating chronic Hepatitis B	Filed
Coartem	Malaria	High-risk initiative for Novartis; pledged 120m treatments next year, sold at not-for-profit prices. Waived the patent on the drug in the developing world. In July 2005, Novartis established a close partnership with Kenya-based East African Botanicals (EAB) to significantly increase production capacity. Originally, Chinese gov't partnered with Novartis to make a malaria drug that would make it through extensive clinical trials and be produced to meet international standards.	On the market
Galvus	Diabetes	Oral drug for diabetes.	Phase III
Rasilez	Hypertension		Phase III
A-60444	Respiratory syncytial virus (RSV)	Global license agreement with Arrow Therapeutics; RSV is an area of high unmet medical need.	Phase II
FTY720	Multiple Sclerosis	Oral treatment, still in the early phases of development; taken once per day.	Phase II/III

* chronic obstructive pulmonary disease

Figure 6.1 NIBR revised R&D process



Source: NIBR company information

6.2 NIBR: Organizing knowledge in a knowledge organization

NIBR (Cambridge) thrived on knowledge. It would almost be impossible for it not to as a pharmaceutical research organization strategically located only footsteps from M.I.T., Harvard University and Boston's world famous hospitals. In a business as fueled by knowledge as the pharmaceutical industry, NIBR needed to effectively structure the knowledge flows within its Research headquarters (Cambridge), global institutes and throughout Novartis' worldwide organization. NIBR (Cambridge) was managing its knowledge through three separate efforts: storytelling, education and the drug portfolio.

6.2.1 Organizing Knowledge through Stories

Brigitta Tadmor, Ph.D., joined NIBR in Summer 2005 as Vice President of Communications. Since her arrival at NIBR, Tadmor has observed that on a global scale Novartis was a fragmented organization. As such, a main goal for the communications department was to make communication coherent both within the department itself and within the larger organization. No one outside NIBR (i.e. rest of corporation) had a good grasp of activities and processes at NIBR.

Before Tadmor arrived, the firm had an internal publishing unit that produced *NIBR Science*, a quarterly magazine, highlighting NIBR's activities. She chose to abandon *NIBR Science*, feeling it's highly scientific nature limited its effectiveness and accessibility to all of the organization's members. Coinciding with jettisoning the quarterly magazine, Novartis developed seven key global objectives. Tadmor accepted the responsibility for one objective: the storytelling initiative. This particular initiative resulted from management identifying a key capability and knowledge gap: the lack of a mechanism to tell the firm's stories, to communicate challenges and successes. Dr. Mark Fishman⁵³ and Dr. Dan Vasella⁵⁴, both top managers and physicians prior to joining Novartis, partly created and developed the project to explore the drug company's more "human side" (i.e. how drugs really change patients' lives). Tadmor hoped the

⁵³ Director of Research, NIBR.

⁵⁴ CEO, Novartis.

stories would create a paradigm shift within her own team: “they will be at the heart of what the communications team is doing now.”⁵⁵

As VP of Communications, Tadmor saw her role involving more knowledge management than communication. Storytelling was critical to her position, acting as a tool to analyze a situation, or a creative means of breaking processes into small steps. Further, it was an effective way of “capturing the knowledge a person has in his/her head”.⁵⁶

Tadmor believed stories would accomplish a number of goals at NIBR:

- Provide an effective way for different units to talk to each other. In particular, stories can improve Research’s way of communicating messages to non-scientists and other business units.
- Act as a vehicle for talking to the board, the media and recruiting new talent. Externally, NIBR could distribute stories to patient advocacy and policy groups. Further, story leaflets/booklets were a portable and convenient “takeaway” from presentations made by NIBR’s executive team.
- Compensate for the fragmented/international nature of NIBR/Novartis.
- Explain key organizational themes and messages. For example, stories could illustrate what an open/collaborative environment means.
- Capture the culture and motivations of NIBR’s scientists.
- Place challenges in an appropriate context.
- Create a deeper understanding by qualitatively looking at innovation and benchmarking.

Tadmor firmly thought effective stories could transform and change. As such, writers would act as change agents. Tadmor was teaching the fifteen people on her team how to actively look for stories and interviews in every aspect of their job. Forming relationships and establishing a rapport with members throughout various aspects of the organization would facilitate story creation about the firm’s recent drugs. Additionally, team members needed to possess clear thinking and a rich, non-technical command of language that adds a human element to the story.

⁵⁵ From interview with Brigitta Tadmor, Ph.D., Global Head, NIBR Communications at NIBR (11/1/05).

⁵⁶ From interview with Brigitta Tadmor, Ph.D., Global Head, NIBR Communications at NIBR (11/1/05).

A Wall Street Journal Europe reporter (without a scientific background), originally hired to compile the Novartis Annual Report, was assisting Tadmor with her ultimate goal of creating a story library. The reporter's priority was to create a story template that included visuals to make the story more personal.

6.2.2 Organizing Knowledge through Education

The Education Office at NIBR internally recycled knowledge. According to Emily Walsh, Manager of Science Development and Education, it was considered the “action arm” of the Program Office (which manages the drug portfolio). Walsh attributed the creation of this office to Dr. Mark Fishman, who “brought tons of new ideas with him and affected a sea change within the organization.”⁵⁷ Walsh earned a Ph.D. in Human Genetics; when she finished her postdoc, Walsh was NIBR's first Education Office hire, primarily responsible for managing strategic curriculum development. The six “recovering scientists” in the office believed it was their mission to empower the organization's “bench scientists” to share their knowledge.

Novartis' central mission, to deliver good medicines that directly impact disease and improve patient's lives, drove the trilogy of knowledge mechanisms at NIBR: the Education Office, Communications and the Global Discovery Group. The Education and Communications Offices tried to get everyone within the organization “speaking the same language.”⁵⁸ Communications conveyed strategic messages and an overview of NIBR's activities; it highlighted how drugs impacted patients for the organization, and wider audiences. The Education Office aimed to get everyone to speak a common scientific language: it was imperative for chemists, biologists, managers, and administrative assistants to share a basic language. Walsh viewed her role as that of a “knowledge interpreter” who distills key messages and makes them broadly understood (see

⁵⁷ From interview with Emily Walsh, Ph.D., Manager, Scientific Development and Education, at NIBR (11/1/05).

⁵⁸ From interview with Emily Walsh, Ph.D., Manager, Scientific Development and Education, at NIBR (11/1/05).

Figures 6.2 and 6.3 which visually depict the relationship between the Education, Communications and Program Offices).

Part of the Education Office role was to help everyone perform his/her job better through determining what knowledge needed recycling and what “live” courses staff would find beneficial. Determining knowledge gaps was the challenge; the office was experimenting with ways to ask their customers to define the current science issues. The office’s main customers consisted of senior management, scientists and lab heads. The philosophy was that by working with customers to identify key points that help scientists innovate, and then communicating these points via case studies (a preferred mode for scientific knowledge delivery), knowledge would be easily recycled within the organization. Ultimately, an online, interactive case study library would make key bits of knowledge accessible. Walsh hoped that an online library and “live” courses would communicate knowledge effectively, without “burying people in information”.

Upon arriving at NIBR, Walsh immersed herself completely in NIBR activities, frequently interacting with lab and unit heads in order to figure out the organization. She found that 40% of NIBR staff came from academia while 30% came from biotech and 30% came from pharmaceutical backgrounds. This meant that the staff, particularly former academics, did not know all the ins and outs of the drug discovery process. This knowledge desperately needed recycling, and Walsh was planning a much-demanded drug discovery process course, covering from target to pill, for late 2006.

In autumn 2005, Walsh had recently completed an eleven-month development of a three-day course on genetics that would adequately bring NIBR staff up to speed. Part of course development included test-driving material, launching the course, and recruiting attendees. Walsh felt an in-person course offered the best way “to deliver knowledge on an area [genetics] that has changed quickly and, at the same time, provide in-depth information”. Given her background in genetics, Walsh served as the content expert for the course, which accelerated its development, cutting out any reliance on external knowledge to build the course. Future courses,

however, could use internal NIBR experts or external academics. At the conclusion of the genetics course, Walsh hoped to find a way to evaluate the course's effectiveness and quantify the impact of future programs/courses/case studies developed by the Education Office. Further, she wished to create another version of the genetics course for the lay person/administrative staff to give everyone a basic genetic vocabulary.

For the genetics course, 50% of the participants were traveling to Cambridge from Europe. In putting this course and other learning initiatives together, Walsh realized that overcoming the cultural differences between the various NIBR sites would challenge the Cambridge-based Education Office. Walsh visited four of the sites and said the culture was noticeably different at each site. For example, Cambridge was the firm's most academic site. Walsh needed to think globally about how to best deliver information/courses, provide access to information, and discover the most appropriate method to recycle/reinforce knowledge given these different cultural environments.

The Education Office also facilitated idea exchange between two key NIBR disciplines: biology and chemistry. This was because, according to Walsh, "the best science goes on at the interface of two disciplines, but in order for this to happen, people must speak the same language and be able to communicate well with each other."⁵⁹ NIBR's research arm operated by taking ideas and turning them into molecules (chemists), using targets specified by biologists. While the nature of biology allowed different subgroups to hierarchically organize into Disease Area Head, Unit Head, Lab Head and then two to five associates or postdocs, NIBR took a new approach to organizing the chemists.

Chemists used to be assigned to disease areas, but were reassigned to the Global Discovery Group (GDG), which worked better for knowledge recycling. Chemists moved between different projects, which may or may not have been within the same disease area or functional group. The

⁵⁹ From interview with Emily Walsh, Ph.D., Manager, Scientific Development and Education, at NIBR (11/1/05).

GDG broke down the barriers between chemists, forced them to talk to each other, and as a result, become more productive. However, getting biologists and chemists to communicate was more difficult due to their different backgrounds. Walsh said, "Biologists and chemists are interesting groups that oftentimes have a hard time communicating with each other. They each chose their training path (chemistry or biology) essentially because they were avoiding the other discipline."

Finally, recruiting knowledge to the organization was within the scope of Education Office responsibilities. NIBR actively recruited from postdoc programs to acquire knowledge, as oftentimes academics were closer to cutting edge research. Walsh explained, "There are some types of research that can only be done in academia that you wouldn't do in a pharmaceutical company. Academia has the hospitals and patient access." NIBR wanted to attract smart PhDs who desired an opportunity to have a clinical impact on patients and working in an environment in which they were constrained only by their imagination and the limits of biology (i.e. not money or other resources). NIBR placed a high value on innovation and understood that scientists needed freedom in their labs to "do good science". Co-locating talented scientists would drive the quest for more knowledge, said Walsh, "that is the bet we're making, that by putting all these people here, it will inspire knowledge seeking and people will do good science. It is a big experiment, really."

NIBR was experimenting with the levels of innovation and control within their research labs. The ability to tolerate failure must accompany innovation: not everything will work out. Innovation was key in pharmaceuticals, because ultimately the number of druggable targets was a limiting factor. Walsh insisted, "the druggable universe is finite, but there are ways around this. That is where the innovation comes in." NIBR developed a capability to rapidly identify when something failed, so that resources could be re-invested in another area, where it might pay off. An example was the GDC group that redeployed chemists all the time. Part of NIBR's goal of "unconstraining science" included moving towards milestones and responding to failure by quickly creating new plans.

6.2.3 Organizing Knowledge in Drug Projects/Portfolios

Jason Ravenel, Ph.D.⁶⁰, worked at NIBR as the Associate Director of the Program Office, part of the development arm of the organization. He managed worldwide research portfolios (approximately 50 projects/portfolios at the time of the case interview); this involved improving organizational interactions, creating timelines, prioritizing, decision-making, lead optimization, and designing governance mechanisms. He worked with all NIBR sites, covering ten disease areas; development was based mainly in Basel and New Jersey.

Ravenel described NIBR as an “information company,” because 30% of NIBR activities involve discovery/Research and 70% consisted of generating information/data including data from early clinical studies. Novartis was unique in having separate organizations for Research, and Development, and separated commercial aspects of Novartis’ pharmaceutical business from R&D. The Research Head, Dr. Mark Fishman, addressed the scientific and knowledge issues within NIBR, while the Head of Pharmaceuticals, Thomas Ebeling, operated Novartis’ commercial side. Ravenel believed that “you must have a Ph.D. to work here,” because “everything here is science based.” He personally thought that a science background was harder to acquire than, say, a business background. The only MBAs within Novartis’ organization worked in marketing or brand management.

According to Ravenel, a global research organization (like NIBR) benefited from the ability to recruit a talented and diverse workforce. On the other hand, within the global organization existed cultural, language and time zone challenges, including 25% of senior executive time spent on airplanes. As a Swiss company, Novartis performed very well in Europe, however, the logistics between Basel and the U.S. posed a time zone challenge that would have made it exceedingly difficult for NIBR to position itself on the West Coast (which was considered) as opposed to the East Coast. The strong presence of academic research institutions and biotech firms in Boston also was a motivating factor:

⁶⁰ In oncology.

NIBR will always want to deal with the biotech company that is doing the best science, but if you can walk or drive there and meet with them every day if need be, that makes everything easier, including logistics. Part of networking is location. Also, success of deals with biotech after they're done often has to do with close proximity and joint project teams. (Ravenel)

The best part of being the Associate Director of the Program Office was acting as a “knowledge node”. Ravenel collaborated with senior leaders all over the globe. Ravenel was positioned at the end of the research phase, one of two major knowledge nodes within the R&D process.

Eighteen months ago, NIBR reorganized the R&D hand-off process within Novartis.

Consider that pharmaceutical product development was exceptional because the product was set in stone very early; less than one-third of the way through the entire process, the product stopped changing. At NIBR, Research moved candidate molecules through pre-clinical testing and proof-of-concept trials, then Exploratory Development took over and worked on the human side, which included clinical trials and regulatory studies. The hand-off between research and development posed a challenge. Project teams of 10-20 people with various backgrounds made up Research. Some team members moved from Research to the Exploratory Development team; NIBR was considering the possibility of having a single project manager that goes from Research all the way through early development (early clinical studies). Once the early clinical development was completed, an International Project Team (IPT) took over (around phase II clinical trials) and brought the drug through late-stage clinical trials to product launch. (Thus, candidate molecules followed a pathway from research to exploratory development to international project teams.)

Ravenel worked at the interface/hand-offs between Research/Development and Development/IPTs. Like in other pharmaceutical companies, these junctures used to function like a Chinese wall in which drugs were tossed blindly over the wall. There was no two-way knowledge transfer between Research and Development and many drugs failed to make successful transitions from pre-clinical to clinical studies or failed during the clinical development phase. NIBR created new governance mechanisms and incentives that aligned performance objectives between researchers and clinical investigators in an attempt to reduce the

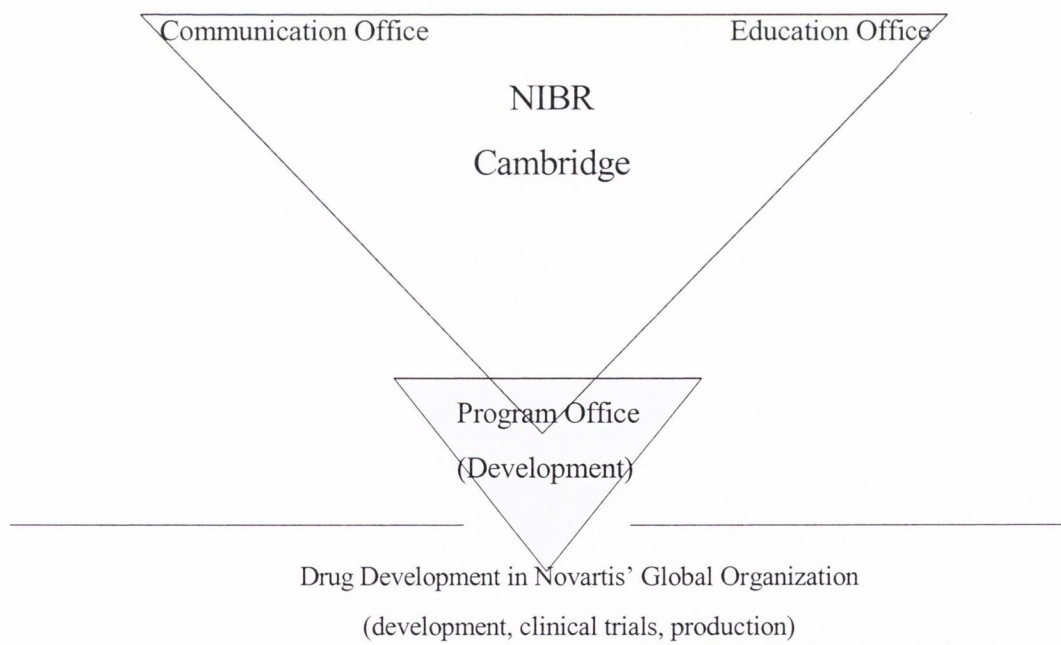
high attrition rate. Additionally, some development activities moved to Research. For example, formulating compounds into pills and the accompanying chemical synthesis moved back to Research (from Development). NIBR also moved pre-clinical tests earlier into the research process to generate data on a compound's "drug-like" qualities early on, in an attempt to help the decision-making process as to which drug candidates should go forward into human trials. Ravenel believed these two particular efforts were working, but it would take several years to evaluate - timelines in pharmaceuticals were lengthy, often taking many years from Research to IPT.

Once a clinical candidate was viable, it went to the disease area board within R&D. If approved, it moved to the global board of senior executives who approve the major drug development transitions, which constitute significant investments (i.e. moving to clinical trials). Drug candidates must be presented to the global board with a clear clinical trial plan grounded in established scientific principles, particularly because the board prioritized drug candidates and evaluated candidates based on science, not money. Knowledge in the drug approval process flows amongst the relevant boards via a written, standardized document capturing all the relevant information.

Like many large organizations, Ravenel did not think NIBR captured knowledge very effectively, but better knowledge capture would make Ravenel's job "tremendously easier". He lacked the confidence that he always had the information he needed. Local knowledge stores quickly become outdated and he must rely on other people, in various locations, to keep his knowledge up to date. However, advancing knowledge capture systems would require capital and leadership. Moreover, the organization needed to learn to leverage both the knowledge that exists in people's heads and the knowledge that was already recorded via people's computers. Ravenel thought creating a library or way of cataloguing slides and presentations within NIBR would be a good start. Furthermore, concepts for knowledge management systems already existed and there was "no need to re-invent the wheel."

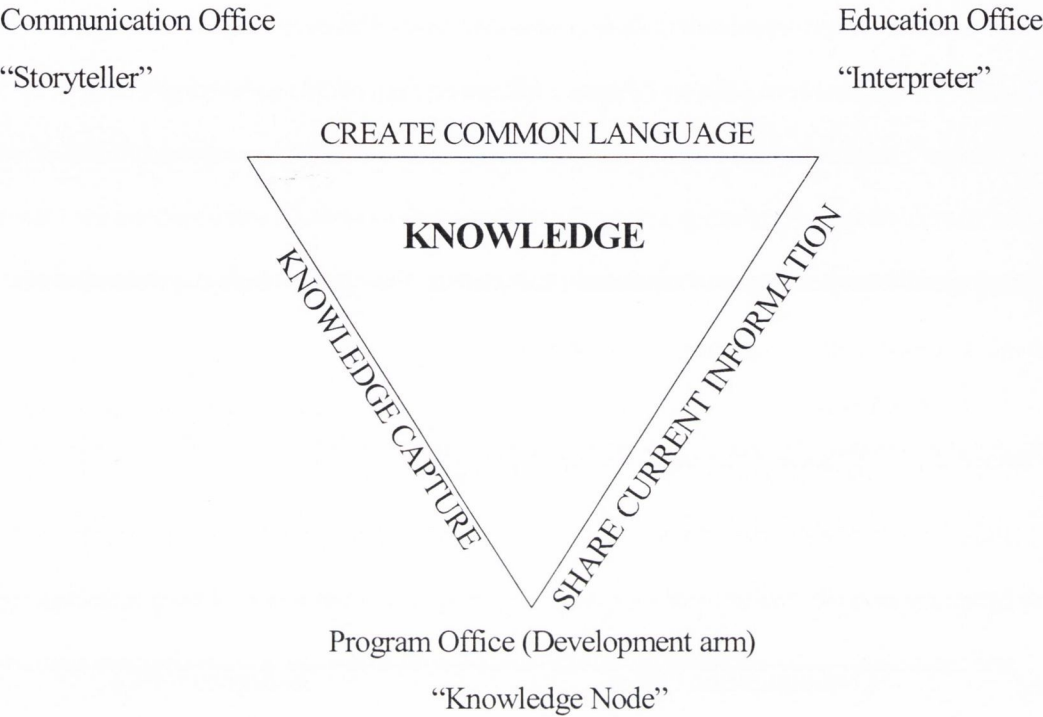
Ultimately, Ravenel believed knowledge was primarily an IT problem. NIBR’s informatics were not designed well. He based this opinion on his experience at McKinsey, which he believed was a true knowledge organization: their only assets were smart people and knowledge. At McKinsey he experienced what an IT system/infrastructure could do to leverage human knowledge⁶¹. Right now there was an informal network to access human capital at NIBR. He also subscribed to the idea of creating a directory by having employees fill out a form (at the time of hiring) about what their areas of specialized knowledge. The value of such a system would be tough to measure, however, once it was created.

Figure 6.2. NIBR and Novartis’ Global Organization



⁶¹ NIBR does not share that perspective, this is just Ravenel’s opinion.

Figure 6.3 Knowledge goals within NIBR



6.3 Novartis, Inc.: Supply Chain Operations

Jim Edwards, Vice President of Supply Chain Management in the U.S. and Global Head of CPO (Country Pharma Organizations) SCM operations explained that the commercial supply chain unit within Novartis existed as the interface between several different functions within the company. Edwards’ role within Novartis required that the 60 countries in which Novartis had product distribution activities, and thereby SCM associates, report to him⁶². Edwards pointed out that as the Novartis SC network was truly global, in theory, Edwards could be located in any country in the world in order to manage and coordinate 60 countries.

⁶² Novartis distributes product in over 120 countries worldwide, but the 60 country figure has to do with how Novartis is defined as a legal entity.

Following the 1997 merger of Ciba and Sandoz, Novartis had 60 plants that fell into one of two categories: drug substance or drug production. In 2006, the company operated 23 plants, or as Novartis calls them, “Centers of Excellence.” Each plant maintained a specific expertise, and as such, the company divested excess or duplicate capacity in the wake of the merger. Edwards explained that an inefficient SC model involves having 10 plants in your network that produce the same product and only meet 50-60% utilization/capacity during two shifts per day. “Most production plants in pharma operate inefficiently.” Novartis decided to focus on using their capacity to the maximum and developed plants that only operated with one or two technologies, which created a network of plants defined by dosage form specialization (i.e. solid, liquid or cream), volume specialization or launch sites. “For example, take products with high volume solid dosage forms and high volume liquids- you don’t want them both in the same plant.” Rationalizing and re-focusing their plants led to an 80% utilization/capacity during two shifts per day rate, which Edwards believed was efficient and about “as good as it gets for pharma”. Consolidating technology, dosage forms, and getting products into the right facility meant that Novartis’ network had very few national production sites: “A product produced in the UK probably isn’t distributed in the UK.”

The commercial supply chain process also required the development of a global model, which Edwards helped to develop six years ago. This model was based on the people/processes/technology model for SCM and was intended to create an environment in which products are sold at high levels of service. Edwards believed that adopting the technology for supporting the new model was key: Novartis implemented SAP and trained their SCM associates in using this technology. Within the SC organization, responsibilities and accountabilities changed significantly on three different levels.

1. Information flow: This included forecast, supply, demand, inventory, and execution models. This level had to be strengthened in terms of developing capabilities. More specifically, the skill set for people/processes and technology had to be enhanced.
2. Extend reach: Must communicate standard processes and standard technologies. The reorganization required the CPOSCM organization to take on distribution in some new

countries and regions. Novartis needed to develop people throughout the 60 countries to meet strategic objectives and manage the supply chain process. Part of the strategic objectives included improving service levels, dramatic reduction of inventory, and achieving desired cash flow.

3. Strategic level: Refined long-term thinking. Developed forecasts for 3-5 year time periods.

One of Edwards' main concerns was planning and execution accompanied by strategic long term planning. With respect to planning, the development unit had the greatest impact on SCM plans: "gaining successful products is our lifeblood." Development, which Novartis divided into two categories: chemical and pharmaceutical, particularly effected SCM decisions regarding decisions to invest or divest capacity. For example, a potential blockbuster required an investment, usually in a chemical facility, and three years was not enough time to go "from no facility to having a validated facility up and running, producing drug substance." Edwards still thought that even stronger capabilities in terms of long term planning were necessary, even though other industries "think we're crazy for five years of planning." Part of the responsibility of commercial operations was to provide viable numbers, and understand these numbers, in order to make informed decisions regarding potentially significant investments. Outside of development, SCM needed to talk and interface with every function with the potential for making a long-term impact on SCM. This included other units under the umbrella of Technical Operations, of which SCM was a part: physical production, engineering and finance (see Figure 6.4 for a detail of where SCM fits in the organization).

Moving a product from development to commercial operations requires SCM to act as the interface between several different functions within the company. One of the most important interfaces was with the larger commercial operations unit that sends a sales forecast (from the 60 countries) that must be translated into demand plans for Novartis' various supply points. Other factors that affected the transfer from development were governed by a standard project management methodology with accompanying standard processes and technology to support it. This project management methodology relied heavily on project teams, which were made of

members from multiple functions within the company. This was a model, according to Edwards, that was essentially put to the test every time a new product was developed, and required well-trained staff that understood the project management model. This understanding was particularly important now, with Novartis' new strategic ambition: to move a product from research to saleable dosage form as quickly as possible with a target of 1,000 days. Their supply chain process model could work with this 1,000-day target because the model allows supply chain investments when needed.

At the product launch point the commercial operations model and SCM essentially "took over" the product and focused on interacting with various departments to make sure that the demand plan is met. Up until that point, a global project team followed the Novartis project management and development methodology that governed the process. In most cases, SCM was represented on the global project team, or was at least represented via a technical operations department member. The commercial operations member on the team also in part represented SCM. Although commercial operations was generally most concerned with representing all the major markets involved in the new product launch process. The global project team was virtual, but any meetings were typically held in Basel, Switzerland.

There were three product launch locations: Switzerland, Ireland, or a facility only 10 minutes from Basel HQ located just over the border in France. The French facility launched products in liquid or cream dosage forms. Edwards believed you did not want too many launch sites in your network. Launch sites must support development demands as a product moves to commercialization; this requires an "intense" amount of interacting with development, particularly as you get closer and closer to launch. "You don't mess with a launch, and Switzerland is the main launch site. You must launch the product and move it into the dosage form specialization site." The launch site achieved quantities for launch and an understanding of the process. While the U.S. was an important Research location for Novartis, in terms of

commercial operations and SCM, it was “just another market, a large one, but just another market.” The U.S. had one Center of Excellence.

6.3.1 Management of SCM Associates

Edwards worked for Novartis for 25 years, and described other employees with similar long-term careers with Novartis as belonging to a generation that was bonded to the company. It was this generation of senior leaders that needed to prepare for higher levels of movement in the younger generations. As a manager in an industry that did not move quickly, it was often difficult to align the needs of the company to the needs of his younger associates. Managers should be able to “satisfy thirst and hunger for challenging assignments,” of a younger generation that typically wanted to move and change every 6-12 months. Production had to get geared up to do just that. Although at the end of the day, Edwards believed that recruits tended not to have the same plan as those who lead the organization. “It is difficult to satisfy this hunger for challenge in an organization where change isn’t part and parcel of everyday life. Organizationally, we need to be more flexible to satisfy this hunger and thirst.”

In order to staff the SCM function within Novartis, Edwards and his colleagues looked to recruit people with an SCM curriculum background for certain positions. While at one time engineering or scientific backgrounds would suffice for SCM professionals, those with an education in SCM or Operations Research better filled certain positions within the SC organization. In some countries, chemical engineers were predominant in the SC organization. Edwards held a place on the Rutgers University SCM board, which meant he had the ability to influence the curriculum and recruit the two top graduates out of the Rutgers program.

As productive as the implementation of SAP had been for the SC organization, there was a distinct disadvantage to the software, said Edwards:

Software has taken away thinking. Associates do not always know or understand the evolution of basic inventory management techniques- SAP does all the calculations for you. You can input a forecast and it comes up with all the answers. Similar to what calculators have done. People forget the basics. If people never understood them, forgot them or if software has taken away that thinking- this is problem when you hit a problem- you need the

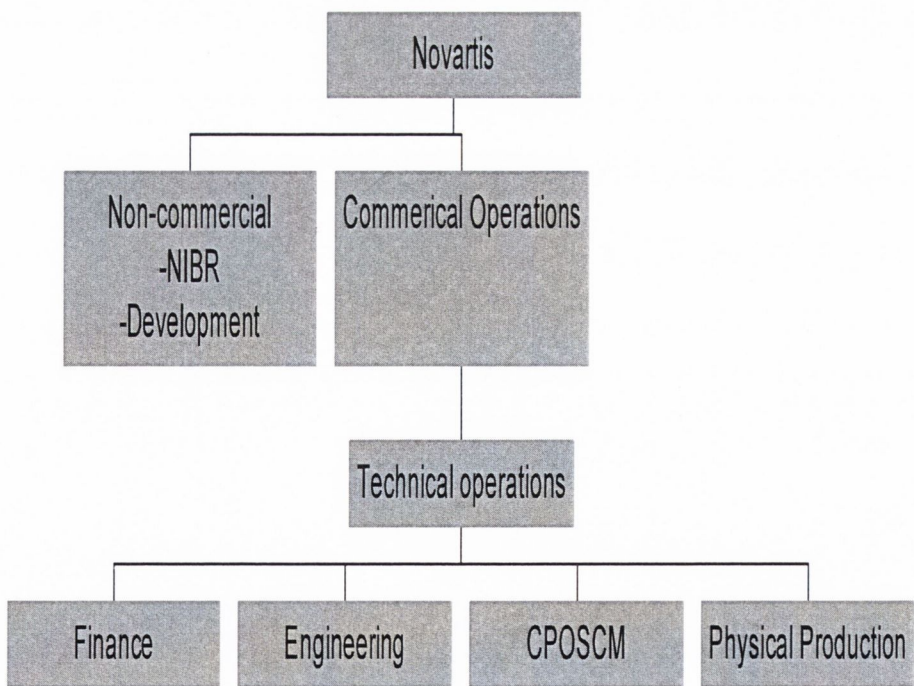
intellectual capacity to analyze why that program is happening and it may not be there. It is all okay if everything is running smoothly. But if you have to do problem solving and people don't understand the core concepts... We need to have ongoing continuing education program so people don't forget. Shame on us for letting software take away thinking.

In terms of understanding SC techniques, Edwards thought understanding just-in-time (JIT) was critical, as a “significant wave of JIT is coming back under the umbrella of lean manufacturing.”

Edwards said that the industry typically defends excessive lead times, but felt these lead and cycle times could decrease.

We can reduce lead times by 80% if we focus on them and inventories come down dramatically and service level increase- we could supply to erratic demand. While lead time is associated with quality control and quality analytical testing, when making a drug substance to sale, quality is not a major part of that lead time in most cases. There are inefficiencies in terms of product movement, not focusing, and eliminating waste out of planning and execution. SCM professionals should turn that model of having high levels of inventory on its ear. Because high levels of inventory can lead to bad service (Edwards).

Figure 6.4. Non-commercial v. Commercial Operations



6.4 Accelerated Production: The Gleevec Story⁶³

Novartis' breakthrough cancer drug, Gleevec⁶⁴, which arrived on the market in record-setting time in May 2001 provided an example of unprecedented collaboration and coordination in drug discovery and development. It highlighted the extent to which production can be effective and efficient with highly aligned and focused efforts. This story was recounted in Novartis CEO, Daniel Vasella's 2003 book "Magic Cancer Bullet".

6.4.1 Management Overview

"Magic Cancer Bullet" provided a perspective on Novartis' organization and management practices. Vasella believed that as the CEO of a major multinational pharmaceutical company, it was his responsibility to "create a fertile environment for drug discovery and development by choosing and supporting the right scientists." The right scientists often took calculated risks and were dedicated to the organization's mission; Novartis was committed to hiring the best, most expert and committed associates. While the nature of Novartis' business involved a high degree of uncertainty, not knowing for sure if a drug would prove successful, Vasella thought that intuition played a part in guiding decision-making at Novartis. Further, Vasella also was strongly influenced by an obligation to push a product if there was a fair chance that it would change the practice of medicine.

Vasella did not begin to oversee the actual drug making process until the start of development and accompanying commitment of significant resources. Drug development involved directing large amounts of capital and human resources to projects. Gleevec forced Novartis to abandon their usual drug development pattern by allocating a large amount of resources for the drug far earlier than normal: they spent a sizable portion of the drug costs in the early phases of the

⁶³ Magic Cancer Bullet by Vasella & Slater (2003 New York: Collins) provided the majority of the information for this section.

⁶⁴ It is worth noting that Gleevec is a brand name. The molecule name is Imatinib mesylate. The development name is STI 571.

development process. Normally they would spread the costs over the entire development and production process. This significantly heightened their financial risk and created huge “opportunity costs” by diverting resources that would have been earmarked for other drugs. The firm had well-established processes that allowed resource allocation as it became clear there was a need, as a drug showed signs of efficacy. Vasella explained that with Gleevec the firm essentially “turned all our resources loose on a drug at the very beginning of the development process.” This went against the firm’s method of proceeding slowly, prudently, and cautiously-one step at a time. However, to Vasella it seemed as if the most important support given to the Gleevec project was not turning over more financial resources to Oncology Head, Alex Matter, but rather “It was more that I was saying to him, ‘Go for it,’ and that apparently meant a great deal.”

Vasella said that managing the birth of a drug involved dealing with complexities as they appeared. Inherent in the drug industry was dealing with the pressure-laden and complexities of patents and pricing. Part of managing drug development complexity involved what Vasella called innovation management and success management; both contributed to imposing order on a process that could have gotten out of hand, particularly in the case of Gleevec where patients demanded the drug as quickly as possible.

- Innovation management meant creating a climate that allowed risk-taking, where employees were motivated and had a sense of ownership of the product; a climate that encouraged quality, speed and good planning. It was also crucial that the organization was aligned along common priorities. The culture at Novartis had learned to grapple with high risk by giving researchers as much freedom as possible without losing focus and alignment.
- Success management entailed explaining the need for continuous investing in R&D, the need for patents, and the need for profits in order to have a successful and sustainable pharmaceutical industry. Vasella believed that there were no substitutes for the pharmaceutical industry. The academic world was better suited to the discovery process than to developing discoveries. No government and no other institution had been as successful in discovering, developing innovative drugs, and bringing them to patients.

6.4.2 Gleevec: The Race to Market

Gleevec was one of the first drugs that provided evidence for the then-new concept of using genetic information and insights on molecular pathways to develop drugs. In the late 1980s, two researchers identified the principal mechanism of Chronic Myeloid Leukemia (CML). A genetic defect caused CML, and CML was the only cancer where the genetic cause was known. Novartis assembled a team to work on a treatment for CML that Vasella described as “people who were not satisfied with just showing how things in the lab worked.” Although because CML had a relatively small patient base, chances of the project being commercially successful were questionable, and marketing managers consistently discouraged management from supporting the compound. Thus, Vasella said that for those working on the Gleevec project, “No one would have been surprised to learn on any given day that the project had been scrubbed and resources put into other projects.”

The pre-clinical and clinical data had overwhelmingly positive results, which made Novartis determined to accelerate their process to produce enough drug substance to speed up and expand patient trials. Novartis chose to place a high level of priority on Gleevec and consequently assigned significant resources to moving to industrial-scale production. Speeding up the production process of the drug significantly increased the costs of failure. The company planned to invest heavily in production up front without waiting for the results. Waiting until the stage of the Phase III trials to scale up production (as was the usual practice at Novartis and most companies) would have meant significantly limiting enrollment into clinical trials and perhaps getting FDA approval without an adequate supply of the drug. The goal was to maximize resources to produce commercial quantities of the new drug quickly enough to save as many lives as possible. While it usually took two to three years to produce sizable drug quantities, with Gleevec, Novartis wanted to decrease the development and production schedule by an entire year.

Novartis, however, could not just add new facilities and hire new people over night. For the most part, they had to rely on what they already had in their network. Typically, Novartis

produced a drug first in a pilot plant in Basel, and then in a chemical production plant, also in Basel. Because everyone on the development and production teams in Basel had experience working together, the hand-over from development to production went smoothly. The production process could be handed off to another plant once all the “teething problems” were resolved in Basel, following the “prototype adequate” campaign.

With a demand for truly large quantities of a drug, production shifted to either production facilities at Ringaskiddy, Ireland or at Grimsby, U.K. Ringaskiddy produced drugs for Novartis since 1994, but never acted as a launch facility, the place where the process of first commercial production of the drug substance actually begins. Usually Ringaskiddy entered the picture after a drug was launched at the Novartis production site in Basel. With Gleevec, Novartis decided to go straight to launch campaign, bypassing the “prototype adequate” one. This meant moving directly from the development pilot plant in Basel to the major production site in Ringaskiddy. For the first time, the company skipped the Basel production step. Instead, they sent technical developers from Basel to Ringaskiddy, which was a risk since these teams had never before worked together and development and production people do not always have the same work styles.

Thus, Ringaskiddy took on the entire launch of a drug. Novartis chose a commercial site earlier than usual, based on successful patient trials. The firm prioritized expanding production capacity, believing that moving production to commercial scale manufacture facilities and increasing the technical resources and capacities devoted to the product would make sufficient supply of the drug available for the accelerated clinical trial program and ultimately, for the commercial market. Novartis accelerated the trial process, beginning Phase II trials in June 1999, only a year after Phase I had begun in June 1998. On average in oncology, Phase I trials take two years; Phase II trials, one to two years, or three to four years for Phase I and II. Novartis had developed an Expanded Access Program that allowed access to the drug to a much larger number of patients than usually enrolled in a “classical clinical trial”; production at Ringaskiddy was needed to support this.

Gleevec was a difficult drug for Ringaskiddy to make. It required a number of chemical processes and a 12-step manufacturing process that included seven isolated steps as well as 11 other chemical steps. To manage the complexity, Ringaskiddy received all the raw materials and focused on seven of the 12 chemical steps in the manufacturing process. With seven steps completed, the substance was sent to Stein (Switzerland), where it was put into capsule form. Ringaskiddy employees were given more tasks to perform each day than in the past but employees became personally involved in the success of the drug. Ringaskiddy moved quickly by improvising. Several difficulties arose, including the following:

- Instructions on how to do testing came from Basel in German; they had to be translated quickly.
- Pressure to complete data analysis quickly. Four people worked on the testing of Gleevec, and before they finished, others at the plant were ready for the first step of production. Novartis could not afford any hold-ups in production.

Ringaskiddy had to meet impossible deadlines and they knew their reputation depended on how well they accomplished their mission, as such many employees worked overtime to help achieve goals. They met the August 2000 production deadline, which supported the Phase III patient trials, exceeding their 1,400 kg goal and producing 1,536 kg of Gleevec. They found ways to speed up production of the drug, coming up with ideas for more efficient and more rapid production. When the plant needed to meet increased demands for the drug substance, they re-evaluated their production schedule and transferred two early steps of making the drug intermediate to the Novartis facility in Grimsby, U.K. As a result, Ringaskiddy focused on the remaining five steps, and set up equipment so that it could keep the five-step process running continuously. All five steps were up and running in parallel by the end of October 2000. During the launch campaign, it performed the steps one at a time. The target date for commercial market was set at June 2001.

In July 2000 the FDA granted fast-track designation to Gleevec. Novartis knew that only under exceptional circumstances would the FDA approve the drug on the basis of Phase II results.

A priority review would shorten the actual review time of a New Drug Application submission to first action from 10 to 12 months down to six months. Novartis filed the New Drug Application only 32 months after the first dose in man, more than halving the typical drug development time of approximately six years.

During the FDA review process, the FDA requested a name change for the drug. Novartis suggested changing from the original name, Glivec, to Gleevec. This change meant that the drug name had to be changed everywhere that the original name appeared for North American packaging. The cost of changing the artwork on the package insert and the box ran to more than a few hundred thousand dollars. With that hurdle cleared, Novartis asked the supply chain team if it could ship the drug within 48 hours of FDA approval. This was a significant reduction in the time between approval and getting to market. The normal time to market was 11 to 14 days. The supply chain team responded that this was a tough goal but they would accept challenge knowing it would be possible with the FDA's cooperation.

In early May 2001, Ringaskiddy underwent the final FDA audit, which ensured that sufficient data was available to validate the manufacturing process. The audit involved FDA inspectors visiting the drug production site, checking equipment, and reviewing all documents filed by the company, looking for signs of non-compliance. The FDA took the highly unusual step of approving Gleevec within one week after the drug substance and dosage form inspections. The entire inspection and approval process took no more than two weeks. The usual approval process occurred three, six or nine months after such inspections. The FDA reviewed Gleevec in two and a half months, an all-time record for a cancer drug and for the evaluation of a highly complex novel drug. Novartis succeeded in shipping Gleevec to market within a day of the FDA's approval. Novartis credits Gleevec's record-breaking arrival on the market to a constructive collaboration with the FDA. Speedy approval was obtained from various authorities around the world; by the fall of 2002, health authorities in almost every significant country had approved Gleevec.

Although Gleevec initially was not a commercially attractive project, Novartis rapidly invested in manpower to scale up manufacturing and to expedite clinical development. In the end, Gleevec became a commercial success, which tempted Vasella to say that perhaps rewards come to people who do the right things, irrespective of short-term issues. Vasella believed that Gleevec was an example of Novartis' values: alignment within the company; caring for the patient; emphasis on innovation; an ability to improve the quality of life, to prolong life, perhaps even to cure a deadly disease.

6.5 Summary

At a time when many pharmaceutical firms were looking to improve or modify their R&D programs, Novartis made an important contribution to this research by providing details on its newly developed approach to R&D. In terms of integration and knowledge, Novartis appeared to be coming to grips with the shortcomings they had identified within their organization that were leftovers from the traditional R&D, or Chinese wall, drug discovery and development model. Further, NIBR was aware that even with the old R&D model overhauled, the organization still struggled with the fragmentation caused by its global nature. Examining Novartis' SCM unit, however, demonstrates that the firm wants to expand collaboration at all levels of the organization, hoping to make drug development and delivery more reliable, more successful and ultimately, more profitable.

Chapter 7: Case Description- Novo Nordisk A/S, Inc.

The opportunity to investigate an additional pharma firm emerged at a late stage in the data collection phase, but because the firm was smaller in size and scope than Pfizer and Novartis and allowed a high level of access, Novo Nordisk was added to the case research. Thus, this chapter reports the findings from case research conducted at Novo Nordisk's headquarters outside of Copenhagen, Denmark. Much of the data collected at Novo Nordisk was within the context of one significant drug development effort: the Liraglutide project. This was significant in that Liraglutide contrasted rather dramatically with Novartis' Gleevec story.

In 1989, the rival Danish firms, Novo Industri and Nordisk Gentofte, also the world's second and thirds largest suppliers of insulin, merged to create a large firm, Novo Nordisk, that could compete more effectively in international markets, cope better with rising R&D costs, and accelerate the pace of new product development. Novo and Nordisk had each possessed strong research organizations; joining these led to new product possibilities, in existing disease competency areas and in new disease areas. Novo Nordisk focused in four disease areas: diabetes, hemophilia, hormone replacement therapy, and growth hormone therapy. In 2004, the company announced plans to expand into other disease areas, such as inflammation and oncology.

With 35% of the world insulin market, Novo Nordisk's main competition was U.S.-based Eli Lilly, the market leader. Eli Lilly beat Novo Nordisk to market with a fast-acting insulin product, Humalog[®] in 1996; Novo Nordisk introduced its own fast-acting product, NovoLog[®], in 1999. To loosen Eli Lilly's grip on the U.S. market, Novo Nordisk formed an alliance with Schering-Plough in 1998 to market a newly approved oral non-insulin drug for the treatment of Type 2 diabetes: Prandin[®]. The company launched more diabetes-related products between 2001 and 2004. By 2006, Novo Nordisk had achieved a 51% share of the total insulin market worldwide. In 2005, Novo Nordisk's sales were DKK 33,760 million (just under U.S. \$6 billion at the prevailing exchange rate), with diabetes care contributing 73% of the total. The headquarters

remained near Copenhagen, but the company competed as a multinational with fewer than 60% of employees working in Denmark.

7.1 Background to Liraglutide⁶⁵

Novo Nordisk felt it would be most appropriate, for the purposes of this research, to explain the R&D process by following the story of one drug, Liraglutide. Liraglutide was Novo Nordisk's new type 2 diabetes drug that entered phase III clinical trials in early 2006. Liraglutide worked on the bolus insulin secretion and, when stimulated by food intake, helped the body produce the right amount of insulin around mealtimes. Also known as Glucagon-like peptide 1 (GLP-1), the hormone was derived from the intestine. Novo Nordisk created a GLP-1 analogue that was administered once per day and then worked for 24 hours (as opposed to only one hour after meals) to increase insulin secretion depending on blood glucose levels.

Liraglutide was not a replacement for insulin, as it required the presence of some functioning beta cells in the pancreas. It was considered a step between oral anti-diabetics (OADs) and insulin for type 2 diabetics. It could delay the onset of insulin therapy for type 2 cases by providing better disease control and eliminating high or low blood glucose levels throughout the day. This drug had the added benefit of decreasing body weight, while insulin therapies typically caused weight gain; lowering body weight, a factor so significant in type 2 diabetes that the disease is sometimes referred to as "diabesity," was an important effect of the drug. Some patients would find this a less attractive treatment option because it was an injectable drug, but it was not chemically stable in forms other than an injectable.

⁶⁵ For a more detailed explanation of diabetes see appendix IV.

7.2 Research: From Idea to Project- Pre-Discovery⁶⁶ and Discovery⁶⁷

Table 7.1 Timeline for Research phase- Liraglutide

August 1996	Project enters Discovery Portfolio
February 1997	First synthesis of the compound

Lotte Knudsen⁶⁸, Scientific Coordinator for Liraglutide and longest member of the project, began working on the GLP-1 hormone as early as 1991 in Research in Novo. Knudsen explained that there are a number of ways for Discovery teams to get ideas for new drug projects:

- By looking at what is new in research;
- To make a drug similar to one of the company’s top-sellers (“me too” drugs); and
- Internal ideas.

The Novo Nordisk drug portfolio consists of drug projects that exemplify all of the above methods of idea generation. According to Knudsen, the internal ideas are the truly innovative ones:

We have a few ‘Albert Einstiens’ here. These people have their own personal theories. They spend a whole lot of time thinking through basic [physiological] mechanisms and are good at that sort of thing... thinking ‘that could be something.’ If someone has a really good idea then you might be allowed to push forward with it.

However, the new idea generation process must take into account Novo Nordisk’s disease area profile: this is a company that specializes in diabetes care and growth hormones.

You cannot have total anarchy. You have to have some kind of steering of innovation. Free innovation is not a good idea. We’re supposed to be innovative, but not anarchists. Chance of success is a lot less if you just let everyone try ideas- anarchy. If we spread products through too many disease areas, it will cost too much to market them. Novo learned that they couldn’t have too many different areas of working. But it goes back and forth all the time and has to do with changes in top management. Sometimes it is “in” to have many disease areas. Then there is a crisis and then you have to focus [on fewer

⁶⁶ Pre-Discovery lasted through 1994.
⁶⁷ Discovery lasted from 1995 through August 1997.
⁶⁸ Knudsen was educated as a Chemical Engineer, but early on started working pharmacology and remained in pharmacology. Her education was “slightly off” from what she ended up doing, but after a few years it didn’t really matter. Although Knudsen was a scientist, she did not work in a lab. In Denmark, lab technicians with a bachelor’s degree and who trained in lab work performed basic research. Knudsen gave direction, but her lab technicians did the practical work and form initial conclusions. External professionals conducted clinical research, although Novo scientists constructed the protocol and guidelines in some cases.

areas]. It sort of goes up and down with respect to how many diseases. Most logical not to have too many, but allow a certain degree of free innovation, but not too much. Only certain people can handle free innovation. Innovative does not mean anarchy. (Knudsen)

Knudsen went on to explain that there is innovation at the level of new product idea generation, but within research, there is the day-to-day nature of innovation. There are processes or hurdles that the team must conquer throughout the course of a project, and to move forward through these hurdles, “you should be as innovative as you like.”

The GLP-1 project stemmed from Novo looking at what was new in research⁶⁹. Before GLP-1 reached Novo Nordisk’s Research lab, it had sparked clinical research in academic and hospital settings. Novo learned about the hormone via a professor at the University of Copenhagen. The professor connected the pharmaceutical company with GLP-1 scientists around the world, which gave Novo a slight head start on other pharmaceutical companies working in diabetes. Initially, the hormone was identified at Massachusetts General Hospital (MGH), in Boston. Operating outside of the pharmaceutical regulatory environment, doctors at MGH advanced research on the hormone more quickly than would have been feasible within a commercial organization. MGH isolated the hormone, determined that it was efficacious in diabetics, and tried the drug in humans. Ultimately, MGH sold it to a US company, which then sold it to Novo.

Since Novo purchased the hormone from an external company, turning GLP-1 into a marketable therapy was a highly focused effort. Purchasing the hormone eliminated a need for the normal extensive screening or search for new chemical entities (NCEs) that happens when looking for innovative new drugs. “In looking for an active compound you have a theory about a target (usually a receptor or an enzyme) and you know it should be possible to find a small molecule that can be formulated to work on this.” The team then goes through a random screening process in which they go through their library of a million compounds collected through company projects and research over the past 30 years. Some compounds in the library

⁶⁹ Interesting to note the historical roots of this research area as well. Knudsen explained the presence of an historical interest in GI hormones in Sweden and Denmark; this interest started in the 1960s and created a new field devoted to identifying and determining the effect of GI hormones.

may have been purchased or developed through collaborations with other companies. Scientists screen millions of compounds that could work and find one that is sub-optimal to hand to chemists for optimization. “This is random lead generation, which leads into the discovery of the right compound.”

With GLP-1, however, the team was able to shortcut the library screening process because at the project’s inception, the basic research on the hormone had been completed. Thus, scientists were able to target specific biological and chemical processes that could work with the new hormone. It did not take long for the Novo team to realize that GLP-1 was difficult to work with, primarily because it was difficult to make the hormone chemically stable. Because GLP-1 was based on a peptide, a natural hormone, and was delivered to patients in a liquid formulation, scientists had to struggle to make it stable. It is much easier to make a pill stable than an injection; this is because a pill is inert. The team also aimed to deliver GLP-1 as a natural hormone to patients, as the body does not make antibodies against natural hormones like it could with an analogue.

As the project formally entered the discovery phase, Knudsen became Project Manager for Discovery; from 1993 until 1995, Novo research scientists experimented with the hormone. Researchers struggled to determine optimal administration of the hormone and discovered that for best results, the hormone had to be given constantly, 24 hours/day, via an infusion. The clinical infusions yielded remarkable results and the product moved to the development stage. However, Development sent the drug back to Discovery when clinical data showed that a constant 24-hour infusion produced an undesirable, and relatively serious, skin irritation (see Figure 7.1, The Iteration Cycle for Liraglutide). Novo could not produce a drug that had intolerable delivery side effects.

When setbacks such as this occur, the entire team was charged with fixing the problem. Knudsen explained that team-problem solving strategies were cultivated in the Danish school system. Project teams were comprised of members with diverse backgrounds, and the project

group leader was responsible for creating an environment in which members could freely speak and criticize in order to learn.

The person who runs the project group sets up environment where you can all freely criticize each other and no one takes offense and is only happy to receive comments that may lead to higher level of understanding. Those in the project group must trust each other. We build trust through team building days, project information days... If project groups don't work and it is extremely frustrating... sometimes one or two persons can totally destroy a project group. One person can destroy the working climate- then you are not going to get anywhere. (Knudsen)

This team problem solving approach moved ideas to a higher level, provided the best way to solve problems, and prevented the company from giving up on a potential drug too soon. Knudsen continued on to contrast the Danish approach to problem solving with American companies:

Project work in American companies is very, very different. In American companies, when you have meetings you present what went well and problems are solved in a different way. In Denmark, we talk about problems and provoke each other. It takes a long time to get to the point where we can freely criticize each other. But, you may hear something that you hadn't thought about because everyone thinks in a unique way. This can help solve problems. Of course, some problems are not solvable- move on, dump the project... When solving complex problems, having to dump things is inevitable.

The team tried a number of strategies to solve the skin irritation problem, testing new compounds on pig skin, similar to people's skin, and would indicate tolerability of an injectable. While the compound was back in Discovery, two decisions were made based on developments in insulin innovation. Immediately after the skin irritation episode, the Novo team decided to develop GLP-1 as an analogue. Up until this point, Novo kept GLP-1 in its natural hormone form; continuing to do so would continue to irritate skin. Additionally, several years of increasing marketing demand for once per day dosing meant that GLP-1 should become a product that was dosed once per day and worked for 24 hours.

Thus, keeping GLP-1 as a natural hormone was not going to work. Knudsen explained that in the discovery process:

Things that don't work [are] not generally thought of as failures... Often you learn the most from ideas that do not work. That is very important information when you try to make a new drug... you can conclude more from what does not work... At times, [you are] only as smart

as your background or information available allows you to be. Sometimes you run into a stop sign and you think about it and realize you could have learned that earlier had you thought about this and that or had spent more time thinking... You have a theory, you plan an experiment and that tells you something. You have an idea, test something and are surprised- that forms the basis of another idea. Most projects are born out of some kind of theory- 'this causes this'- this is science-based in a way that some other kinds of invention/discovery may not be.

It took another 18 months to find a molecule that would meet the new requirements for the Liraglutide product (this was fast, it usually takes 3 years). The team borrowed and transferred the long-acting, once/day technology from its insulin projects and made several hundred potential molecules based on GLP-1. "This drug was made in a completely different way than the small molecules. It is always impossible to predict what a certain compound will do because we have a million systems inside our bodies and we only understand a few hundred of them." Iterations to produce a lead candidate happened every few months in a cycle that gathered ideas, tried 10-20 compounds, reflected on findings from the 10-20 compounds, and then began the cycle again. Eventually, the team found a molecule, Liraglutide, which became a lead candidate and moved into Development.

When the Liraglutide project moved to Development in 1997, Knudsen remained with the project as Scientific Coordinator, with the responsibility of "staying on top of the science" and working on publications that would form the basis of "early PR" for Liraglutide. Knudsen also assumed the scientific responsibility for the patent work. She maintained three or four functions within the project dealing with the chemical part of the compound and toxicology. This was the first time in Novo Nordisk history that a scientist remained with the project once it left Discovery.

7.3 Development: From Lead to Candidate

Table 7.2 Timeline for Development phase- Liraglutide

August 1997	Project enters Development Portfolio (M1)
January 1998	First master cell bank produced
August 1998	First GMP-produced batch
September 1998	Initiation of toxicity/safety for phase I
February 1999	Decision to initiate clinical trials
April 1999	Initiation of clinical phase I trials (first human dose M2)
August 1999	New cell construct selected for clinical development and marketed product

Susanne Rugh⁷⁰, Head of R&D Quality Assurance, joined the Liraglutide project in 1997, as the project reached the M1 milestone and moved to the development portfolio. Rugh led the transition from the discovery phase through to first human dose. She was responsible for the quality assurance for all research processes and development activities. Additionally, as project manager she had to ensure that in development, the drug was produced according regulatory practices, in particular Good Manufacturing Practice (GMP) standards, for human clinical trials. However, despite the complexities of her role, Rugh believed, “This is the exciting phase because this is where you shape the product.”

Rugh’s job focused on getting the development organization involved in the project, because Discovery had been “pure research” which involved molecular development, non-regulated pharmacology and biology testing. A number of new practices were tried and adopted in transitioning Liraglutide from Discovery to Development. The Liraglutide project was the first with a “Shadow PVP” (shadow project manager) who started eight months before the formal hand-off to development to get the project ready for transfer. Additionally, a small development

⁷⁰ Susanne Rugh worked within Novo Nordisk’s “House of Quality,” and specialized in proteins. Her background was as a biochemical engineer. She had earned a degree in business as well. Rugh had spent her entire career working at Novo Nordisk, but had held a number of positions.

team was assembled six months before the project came out of Discovery, in order to make research more aware of the development organization, thereby preventing delays. In particular, research had to communicate with the CMC (chemistry, manufacturing and control) team about the purification process; some solvents used in lab-scale purification were not allowed in large-scale production (for environmental and toxicity reasons)⁷¹. In late-stage research, the expertise provided by Development regarding scaling production had to be integrated into the process.

Facilitating this new collaboration between R&D was a challenge. The goal was to involve Development earlier in the process so that production of the first GMP batch was smoother and the team did not have to start all over with this process. “This was an adjustment for research. [It was] a major adjustment for them to think ahead to what would be needed for regulation. This meant they had to document exactly what they were doing, particularly on biological and mechanism testing- which is needed when they go to file,” said Rugh. Rugh admitted that initially, research was averse to thinking about regulations and GMP documentation. Discovery scientists felt constrained by GMP, and they preferred to create more molecules than stay with the same project:

Discovery is really made up of innovative people. Many [of them] would die in a development setting with regulations and GMP. They feel too constrained by changes and actually having to go very deep into a purification method to improve the yield and the bottom line. Discovery people are not interested in yield. They would rather make more molecules, test new mechanisms and go on to the next project than hang on to the same process and work on improving that, which by the way is fine because we need all the different facets... (Rugh)

Discussions regarding the necessity of this shift in research responsibilities occurred, and there were fast adaptors and slow adaptors, but that goes along with any drug project. Ultimately, the changes initiated in the research and development relationship on the Liraglutide project were incorporated into other Novo drug projects.

⁷¹ Rugh liaised with the CMC group, a part of pharmaceutical development described in the second part of this case report.

With a biotechnology project, a wider array of development sub-groups participated than if the project involved a small biological molecule. Rugh managed the different development groups involved in shaping the product, which encompassed over 20 skill types⁷² that needed to be involved as early as possible to speed up development. However, not every project can pull together 20 skill groups at once because of resourcing issues; only super candidates, as designated by the research group based on their testing, receive access to all the skills they need. Rugh acquired the skill types to cover all the bases this project needed. She knew that it would be important to foster a substantial interaction between many of these skill types in order to get to the best product for the clinical indication and meet the product profile.

Team members from analytical, formulation, API process, and categorization were extremely instrumental in the Liraglutide project. Categorization, the process of defining a product's physical and chemical characteristics, was especially critical with the Liraglutide project. Clinicians needed a soluble, stable product that had a 2-year shelf life. The team's challenge also included achieving the long-acting profile with a protein/peptide molecule that was difficult to handle. During development, many team members often exclaimed, "this compound is WRONG," because it was not behaving like the normal insulin product/molecule. Team members were insulin pros, most comfortable with and accustomed to working with insulin molecules. The team worked more than usual on the solubility/chemical/physical characteristics of this molecule because they lacked prior information about these parameters as the molecule belonged to an entirely new class of drugs. The Development team relied on what had been learned in animal and mechanism studies and had extensive discussions with researchers and clinical about these parameters.

The Liraglutide project involved keeping a substantial number of departments and team members actively involved for longer than usual was necessary for a drug project. The

⁷² Skill types is a formal phrase Novo uses to think about resource planning. The formalization of this term occurred in the last few years, but has always inherently been there, according to Rugh.

“discovery, mechanism and pharmacology” people stayed with the project. Although this was not a standard practice at the time, it became one within Novo Nordisk shortly thereafter. Keeping these pre-clinical scientists involved in the project was fruitful in developing more mechanistic/testing methods in response to clinical findings. Rugh explains “if they see something in the clinic, we can back it up from science side or dismiss it as a random find.” At the same time, this led to what Rugh terms “healthy disagreement” stemming from the fact that pre-clinical people have different perspectives, different knowledge, and different backgrounds on drug development. In particular, there was significant disagreement and discussion regarding making the Lira molecule stable enough to have a two-year shelf life. According to Rugh, “this created lots of interesting discussions and created a number of tasks for people to work on. The mechanism of this drug is new in diabetes and extremely exciting; there were fruitful cooperations between groups to achieve a marketable product.” Overall, Rugh felt that there was good cooperation between the scientists and clinicians on the Liraglutide project, which facilitated a collaborative clinical trial design.

Keeping such a variety of perspectives on the project required resource planning. People from various departments had to be allocated to the project. The Liraglutide project had partially resourced project status. At the time, Novo Nordisk was managing a full drug portfolio and had to balance GLP-1 with other projects in the company’s portfolio. Management believed its main competitor, Eli Lilly, was threatening Novo’s core insulin business. GLP-1 was not an insulin project, and Novo firmly believed insulin was the best molecule for treating diabetes and that the firm’s focus should remain on insulin analogues. Further, GLP-1 was for type 2 diabetes and Novo did not have many type 2 products. Novo had planned to build an injectable type 2 business on Novomix[®].

Despite an extremely enthusiastic project team that believed in the product, as well as team members not officially allocated to the project working overtime for it, the Liraglutide project moved slowly:

My main frustration was we were certain we had an interesting new product and mechanism, but the project was partially resourced, meaning that we had problems getting access to pilot plant capacity which slowed down the development of the project. For the project group that is quite frustrating- to see, but not be able to sell a message to management to up-prioritize. Everyone involved knew that this was a good product. It was extremely easy to convince heads of departments to allocate resources that they really didn't have to this project (Rugh).

Liraglutide project champions could not convince management to advance the project, even though Eli Lilly had a similar product in its pipeline. Project managers also alerted management that Liraglutide was a potential obesity drug, but the thinking on obesity was not quite mature, so the obesity drug was viewed as “a total wild idea”. Even with the data and science presented to management, an oral antidiabetic won the resources the Liraglutide project coveted⁷³.

7.3.1 Mid-stage Development: Clinical Trials

Table 7.3 Timeline for Clinical Trials through 2002- Liraglutide

June 2000	First presentation at US conference (American Diabetes Association)
September 2000	First presentation at EU conference (European Association for the Study of Diabetes)
December 2000	Second GMP batch produced. Purification done outside NN due to capacity constraints.
December 2001	Incomplete results from the phase II trials on dose-response curve and maximum tolerated does, hence decision to conduct dose-optimization trial before starting phase IIIa
August 2002	Inititation of phase II dose-optimization trial

In 2000, the Liraglutide project team received the first Lira clinical trial data and side effect profile that included nausea and vomiting. This first trial showed that the side effects were the most intense at the maximum dose level. Although it prevented the drug from progressing more quickly, in 2002, Novo attempted another round of patient studies with different dose groups. This new study increased the maximum dose level, but brought patients up to the maximum dose in steps. This step increase in dosage limited the side effects once patients got to the highest dose. Side effects occurred more at the onset of using the drug, but faded after a few days of therapy. Thus, stepping doses were planned for phase III studies.

⁷³ Although the OAD became fully resourced, it ultimately died in phase III.

Table 7.4 Timeline for Clinical Trials 2003-2004- Liraglutide

March 2003	International non-propriety Name (INN) is established (Liraglutide)
April 2003	Positive results from the dose-optimization trial lead to “clinical proof of concept” (M4)
August 2003	Production of drug supply for phase IIIa is initiated in the fermentation and recovery facilities
October 2003	Initiation of phase I clinical trials in Japan
December 2003	“Fast track designation” application submitted to FDA but option declined in January 2004
Spring 2004	“End of phase II” meetings with the FDA and EU health authorities
April 2004	Ground-breaking of new purification facility PIA-III
July 2004	Passage of “Phase III Go” (M5)
September 2004	Preclinical safety findings observed in rats and mice
October 2004	Decision to postpone phase IIIa and conduct a midterm human safety study and further preclinical investigations

The tide turned in 2003 when subsequent clinical trials and data showed promising results and that the side effects were manageable. Management thus decided the project could move to final stage trials. However, animal trials were always one step ahead of human trials and prior to initiating phase III trials, pre-clinical animal model data showed adverse affects on the thyroid. This could have serious implications for human safety, and Novo was not sure about starting human trials without exploring this further.

At the end of phase II, Novo expressed their safety concerns at their FDA meetings. Initially, the company thought perhaps they could move to phase III with some conditions. However, moving forward to phase III with conditions could adversely affect the labeling of the final product; furthermore, it was not a good idea to investigate a significant safety issue in phase III. Thus, in response to pre-clinical safety findings in mice, Novo decided to initiate a second phase IIb study to examine long-term effects of taking Liraglutide. This final phase II safety trial proved that the thyroid issue was only present in rodents, not humans. This emphasizes the fact that animal models are not always perfect for humans.

After four years in mid-stage development, and addressing the safety issue in the additional phase II study, Liraglutide was ready to move to phase III clinical trials in early 2006. In June 2007, at the 67th Scientific Sessions of the American Diabetes Association (ADA) in Chicago, Illinois phase II clinical trial results for Liraglutide were announced:

...the investigational treatment liraglutide, a once-daily dose of human GLP-1 analogue under development by Novo Nordisk for the treatment of type 2 diabetes significantly improved glycaemic control (HbA1c) by reducing both fasting and post-meal glucose levels in people with type 2 diabetes... Results showed that Liraglutide was effective and well tolerated within a wide dose range, allowing nearly 75% of patients receiving the highest dose to achieve glycaemic control (HbA1c<7.0%) without hypoglycaemia... 'A well-tolerated agent with once-daily administration that can allow a majority of patients to achieve good glycaemic control with a low risk of hypoglycaemia and no weight gain is very promising and will be a considerable advance in diabetes treatment.'⁷⁴

Novo Nordisk's stock price jumped following this announcement.

7.4 Chemistry, Manufacturing and Control

Technically, Novo Nordisk classified Chemistry, Manufacturing and Control (CMC) as part of the pharmaceutical development process, but the CMC function essentially bridged development, manufacturing and drug registration phases (for a visual depiction of where CMC fit into the drug development process, see Figure 7.2). Novo Nordisk operated their R&D and manufacturing activities in parallel, meaning that while drug candidates underwent biological and pharmacological profiling, manufacturing processes were developed and validated and the final product was designed and formulated, including device development for biopharmaceuticals. At Novo Nordisk, a CMC team joined a potential drug project late in the research phase and remained with the project through the submission of regulatory documents. Drug projects belonged in one of two pharmaceutical product categories: peptides/proteins and small organic molecules. Peptides or proteins usually were produced by recombinant technologies involving fermentation and purification and were most often formulated into injectable preparations. In

⁷⁴ From: <http://www.novonordisk.com/press-> Phase 2 results show once-daily dosing of human GLP-1 analogue liraglutide brings patients to HbA1c target (25 Jun 2007).

contrast, small molecules were manufactured by organic synthesis and were most often delivered as tablets.

In the late research phase and during the pre-clinical development phase, the CMC areas focused on the molecule itself: how should it be produced, what kind of impurities and degradation products could be expected, the physical/chemical properties of the molecule including pre-formulation, and support for the pre-clinical studies within this phase. During the exploratory clinical development phase (phase I and II clinical trials), the majority of the CMC development was performed, leading to decisions on the final manufacturing methods for the active pharmaceutical ingredient and the drug product, specifications, analytical control methods, and choice of delivery system. In parallel, products for use in phase I and II clinical trials were developed, documented, produced and labeled for clinical trials. For the large phase III clinical trials, the final product was used. In this regulatory clinical development phase, transfer of CMC activities to Production and Control Laboratories occurred and the manufacturing was up-scaled to commercial levels. For more specific details on the CMC process and phases see table 7.5.

The formal drug registration file involved a detailed section regarding chemistry, manufacturing and control (CMC), which described the medicinal product in terms of chemistry and pharmaceutical properties as well as a description of how it was manufactured and analysed. Development reports were written and the entire CMC development documented for use in the regulatory file and for inspection by regulatory authorities.

Table 7.5 CMC Phases

Phase	Description
Up-scaling of production method	Scale from lab to industrial scale
Purification technology	Proteins and peptides derived from recombinant technology through fermentation and/or chemical/enzymatic synthesis are purified before use as a pharmaceutical ingredient. The drug substance is produced in pilot plants that have specialised in different techniques within fermentation and purification. The drug substance is produced according to Good Manufacturing Practice (GMP) in order to be used for toxicity and clinical trials. This also means that every operation in the pilot plants is documented and validated and that equipment at all time is in control, in other words, maintained and calibrated.
Analysis & physical chemical characterization	Protein analytical separation techniques encompass primarily electrophoretic and chromatographic methods to determine the identity, strength, purity and stability of protein-active ingredients in drug substance or drug product preparations. An accurate analytical profile of a drug and its formulation fulfils the requirements of regulatory agencies, and is essential since the presence of impurities can affect the safety and efficacy of the pharmaceutical product.
Formulation technology	Formulation development is one of the critical steps in developing a protein as a therapeutic product. Before the protein (i.e. insulin) can be administered to the patients a dosage form must be developed which possesses the best technically obtainable attributes to treat the medical condition in question. The main challenge within protein formulation activities is the development of dosage forms possessing a sufficient stability profile. Other critical elements guiding formulation development activities are regulatory guidelines and pharmacopoeias. Depending on the specific dosage form, certain pharmaceutical quality characteristics must be fulfilled e.g. strict control of particle size and distribution for suspensions and compliance towards preservative effectiveness tests for multidose injectables.
Labelling and packaging	Investigational Medicinal Products (IMPs) are the test drugs used in clinical trials for the development of new drugs and the life-cycle management of existing drugs. The labelling and packaging of IMPs is handled in accordance with specific clinical protocols as one-off packaging runs. The labelling and packaging processes are manual or semi-automated and are conducted following GMP.

Mette Uve Jars⁷⁵, PhD served as the CMC Project Manager for the Liraglutide project. She was involved with the Liraglutide project since 1998. Jars' roles within this particular project have expanded and changed over time: She began as the Analytical Coordinator, then became responsible for managing all the controls until 2001 when she was promoted to CMC Project Manager. The CMC Project Manager role was established in 1998; previously, this job belonged to the Project Vice President.

The CMC process, according to Jars, developed all the technologies to produce material from purification to fermentation and formulation. It included analysis, API development, product formulation, and quality analysis with all potential supplies for the drug.

We develop technologies so you can ferment it [the drug molecule] and generate enough material and recover it [drug molecule] to remove impurities and then use the purification process to purify to 95%. During that process, you make it in isolation and make a derivative of the molecule. You end up with an API, and in theory, you can formulate it in several ways to make a product. There is lots of development going into making the right formulation (Jars).

Part of the goal of the CMC process was to produce the correct drug concentration for patients. In the case of injectables, the concentration had to be correct so that the drug was pleasant to inject, with minimal to no pain; part of achieving this also depended on the injectable device.

Jars emphasized that part of her role was to maintain control over the entire CMC process. A key aspect of this included developing analytical methods that detect impurities related to the process as well as to the molecule itself. There were over 40 different analytical processes in place to control the product; many analytical methods were standard procedure used consistently on other drug projects. Besides exerting a certain level of control on the CMC process, analysis was a comprehensive and well-developed facet of CMC. It was designed to characterize the product, get the product in line with its set of specifications, and determine if the product was safe to administer to people.

⁷⁵ Jars earned both a Master's and PhD in science from universities in Denmark. She also earned a Bachelor's degree in business at Copenhagen Business School. When she was working for Novozymes in Seattle, she decided to go back to school for her PhD because "being in the U.S. and not having a PhD in science means you're a lab technician for the rest of your life, so I began a PhD."

The CMC team produced certain deliverables throughout the course of the development lifecycle in order to proceed from one stage to the next. At the start of the Liraglutide project, the CMC team's first goal was to make a pre-clinical batch for the animal and short-term studies. Pre-clinical batches did not require "perfect practices in terms of how you run procedures." The batch that followed pre-clinical, however, was more refined since it was tested in healthy human volunteers. Jars explained that as soon as the drug was produced for human testing, the team was obligated to meet strict regulatory requirements and a certain level of documentation.

Jars estimated that a significant amount of time and energy (resources) was spent on documentation:

Any procedure being run anywhere in the company has to be described. This includes manufacturing, pilot plants, development labs. Everything is written down within departments. Many procedures are very well described. There is a filing system for organizing and keeping the documents, and they can be easily exchanged via email.

Jars felt that, at times, the energy spent on documenting technologies could impede your ability to just try things. It was partly for this reason, that "you initially try to move forward with standard procedures and use existing technologies within the company... although every time you take a new molecule it is unique, which means some of the things you usually do may not work." If this was the case, the team could sometimes start with processes in place when the molecule was delivered from discovery to development. These processes tended to prove the molecule's biological activity and from there standard techniques (i.e. assays) worked on controlling and defining impurities related to the molecule. When developing new processes to suit a molecule, the team started with lab scale testing.

When possible, the CMC team tried to conserve resources and save time by producing and sufficiently documenting a pre-clinical batch that would also serve as the first GMP batch. This was a savvy thing to do because it eliminated time and effort needed to prove that the material used for the first human trials was identical to the material used in pre-clinical trials. Regulatory requirements meant that every time something was changed in the CMC process, comparability

needed to be demonstrated- that the current product or process was as good or better than in the past and potential negative effects were minimized.

Comparability was another reason for tight control of the CMC process. Batches were produced in campaigns because everything needed to be done in the same way: all batches produced in a campaign must use the same processes, controls, and specifications. While a campaign was occurring, simultaneously, improvements were being made at lab scale and in the pilot plants; proposed improvements could be implemented in the next campaign once the team demonstrated comparability. Changes and improvements were only allowed at particular release intervals.

It was quite expensive to change something and demonstrating comparability required a substantial amount of resources. However, early on in CMC process development it was easier and less expensive to change or improve things: “Early on you’re relatively free to change things as long as you always demonstrate comparability.” Jars explained that “a change in one part of [the CMC] process influences the rest of process, the rest of the supply chain. You must be very careful every time you make a change...” For example, changes made to the API had the potential to affect the final product. Problems that were traced to the API must be solved at the API level and then the rest of the process adjusted accordingly.

Jars further explained that she must consider the benefits and risks of making a change, as she cannot make a change for the sake of change; there must be a concrete reason for changing the process- often changes were dictated by problems within the process. For example, a change that improved yields was acceptable because “the cheaper you can produce an API, the more money you can generate in the end. So, you improve processes in terms of yields, being cheaper.” Proposed changes may slow down the project, so she must weigh the risks of implementation. Jars said, “you can always implement later on. It may not be worth the risk to implement right away. If something else is delayed, you may decide to make certain implementations. Try and

move these things along with you in case you have a chance to implement.” Thus, she could reserve proposed changes and implement them when the project slowed down at a future date.

The real tests in the CMC process occurred at the implementation level, “the real test is implementing. You may get surprises that you have to test or solve.” For example, “you may change to another supplier, who is in theory the same, but influences the process and there is no way of knowing that.” This was not a failure, according to Jars, as it was impossible to test everything and she needed to consciously take some risks. “You cannot run a project without risk. You take a risk and occasionally you are wrong. And sometimes you take a risk based on [its] potential benefits.”

Part of Jars’ job was to identify and mitigate risk. She thought it was important to...

Find ways out in case you take a risk and it does not work out as expected you need to have a way out... you have to know how to react if things work out differently than you expect. If a risk proves bigger than you thought it would be, and you have plans you can’t follow, you will need to go back and re-think.

Jars also strived to heighten the CMC team’s awareness of risk because it allows a better opportunity to work around the risk, and in some cases, get the risk eliminated. On the Liraglutide project, the CMC team faced a substantial amount of risk over the course of the project.

The team successfully managed to eliminate lots of risk in the last year by getting everyone’s attention on risk and knowing where they [the risks] were- we could eliminate them- we were also able to get the resources to eliminate risks. Had we not made them [the risks] clear to management, then we may not have received resources to eliminate risks. (Jars)

With the need to control risk, manage comparability and preserve resources, the CMC team always tried existing methods and technologies. “Many things you can repeat from the past. Everywhere you can use existing methods- you do... Value can be generated from using existing technologies wisely.” Although CMC had a dedicated group that worked with developing new processes, running many experiments, and when necessary, testing processes at large scale, for “some things you can only test in large scale.”

The uniqueness of a particular molecule would typically determine the extent to which resources must be invested in developing new processes.

There are things that are unique about your molecule and those require the most resources...You discover things about your own molecule but also about class of molecules. Trying new things has to do with resource allocation. [Managers] must decide when to invest resources and develop technologies specific to your molecule.

Making a decision to spend resources developing a process for a new, unique molecule accounted for questions regarding risk. If the project was high risk, then Jars could avoid investing resources early on and choose to continue working with other methods and technologies. However, investing in resources earlier could advance the project faster in the later stages. Jars explained, "If the project risk is low, you generally want to frontload as many new development activities as possible because the more knowledge the better. If there is going to be a problem, you want to see it as soon as possible." A problem that occasionally occurred in CMC involved developing a new process that was patented by another company.

Sometimes you are trying to develop a process that has been patented by another company- despite the fact that it works for you. So, you must find new ways around things, existing process patents. You may suddenly realize someone has patented a process... It also happens that sometimes someone does something early on that you don't see as important- you may still take a patent on it, but you may not know how you're going to use it until later... At the time you discover, you may not know if you need to implement it, but you patent it- patenting is a way of protecting yourself (Jars).

Assessing risk and resources with new, unique molecules also considered what other projects were in the company's portfolio and existing flexibility to distribute resources in different ways. Developing new processes required more time and resources. Getting resources allocated to a particular project depended on prioritization. If there were issues with a higher priority project, it was possible that resources and people from the project would be re-allocated to the higher priority project.

For example, as the CMC team worked towards scaling up the Liraglutide project, the partially resourced status caused a major bottleneck in producing GMP and clinical trial batches. The project did not have access to internal pilot plant manufacturing capabilities that were

necessary for completing the purification process and solving other production-specific issues. Lack of access to a pilot plant slowed the project considerably and frustrated the project team. Eventually, the project team decided to outsource production to a plant in a nearby European country, thereby going outside of Novo Nordisk's world-class engineering and manufacturing team. The project team took the API fermentation product to the outsourced plant for purification. The outside plant helped develop the API, but wanted a long-term contract for a share of API production when the drug reached the market. The project team made an expensive deal with the outside plant to perform the purification as a once-off event. Working with an outside plant helped provide enough product for continued clinical trials in humans.

Part of the CMC team's responsibility was to produce the drug for clinical trials, so the project must move forward, which sometimes means "you develop a process that is just good enough to get you by." There were always potential improvements that could be made, but then a product would never get to market. "You must get all the technologies right before the IIIa phase, as this requires large clinical trials which are expensive, and expose a large group of people, so everything must be safe." To make changes in your process after the IIIa phase meant you had to again demonstrate comparability because the company would be launching something (a process, technology) that had not been exposed or tested with a large group of people.

The CMC team never began with a product that was already 100% pure. This would be impossible to deal with, the bar would be set too high and it would be hard to do better in the next iteration. CMC always "starts with something dirty and moves toward something pure from a CMC point of view. This allows you to make changes over time. Something extremely pure means you'd have to go back and redo pre-clinical trials because you cannot prove you have something better." The CMC team aimed to make a safe, standard formulation. Safety was tested in animals and then in humans. The long-term toxicology studies in animals and the short-term human trials happened at the same time. Clinical studies were always ahead with animals, due to

the documentation level required by regulatory authorities. As long as trials were ahead in animals, then in theory, you could move forward to human use.

The CMC team subjected each project to technical design reviews in which the team reviewed processes and considered different options based on experience. These technical reviews were a collaborative activity involving managers and scientists, SVPs of areas, and project directors; essentially all the people who wanted to move the project quickly met with the people in charge of technologies. At these reviews, participants were expected to “say out loud if something isn’t going to work.” Jars also invited manufacturing to meetings to go through processes and discuss improvements. According to Jars, people spoke up at meetings because at Novo it was acceptable to voice concerns; there was a sense of professionalism in which most people were proud of their work and therefore, more likely to say if there is a potential problem.

The CMC team ensured technologies worked and that there were no unpleasant surprises. Part of doing this was understanding that “No one can solve their own problems individually- all these areas influence each other. You can’t say ‘this is just your problem you solve it’. You have to say ‘how can we solve it?’” Jars spent substantial amounts of time trying to communicate this message to a team that initially held a very silo mentality. The silo mentality had to be replaced by an attitude of “we all have to get this right or it will not work.” Part of managing the CMC team involved the challenge of managing “very bright people,” said Jars. Most of Jars’ team members were scientists with pharmacology degrees at a Master’s level or higher.

There is lots in people’s heads- do not underestimate people involved and knowledge in their heads. People involved are important. Sometimes you need to make connections to experiments done 5 years ago. So you cannot always look things up. Sometimes you must remember things to access people’s knowledge or connect things written down in different areas that haven’t been connected before to find solution (Jars).

In CMC, team members leaving the team could cause problems. While Jars believed that “in theory, we can all be replaced. We like to think we are not, because it makes us feel important.” There were, however, people who were harder to replace than others. The CMC core team for a drug project was made up of specialists that work together. “No one works as individuals in CMC

core team... so the knowledge is there so someone from a sub-team could take over or assist a new person taking over on the core team.”

As the leader of the CMC process, Jars defined her role as follows:

I love large, complex problems that we need to find solutions to. I love that there are so many people involved and we all work together to make this work. It is fun to be the spider in the web who makes sure holes are covered. Holes come from different areas and everything must work at the end of the day. As you go through the supply chain, I put my focus on what I feel is most critical to moving forward. There are times where I've spent all my energy on fermentation and recovery- and other times I may focus on supply. All parts are extremely interesting. I try to keep big picture and focus on holes that need to be filled. In my job, we're always working two, three or four years ahead. Trying to think of ways we can save time. For example, on one project, fermentation/recovery had problems getting facilities and processes running and it became clear that if we moved process into another facility at a time at which it wouldn't be normal to move it- then [by moving the process] we could save lots of time.

7.5 API Development: A sub-set of the CMC process

The first experts from the CMC team that entered the Liraglutide project worked on API (active pharmaceutical ingredient) development as the drug moved to Development in August 1997. API development was a subset of the overall CMC process. A complete, dedicated Liraglutide CMC team formed in 2000. The complete CMC team developed all the technologies for formulation, fermentation, purification, and produced material for clinical trials. However, the API development happened first because the API had to be physically and chemically stable in order to be formulated for injection in patients.

Ole Schou, Production Scientist, joined the Liraglutide project as Development Manager for the API as the project reached the M1 milestone (development lead selection- lead candidate moved from Discovery into Development). For the same lead candidate, separate project managers were allocated for the finished drug product and analysis. As the Development Manager for the API, Schou was in charge of creating a reliable process, using biotechnology methods and techniques, for producing the API material with the necessary content and characteristics.

The API Development Manager supervised the API production process as the drug product moved through three different development phases:

- Pre-clinical/ phase I trials
- Phase II/ clinical proof of concept
- Phase III/ registration

As API Development Manager, Schou assembled his own team; when he started with the project only two or three people were in place and Schou recruited members and resources. For this particular project, the expertise required included fermentation and purification, as Liraglutide was expressed in yeast via a fermentation process. Thus, Schou focused on recruiting members with expertise in these areas. Schou's team was primarily responsible for developing a process to scale the project, in line with an aggressive timeline, to make it suitable for pilot plant manufacturing. This process tackled the difficult task of working with a complicated protein molecule and increasing the product's volume without compromising purity or reliability.

7.5.1 Finding and Developing a Process

Most protein products were developed using biotechnologies that assisted in isolating the protein, chemically modifying the molecule, and purifying the molecule. Because Novo had expertise in manufacturing proteins, most attempts at production were intelligent, rational and based on available techniques already familiar to the company.

In developing the API process for Liraglutide, team members had initial ideas on how to create the process from prior experience and accumulated knowledge in scaling up drug projects.

Knowledge from the past helps with the future... Accumulated knowledge helps us know what to do- carries over... People know much more than they are working on- come [to the project with] suggestions... Most people come up with ideas and then do them. Most people have so much experience that you're just confirming what they want to try... (Schou)

Processes developed in Discovery generated ideas for the API process. With Liraglutide the API development team started over because the research API process was only suitable for lab scale; a modified way of making the API was necessary as chemicals that were suitable for use in discovery were not suitable for larger scale.

To start, the team broadly scanned the field to find potential technologies. While many scale-up techniques were codified, there were certain phases the team needed to move through and adjust according to the individual project. “Projects are unique, but we use the same type of processes with each project. There are some standard steps, but that depends on how difficult to purify...” said Schou. When the team started on the Liraglutide project, “we were not sure what this molecule was about so we had to try things- particularly for purification, not so much for fermentation.” Schou believed that an inherent part of this process included:

Always trying things that don’t work- processes that we are not sure about are tested because they’ve worked for other products... When something doesn’t work, it is not a failure. In over 23 years [working with Novo Nordisk], there may be setbacks but I’ve never had a project that couldn’t come through... there are steps along the way that are necessary to get to the end.

In scaling Liraglutide, many product characteristics were unknown, so the team had to try new things: “the fact that you cannot predict everything is part of the business,” said Schou.

The CMC team had facilities and equipment that allowed for frequent trials, inexpensive experiments, and lab scale prototypes; the main cost was people’s time, a significant cost if you had too few people working on the project. Once the team found an indication that a particular process or technique could work, they continued until they discovered a sufficient number of confirmations or found a disconfirmation. Although there were not many techniques available, Novo Nordisk tended to use a broader portfolio of techniques to support protein manufacture than most companies. With Liraglutide, the team ultimately borrowed, and successfully used a new technique that originally was invented for recombinant insulin. Still, at the end of phase I, the molecule lacked stability and additions had to be made to the purification process. According to Schou, this was a minimal setback, compared to the consequences of creating an unsafe product.

7.5.2 Working in Parallel and with Other Teams

Manufacturing the Liraglutide API involved the following techniques/stages:

Fermentation → Purification → Formulation

As this project was not sequentially developed, teams were not waiting for fermentation to finish before working on other steps; this structure was referred to as “para development”. Biochemists worked on purification methods while fermentation was developed, ensuring a quality API product that would not jeopardize human lives. This type of strategy required fermentation and purification teams to work closely together and communicate because “something may change in fermentation that affects purification; if you raise the temperature by just 1 degree Celcius, you may get new impurities...” (Schou).

As API Development Manager, Schou had responsibilities on two levels: with his own project team and in coordinating activities with managers in other areas of the project. On his team, Schou delegated tasks amongst team members and kept to timelines with the help of Microsoft Project. At API development meetings, team members often provided status reports and asked for input, confirmation, and invited other members to add relevant information to the discussion. Although people worked on specialized tasks, and Schou believed that “once you’ve been working on something for some time- you know the most.” It was important to have a space to provide input on what other people were doing, because “you cannot develop one process and say that is it, you must put it together with other pieces.”

Schou participated in cross-functional project meetings designed to allow knowledge sharing between different teams, but especially the analysis team and the drug product team. For example, market information does not always enter the picture at an API level, but factors into the drug product level. However, the API team needed this market information because it could affect the priorities regarding specifications and safety. Often, Schou resolved issues by revisiting Research. Schou also closely collaborated with pilot plants and had a production coordinator on his team who worked within Novo’s product supply unit. This product supply

representative was assigned to the project a few years before production began and determined what to design for production, based on projected market needs. In the case of Liraglutide, this was particularly challenging because it was a new product and differed from familiar insulin needs.

Working with the clinical trials aspect of the organization was particularly challenging for Schou because often:

Clinical trials are planned and they don't ask when they can have product, so sometimes they're looking for a product when it isn't available... Sometimes people assume when we can deliver product. We will not sacrifice quality because safety of humans is in the balance. They don't ask how much time do you need, they say you have this time and product must be ready.

The return of clinical data influenced the CMC process, because the entire process was locked after phase II clinical data was returned, even though "we usually are not completely where we would like to be with the manufacturing process... not so much quality but cost of production- in some cases can offset with price... but [we] have to lock the process at this stage, even though we could find something better five or six years later..." Often the guiding question for Schou in these situations asked "Would I like to treat my child with this product?" He explained that if you can honestly answer yes, that the quality was so good you'd give it to your own child, then it was okay to move forward. While Novo cannot allow anything on the market that was not safe, it still created challenging timelines. Timelines, deadlines and project plans fulfilled an important function, in that

Project plans help you to know when you're done... you will never finish if you just keep improving and eventually products must get on the market or we'll go out of business. So many phases must fit together- so consider quality of product for purposes- so you know when you're done. You must also be cost-effective. You must reach set quality criteria and move to the next stage. (Schou)

7.5.3 Team Management

Schou admitted that to be involved in the coordination of all the activities between teams and to get all the pieces to work together was a challenge, but satisfying when it succeeded. The team

environment was critical because it allowed team members to learn from things that do and do not work. The ideal was to have a team that works closely together at all times, and Schou preferred his team to only include people working on one project, as opposed to people spreading themselves between several projects. People leaving the project could pose difficulties for a team, depending on what phase a project was in, because it takes time to bring people up to speed; however, it sometimes happened that a replacement was better than the original team member. The team leader facilitated situations where disagreements arise, and while Schou admitted that generally teams work out disagreements and reach a consensus, sometimes the team leader needed to make a decision primarily based on resources.

Although he was a biochemist by training, Schou's current roles at Novo Nordisk were mostly administrative. Early in his career, he spent most of his time doing organic chemistry and synthesis. In the 1970s, Schou's focus shifted to purification where he helped develop reverse phase purification- a technique still used today, and one of a number of methods Schou invented during the course of his career. As an administrator, as opposed to a scientist, Schou did not think about publications "too much," especially since it was 10 years after insulin development that Novo Nordisk allowed Schou to talk about his role in this project. The other factor with publications was that many departments did not allow the time necessary to produce papers. Documents that were crucial to the development process include lab notebooks, project notes and project reports. Other Novo employees could easily retrieve filed project reports when necessary. While Novo Nordisk was a relatively big company, Schou thought that "we know each other well enough to share knowledge. We can go to people and ask for information on other projects and get project reports."

Schou described the pressure on his current job as "sometimes inspiring...sometimes we have to work very dynamically; sometimes we must make [the] amount of materials stretch." As a manager, he worried about burn out amongst his team members; although it was hard to know

who was burning out due to large numbers of people on a project, but if he heard about a sub team working too hard (and this happens) he intervened to make adjustments.

7.6 Managing the Liraglutide project: Strategy, competition and resources

By the time Liraglutide entered phase IIIa, large clinical trials in humans, it had spent four years in mid-stage development, as opposed to the usual two years; Novo had identified the lead candidate seven years earlier and the product was still not on the market. Further, Eli Lilly beat Novo to market with its GLP-1 product, exenatide, even though Novo “bought its way into patent rights,” and therefore received early access to information and two major research groups in the field. Novo essentially got a 6-12 month head start on other firms before the research on GLP-1 was published. Kristian Tage Hansen⁷⁶ admitted, “We did not move Lira as aggressively as we could have.” Throughout the course of the interviews, managers offered their perspectives on the broader company context that led the project to move more slowly than the managers would have desired.

7.6.1 Competition: Eli Lilly

Eli Lilly partnered with Amilyn Pharmaceuticals following the failure of their internal GLP-1 program. In June 2005, Eli Lilly and Amilyn Pharmaceuticals beat Novo to market with their GLP-1 product, exenatide. Exenatide, a twice-daily injection therapy was the first GLP-1 approved for type 2 diabetes. Although they would not be first to market, Novo felt that they had the better and more competitive product: 24 hour glucose control provided the maximum prevention of late stage diabetes complications, while exenatide was a short-acting drug targeting the insulin spikes that occur in between meals. However, Eli Lilly was already hard at work creating an extended release version of exenatide that could sail through regulatory, as it would not be a brand new product application.

⁷⁶ Kristian Tage Hansen was the Project Vice President from 2001-2004 and held a Ph.D. in Biochemistry.

This was not the first time Lilly had beaten Novo to market; Lilly launched the first insulin analogue before Novo got its competitor product, Novolog[®], on the market. According to Kristian Tage Hansen, if there were benefits to not making it to market first with GLP-1, it was that exenatide “gets a foot in the door”; Eli Lilly had spent the time and money to “hype” the market for this new class of drug. When Liraglutide makes it to market, the battle would be driven by marketing and in trying to capture the exenatide patients with Novo’s once per day product. Susanne Rugh, however, saw another defeat to Eli Lilly as endemic of a larger problem within Novo Nordisk:

We have difficulties in believing in new concepts before someone else has shown that it works. We knew of Eli Lilly’s GLP-1 project from a very early time and we knew it wasn’t as good a compound as what we had. This helped in getting the Lira project somewhat prioritized, but took awhile to get *really* prioritized. The same thing happened with long-acting insulin. Aventis had for quite awhile been working on a long-acting analogue. Our scientists said it would never become a product because we had pursued a similar molecule [and it had not worked]. [Our long-acting program] Was fully resourced, but with a slim program. It wasn’t until Sanofi-Aventis filed [their long-acting analogue] that the fire under Novo was lit. We knew that they wouldn’t submit something non-approvable. And the same thing for the pulmonary insulin. When Eli Lilly filed [that sent a message] “okay, it looks like this is becoming a real thing” and at this point, we won’t be first to market, just like with the long acting analogue, which we could have been if we had put more resources into it at an early stage.

7.6.2 Strategy

The Liraglutide project forced a number of corporate strategy discussions within Novo Nordisk. In the early 1990s, when Novo identified GLP-1 as an opportunity to develop something new for type 2 diabetes, it established an entire research unit devoted to type 2 diabetes to work on GLP-1 and look for other type 2 opportunities. This reflected Novo’s attempts to change their strategy from a company who’s major business was insulin for type 1 diabetes. According to Knudsen,

More people were developing type 2 diabetes, which required oral drugs. We needed to look at something other than insulin for this growing population [of type 2 diabetics]. With type 2 diabetes, as the disease progresses, medication doses must keep increasing because type 2 patients become insulin resistant. Insulin does not work as it should in the tissues in type 2 diabetes.

Liraglutide and Levemir[®] were both competing for the type 2 injectable segment within the Novo portfolio at a time when company decided that “Novomix[®] was it.” The type 2 injectable segment would be built on Novomix[®], as the “business side” had difficulty contemplating that there was room for all of these different products in the portfolio, according to Rugh.

Although Novo was attempting to expand their diabetes products, the company still held the core belief that “We are still an insulin company and the best way of treating diabetes is through insulin. Insulin controls diabetes.” (Hansen) From a management perspective, not only could a product like GLP-1 cannibalize part of their core market, but their insulin business was under attack- Novo’s long-standing fight with Eli Lilly was going full blast. Management did not believe that they could pour money into GLP-1, a non-insulin product, when the company was struggling with their insulin line. Thus,

The Lira project did not have full management endorsement. Management had more short-term perspective. They kept saying that if you want to treat diabetes, insulin is the best. Insulin will control the disease and prevent late stage complications. Late stage complications are really the problem with diabetes. It takes years to build up complications and these occur in direct relation to glucose level control. (Hansen)

Management could not support a project that would eat away at part of the core insulin market. Despite having “project champions all over the place,” Liraglutide became a “sort of ugly duckling.” (Hansen) The project champions continued despite lacking full management back-up. After the first clinical data came back, management lost a little confidence in the project, and began distrusting the “wild-eyed” syndrome that seemed to pervade the project.

It was very clear that many people we got on the project were a higher fraction of the wild cards in the organization than you would usually want to see [on a project]. One of the reasons [for this] was because we talked people into working on this in overtime, so we had to talk people into this who believed in this project. The ones who jumped onto this wagon tended to be those on the more wild side, who liked the project because it was different. They inspire both admiration and wariness, particularly from management perspective... ‘those guys are weird to begin with’. (Rugh)

Furthermore, the indication that Liraglutide could decrease weight, in a disease characterized by obesity was rejected by management as a “totally wild idea.” Rugh explained that, at the time, “the business thinking around obesity was not mature,” so we were unable to investigate this

indication. Recently, management decided to try to add obesity as an indication, reflecting that Liraglutide has been accepted as “a mechanism with very big business potential.” (Rugh)

7.6.3 Resources

As mentioned earlier, Liraglutide had partially resourced project status. The project was asking for competences and resources that insulin needed. Hansen explained, “Management heard what they said but simply had to prioritize insulin.” The project had problems gaining access to people and facilities. There was a constant fight for resources and it struggled to make it to the first human dose.

Part of the battle for resources was against other enthusiastic project teams promoting their products. Rugh remembered that an OAD was competing with Liraglutide for resources and the OAD won the resources to achieve fully resourced status, but died in Phase III because of a lack of market insight capabilities. Although it was not surprising that the OAD won the resources, it was a project belonging to a market that had been proven, “this class of product is known and potential is known” (Rugh). It was doubly difficult to get upper management marketing interested in a product that relied on a new mechanism, particularly in light of the fact that nothing was going to be allowed to stand in the way or compete with Novomix[®].

This was not an insulin project. GLP-1 was a totally new mechanism. At the time, the company did not focus on type II diabetics. We knew very little about the market. We also knew that we were competing with our own products with GLP-1. On the clinical side, resources were the same whether you’re going for a growth hormone trial or OAD. On CMC side, you need different skills for different products and the biotech part of the pipeline was extremely full at the time. So, we got fractions of people. (Rugh)

Given the resource situation, Rugh was amused during one particular portfolio resource meeting when it was discovered that the Liraglutide project had the most CMC resources of any partially resourced project. Further, management had not formally granted many of these resources. The project gained these extra resources through employees who happily worked overtime in order to move this project forward. “Everyone found this exciting, and while they could not refrain from their priorities [designated by management], many people worked long

hours in order to make room for doing activities on this project.” The one resource the project could not attain was access to pilot plants. More team members were needed to staff the pilot plants and because top management decided this was a partially resourced project, pilot plants would not be granted. Management wanted to see more clinical data before granting the resources to solve production issues at the pilot plant level.

From the interviews it was clear that Liraglutide project managers spent a substantial amount of time thinking and worrying about resources. However, the level of resource availability in the early years of the Liraglutide project dramatically contrasted with the present day situation:

In the early years of Liraglutide there was the frustration that we were lacking resources. We lost substantial time because we didn't have resources to reach goals. We didn't have enough people or the right kind of people. But today, Lira is in a situation where it can have a free pick. But, you cannot guarantee success in the early project. Top management must focus on things that are closest to success. At a certain point in time, the rest of the projects have to share what is available. But this can be extremely frustrating. (Knudsen)

Knudsen further elaborated on how she thought about resources as a manager on the Liraglutide project:

If cost is translated to resources then we spend lots of time thinking about resources. We are not limited in the amount of money we can spend at reasonable level. External collaborations make cost an issue. But day-to-day we are not guided by cost... Resources are people, and people's time. That is what decides if you can reach goals. I am constantly strategizing about how best to use people's time.

Rugh firmly believed, “If Lira had been fully resourced from the beginning, it could be on the market now. Nine out of ten never make it, so [you have to go with your] gut-feeling because you are operating on very incomplete info.” In spite of trying to present as much data as possible to get the message to management that Liraglutide was a promising new product, Rugh and other managers still could not convince top management. “My biggest career failure is not being able to convince management that Liraglutide should become fully resourced. It should be on the market by now.” (Rugh)

7.6.4 The Inherent Challenge of Drug Development

Hansen explained that the reality of Novo Nordisk's business was that the biotechnology space was very unpredictable and biotechnology molecules were difficult to work with, as they required mastering a huge amount of detail. The Liraglutide project was no exception to these biotechnology factors. According to Hansen, the Liraglutide project team was very strong and extremely persistent with a huge amount of stamina. Despite a lack of access to resources, team members maintained an emotional commitment to the project.

A few heavyweight champions saved the project. I think it came down to three people. The project manager⁷⁷, Mette, and Lotte; Lotte promotes [the project] on every occasion she possibly could; these three people made a huge difference- if they had bailed or gotten too frustrated it would not have survived. (Hansen)

Knudsen believed that much of the project's success depended upon the project manager being a strong character because this was the person who had to fight for resources (against other projects) in the early days. The project manager was the one who must say to management "this idea has a good chance, but I need these resources" (Knudsen). The project manager needed to be a strong character because he or she was often the ultimate arbiter in deciding which ideas a project pursued:

The team presents different ideas and project manager can decide which way to go. We have to push on one idea, or if it makes sense, multiple ideas, or we won't be able to reach promised goals... If you can't decide on an idea to pursue, you can take it to the next level, called project challenge. This is a group of managers who challenge the project. You present your problem to ten experienced people who work in different units/projects and they can usually give you direction on how to solve a problem. (Knudsen)

It was also the project manager's responsibility to facilitate the team in suggesting goals every six months, and ensuring that the team delivered on goals that are ambitious and aggressive. If the team could not deliver on the set goals, new ones were set.

The Liraglutide project highlighted a set of broader challenges Novo Nordisk faced on a daily basis: to continue to innovate within the pipeline; to innovate quickly enough and save time

⁷⁷ The overall project manager for the Liraglutide project changed on several occasions throughout the course of the project.

wherever possible; to be mindful that because a product's lifetime is finite, the company must continue innovating to find something better. The reality was that drugs survived fewer years because of the intense industry competition. Novo, however, was at an advantage because "we haven't been bought out and had to spend resources trying to merge like many companies who probably missed out on lots of years and new products by merging." (Knudsen) The pressure was on to "be innovative enough to find something better. You cannot come out with something equally good. Must continuously innovate new concepts. And do it fast enough." (Knudsen)

Novo managers believed that given their size and number of genuine new products, the firm had a decent track record with innovation. Knudsen attributed this to the size of the research organization: "We're not so huge that you don't know everyone. You only have to go one step to get to the person that you need to talk to and this is an advantage." Both Rugh and Knudsen would have liked to see Novo improve the development of innovative products; while they thought that the number of innovative products was satisfactory, they were not good at developing fast enough. Although, they believed that Novo was not the only company with that problem.

It is fashionable to say 'we don't have enough new products.' I hear that often at Novo. Failure is not in the ideas, but in developing the ideas. There is a fight between research and marketing. Marketing wants to buy projects and I think, why on earth do you want to buy something when we have so much we cannot develop it fast enough? The problem is not a lack of ideas, but a lack of control of how to develop and focus. I hear 'we don't have enough ideas' from marketing and management teams. 'What do you want more ideas for? Develop the ones that you have!' (Knudsen)

Idea development was part of the problem with the Liraglutide project and, in the end, a few years separated them and Eli Lilly on GLP-1 products. Rugh did not want to see the company forgo any future opportunities in a manner similar to what happened with Liraglutide.

7.7 Summary

Novo Nordisk's drug development process was more striking than Pfizer or Novartis' process because of its iterative and innovative nature. Because each molecule was unique, Novo Nordisk had constructed an iterative approach to developing drugs; processes had to adjust to accommodate each molecule, if necessary, while remaining focused on comparability and reliability, particularly in the CMC area. The firm's approach to problem solving and failure added to the sense that drug development at Novo was iterative; although collaboration, at times remained a challenge, better incorporation of expertise from discovery, development and CMC made the overall drug development and scaling production processes more smooth. While the Novo Nordisk case was notable for the tension between project teams and management, the Danish commitment to teamwork and team problem solving prevailed throughout the Liraglutide project.

Case analysis of all three case descriptions begins in the following chapter (8).

Figure 7.1 Iteration cycle for Liraglutide

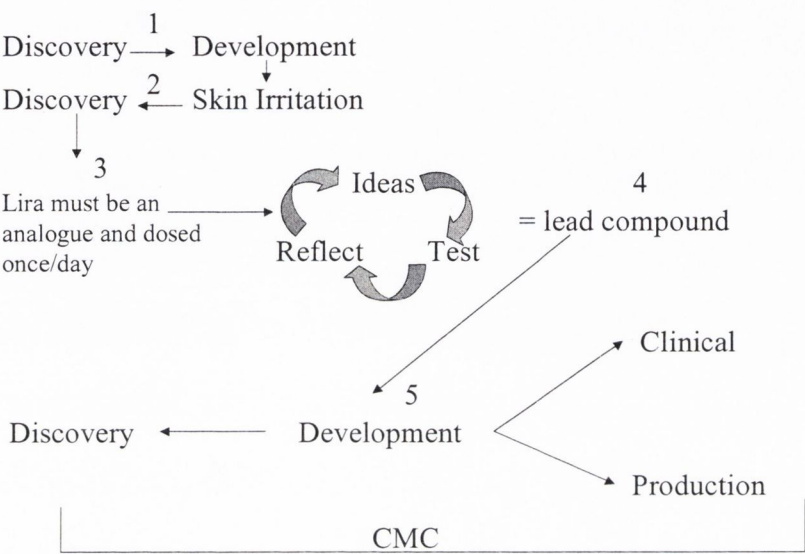
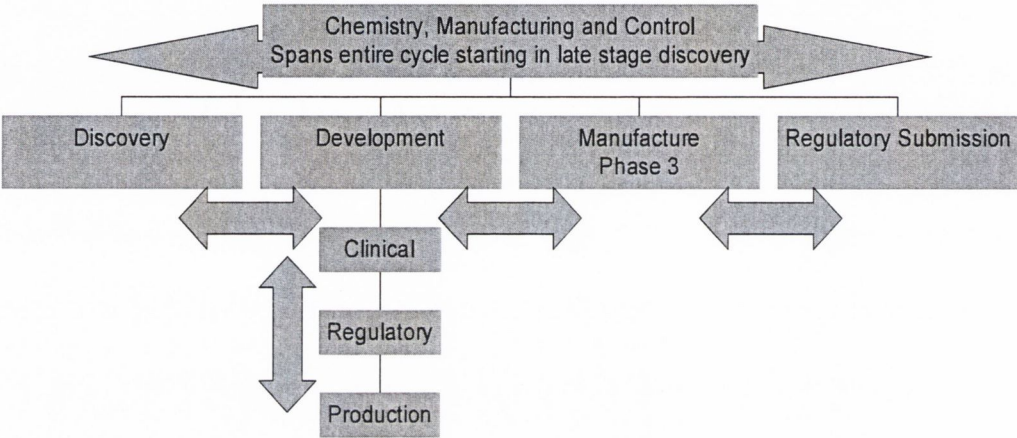


Figure 7.2 Novo Nordisk drug development units



Chapter 8: Case Analysis

It is worth contextualizing the three case study firms in terms of each other and the industry. Pfizer was selected for this research to represent “big pharma”. Pfizer dramatically increased its size through a series of mergers the firm engaged in over a 10-year time span⁷⁸. The Pfizer case description illustrated that in order to manage Pfizer’s rapid expansion, the firm was forced to carve itself into distinct organizational units, the result of which was a number of globally distinct units that all played some part in Pfizer’s product lifecycle. This essentially created an organization in which size and global orientation increased the level of complexity within the firm. While the firm believed in the power of their giant, vertically integrated organization and the Pfizer 2005 Annual Report identified the company’s size and global reach as major strengths, by the time of the 2006 annual report, opinion had changed and Pfizer had new leadership. As a result, Pfizer was embarking on a process of creating smaller, more agile and accountable business units. In particular, it was streamlining its R&D organization into four major campuses, consolidating their research programs by changing its focus to nine therapeutic areas and co-locating all scientists within a given disease area in one location (Pfizer 2006).

In contrast to Pfizer, Novartis actively was continuing to expand. Most notably, in 2005, Novartis extended its capabilities with the \$8.3 billion purchase of Hexal, a German generics firm, and its sister company in America (Eon labs). At the time, this created the world leader in generic medicines with annual global sales of over \$5 billion and a pipeline that contained virtually all drugs due to lose patent protection between now and 2009 (Griggs 2005). In 2006, Novartis bought the remaining stake in biopharmaceutical company Chiron, which would form the basis for a new vaccines business. NIBR had also added two new Research centers to their portfolio: the Novartis Institute for Tropical Diseases in Singapore (opened 2004) and NIBR Shanghai (opened 2006). Counter to both Novartis and Pfizer, Novo Nordisk was maintaining the status quo. Novo Nordisk had avoided M&A activities, and consequently, changing its organizational structure. Knudsen believed this was to Novo Nordisk’s advantage: “...[we

⁷⁸ Two of the larger and more notable mergers included Warner-Lambert in 2000 and Pharmacia in 2003.

haven't] had to spend resources trying to merge like many companies who probably missed out on lots of years and new products by merging.”

In looking at the three case studies, they illuminate how R&D works in new product development in the branded ethical pharmaceutical sector as well as how SCM functions in terms of new product processes to get a drug to the launch stage. At the same time, the case studies offer a description of the daily realities of operating in this industry. Intense engagement with the case study data allowed insights to inductively emerge from the research. This chapter discusses the practical and theoretical R&D and SCM insights that emerged, highlighting the main insight in the title of each section.

8.1 *The branded ethical pharmaceutical sector maintains a strong focus on upstream activities, namely R&D.*

In exploring upstream and downstream pharma activities, what emerges is a picture that is highly drug development (or upstream) focused (Jassawlla and Sashittal 2000; Becker and Lillemark 2006): the industry's firms justify this narrow focus because, quite simply, achieving any measure of success in this industry is completely dependent on the product that results from the drug development process. Without successful R&D, a firm will lack products to fill its pipeline. In considering why pharma has continued to accord R&D the most significant place within the organization, it became apparent that two critical pieces contributed to the sustained R&D focus: a firm's portfolio choices as well as the industry's dependence on scientific progress.

8.1.1 Portfolio choices impact R&D

The case studies showed that each firm strategically chose which disease areas to include in their portfolio. Larger firms, such as Novartis and Pfizer, concentrated on a larger number of therapeutic areas (10 and 11, respectively), while Novo Nordisk, a smaller firm, exclusively

focused on four closely related product areas⁷⁹. Generally, big pharma firms targeted disease areas with a potential and substantial market for new therapies; this market was largely dictated by the global health of the population (Diller 2006).

Perhaps Pfizer was the most archetypal firm and synced with overall industry trends. In the 1990s, when heart disease, hypertension and antidepressants were the focus of many industry firms, Pfizer was making millions on blockbuster drugs such as Norvasc (for heart disease and hypertension), Lipitor (for high cholesterol) and Zoloft (for depression). Like other industry firms, Pfizer recognized that successful cardiovascular drugs would essentially guarantee a consistent, lucrative business because in many cases, patients often remain on the medication for life, thus creating a steady and long term market (Saftlas and Diller 2006). Partially as a result of narrowly pursuing this model, Pfizer suffered a substantial setback in late 2006 when the company decided to stop working on their high-profile new cholesterol drug, torcetrapib, in Phase III development. At the time, Pfizer had shifted its therapeutic areas to align with an industry wide focus on central nervous system, diabetes and oncology drugs, and was in the process of launching new drugs that had received FDA approval, including Sutent (oncology), Lyrica (epilepsy) and Exubera (diabetes).

Novartis attained big pharma status by pursuing a markedly different strategy from Pfizer and other big industry players. In spite of criticism for not producing lifestyle or blockbuster drugs in the late 1990s, when these drugs were popular in the industry and with Wall Street, Novartis shunned these preferences, insisting that it was not a lifestyle drug company, but a life-saving drug company. Instead, NIBR pursued opportunities in where biological mechanisms were understood and where discoveries would meet a high, unmet medical need. While many industry players avoided orphan or rare diseases because of a low return on investment, NIBR prioritized new projects in this area, creating an organization driven by medical need and scientific rationale, not numbers or market size. For example, Novartis planned to file regulatory applications for new

⁷⁹ Diabetes, growth hormone therapy, hormone replacement therapy and haemostasis management.

therapies in rare disease areas such as Multiple Sclerosis, Cystic Fibrosis and Muckle Wells syndrome between 2007 and 2010. In some areas, pursuing rare disease therapies was a success for Novartis: Management invested in Gleevec, a drug project that was not guaranteed commercial success due to the small chronic myeloid leukemia patient population; when management decided to accelerate this project, they had no idea that Gleevec would become a “fairy tale” success story (Vasella and Slater 2003).

Novo Nordisk’s portfolio was much smaller and more narrowly focused than either Pfizer or Novartis. The company’s tag-line was “a focused healthcare company and world leader in diabetes care;” annual reports from 2004 and 2005 read more like a diabetes newsletter than as a report on a pharmaceutical firm. At a time when most industry firms maintained activities within multiple disease areas, Novo Nordisk’s development portfolio remained highly, and almost singularly, diabetes focused, irrespective of opportunities created by the changing industry environment and health of the world population. Because Novo Nordisk was created through the merger of two Danish companies which had been the #2 and #3 worldwide insulin suppliers since the 1920s, Novo Nordisk’s concentration in diabetes pre-existed the current industry environment which viewed diabetes as a popular and high-growth therapeutic area. Historically, there were only three competing companies in the global insulin market⁸⁰ but with the shifting global healthcare demands, big pharma firms were increasingly adding diabetes to their therapeutic area portfolios (Saftlas and Diller 2006). Novo Nordisk’s challenge was not to add a brand new disease area to its portfolio, but to decide how to manage and expand their current portfolio given the growing number of diabetics⁸¹ as well as potential market opportunities⁸². The Liraglutide case, however, demonstrated that Novo Nordisk was struggling with balancing an expansion into

⁸⁰ Eli Lilly, Novo Nordisk were the dominant players, and Sanofi-Aventis had made inroads with its long-acting insulin, Lantus.

⁸¹ In 2003, the International Diabetes Foundation estimated that the worldwide number of diabetics was 194 million and expected to rise to almost 333 million by the year 2025.

⁸² The market for diabetic therapies was expected to grow because of demographic changes, increasing life expectancy, earlier onset of type 2 diabetes, higher rates of obesity and sedentary lifestyles.

type 2 diabetes therapies with the potential cannibalization of the current portfolio, which believed insulin was *the* best way to treat diabetes.

This identified a debate that occurs in firms industry-wide: how many disease areas should one firm have? The answer to that question was constantly in flux and depended upon a firm's profitability and pipeline, as well as the perceived market opportunities determined by the health of the world population. Adding or subtracting disease areas from a firm's therapeutic portfolio had implications for both upstream and downstream activities, particularly with respect to knowledge available to the firm, as well as supply chain configuration at the strategic and design levels (Connolly, Sullivan et al. 2005).

8.1.2 Scientific progress reinforces an R&D focus

The three cases highlighted that drug discovery was inherently undefined, unpredictable and unreliable (Pisano 2006). This was intrinsically linked to the ever-expanding scientific universe: The understanding of the human body, disease mechanisms, and the science of creating drugs remained incomplete- it was a work in progress. The human genome project was a prime example of this. It was intended to advance the understanding of the sequences of the human genome, which directly related to understanding the causes of disease. Therefore, the pharmaceutical industry eagerly invested substantial time and money hoping that advancing knowledge in genetics would have a direct and positive impact on discovering new therapies. Dr. Fishman (at NIBR) believed that because many diseases were caused by genetic defects, identifying the function of the 24,000 human genes in the specific context of the cell, tissue and disease would make a significant impact on drug development. Thus, even though the entire genome was mapped, more progress in this area would be needed to advance drug discovery and development⁸³.

⁸³ Progress would include defining the function of each sequence, all the variations of human genetics, all the genetic mechanisms of cancer, all the signatures of cellular response and how to modulate all genes.

Because their business was so tightly tied to science, at the most basic level, all three pharma companies collaborated with outside partners (in the form of biotech firms, other pharma firms, or universities) in an effort to keep on top of the latest scientific knowledge, research, discoveries and advances (Powell 1998; DeLong and Fahey 2000; Quere 2003; Arnst, Barrett et al. 2004). For example, Novartis reported over 120 collaborations with biotech companies and over 280 collaborations with academic centers. Novo Nordisk allocated 20% of its research budget to external activities. Recent figures on Pfizer's strategic alliances were not available, however, the company had constructed over 1,790 alliances between 1988 and 2002.

In terms of outside alliances, partnerships with academic institutions were particularly important to the industry (Quere 2003). Novartis valued academics and implemented an academic approach to their Research program, primarily because management believed that it was one of the best ways to stay up to date on rapidly and ever changing scientific information. Both NIBR and Novo Nordisk highlighted the fact that academia was often closer to cutting edge research with a higher degree of freedom and access to both hospitals and patients. These academic institutions circumvented the regulations that applied to the commercial environment. As such, commercial research proceeded more slowly than research done within a hospital setting. However, the academic and hospital settings could not fund the volume or scope of research that would be possible with the capital that was available to pharma companies. Many industry leaders believed it was more manageable for academics to advance basic science and improve the discovery process as opposed to developing discoveries for commercialization. A good example of the trade-offs which occurred between the academic and industry environments was Liraglutide. This molecule was discovered in an academic and hospital setting, as Massachusetts General Hospital was linked to Harvard Medical Schools, but the molecule ultimately was sold to Novo Nordisk for development and commercialization.

Perhaps the new drug discovery and development strategy that Dr. Mark Fishman implemented at Novartis best exemplified how scientific progress must feed the industry's

activities. Fishman realized that drug discovery needed new rules, novel capabilities, fresh competencies and a re-designed infrastructure aimed at unconstraining science in their labs, so that scientists were limited only in terms of their own imaginations and the boundaries of biology. Fishman believed that re-designing NIBR's process with tighter links to scientific advances and knowledge would improve economic opportunities. At the root of this re-design was a paradigm shift towards understanding basic science as a critical bridge to producing new drugs. Basic biology, as well as pathway biology, genetics and chemistry would lead to an understanding of the mechanisms of disease, which could be targeted in drug discovery. Without understanding the mechanisms behind disease and exactly what caused disease, it was more difficult to create a drug. If the molecular details of disease were defined, then NIBR scientists would be well positioned to create a drug targeting the underlying causes of disease.

Novartis made major changes in how it leveraged chemistry, physician-scientists and clinical trials in order to capitalize on using science to drive their process. Chemists were critical for improving early decision-making capabilities. By developing quality control steps to address the link between unsuccessful toxicity studies and high rates of unexpected attrition, they improved the overall quality of candidate compounds, identified highly toxic compounds at an earlier stage, and allowed failures to shift to a less costly development stage. Novartis also tapped into the scientific expertise of the Translational Medicine Group, comprised of physician-scientists, to bridge a gap that NIBR perceived between biology and clinical trials. The physician-scientists understood disease and clinical medicine, thus providing better matches between drug targets and disease indications and facilitating the transition from bench and animal studies to human trials. Novartis made major changes to their clinical trial design to reflect scientific progress in this area and to also facilitate early decision making that would either advance or scrap projects to save money and time. Grounded in scientific rationale, Proof-of-Concept studies were a key component of Novartis' new clinical trial design, which combined phases I and IIA to determine if the concept behind the drug translated to the clinical setting. Further, these trials used patients

with rare or neglected diseases, instead of healthy volunteers to expedite the treatment of such diseases and allow for the extrapolation of results to a wider population. Sometimes in more common syndromes, patients would suffer the same symptoms, but the underlying cause would vary; this confusion could be avoided with Proof-of-Concept trials initially designed for patients with rare diseases. Fishman believed that projects focused on diseases that were epidemiologically small and well defined, increased their scientific tractability. Conversely, diseases with large patient populations were epidemiologically large, more complex and therefore scientifically not tractable (Fishman November 17, 2006).

Part of the struggle with Novo Nordisk's Liraglutide was rooted in the fact that the team was creating a new drug in a new therapeutic class. Because the project was unlike any other compounds in their portfolio, the level of uncertainty was relatively high. Further, without an extensive and established scientific understanding of GLP-1 and an evolving understanding of type-2 diabetes, the team was operating on incomplete information, yet trying to match a product profile defined by Novo Nordisk's marketing team. Only through clinical studies could the team gather more complete information regarding the drug's side effect profile and the best way to administer the drug. In Liraglutide's case, the team never could have predicted, from the body of scientific knowledge available to them, that a positive side effect would include the drug's effect on weight loss. Since the medical community linked obesity to type-2 diabetes, this was a significant side effect that could positively differentiate Novo's type-2 drug from that of competitors.

The industry operates within, and is dependent upon, a scientific universe that is not completely defined, but critically impacts R&D; the body of knowledge and definition of this universe expands and changes constantly (Pisano 2006). This contributes to an environment in which nothing is ever the same. In discovering and developing drugs, scientists try to logically understand the molecules within the current, knowable scientific universe, but both the Liraglutide and Gleevec cases referenced trusting that "gut-feeling." With Gleevec, following an

instinct, which was backed by some convincing science, led to a stunning success story (Vasella and Slater 2003). On the other hand, at Novo Nordisk, management demanded extensive, convincing clinical data that demonstrated promising results; management refused to take a chance on incomplete, but promising information.

Within this uncertain environment, all three firms were striving to improve development timelines and deliver new medicines into clinical trials as quickly as possible. Firms aimed to reduce time from clinic to market and were hoping that continued innovation and collaboration across all areas of the firm, along with sourcing the best technologies and early stage compounds, would shave even more time off the drug development process. Organizations were focusing on creating new development paradigms after deciding that traditional development stages were no longer sustainable and left projects vulnerable to late-stage attrition.

8.2 The priorities for the pharma supply chain are not to attain operational efficiencies, but rather strategic or design-level efficiencies.

The development of an evaluative SCM framework (see Figure 3.1), contributes to the SCM literature by helping to define the nature and function of supply chains in this developing discipline (Burgess, Singh et al. 2006; Cousins, Lawson et al. 2006; Harland, Lamming et al. 2006; Storey, Emberson et al. 2006; Vachon and Klassen 2006). The case study firms' supported advancing the development of the strategic and design level of SCM (Beamon 1998). The case research suggests that pharma is counting on strategic and design level changes, more than strictly operational ones, grounded in effective management of knowledge and supply chains, to result in reduced levels of uncertainty, decreased cycle times, lower cost, improved quality and better management of complexity.

The SCM literature proposes that firms will benefit from considering supply chain issues at a very early stage of the design, so that all parties are aware of requirements and constraints, and how decisions made upstream can impact management and design of the supply chain (Haque

2003). The case research illustrates that in an industry like pharma, where making operational-level SCM improvements is markedly constrained by regulatory approvals and the need to guarantee product safety, case study firms instead focus on improving strategic or design-level efficiencies.

To better achieve the strategic objectives of their organization, firms have re-designed up and downstream processes; a primary example is the re-design of the R&D process so that it is more reliable and can predictably feed the downstream functions. Additionally, firms have tried to coordinate R&D and SCM as soon as possible to predict product evolution in order to facilitate the regulatory process. The emphasis on strategic/design versus operational levels directly related to the fact that operations were dependent upon drug development; it becomes difficult for firms to excel operationally in an environment where products do not conform, but instead each project that entered the pipeline was unique.

8.2.1 Operational-level SCM Issues

Pfizer's supply chain team made it most apparent that the industry was acutely aware of operational pressures; Kieran Ruddy, a former electronics engineer in the computer industry, said unequivocally and without hesitation that pharmaceuticals was "catching up" to supply chains in other industries and it would take at least a couple of years to catch up to other industries. Pfizer's team strived to get a product to the right place at the right time and determine commercial efficiencies to help maintain low cost, thus delivering more value to their customers. Customers significantly impacted the supply chain, because it was critical to maintain an adequate supply of medication to customers; therefore, Pfizer used at least two suppliers for every outsourced component. Eliminating waste, particularly in terms of inventory, was an issue on which the three case firms disagreed. Pfizer, for example, did not mind holding higher levels of inventory because given the extensive number of quality tests performed on supplies, the firm preferred having an abundance to avoid stock outs and delays because it could ultimately

adversely affect patient health. Novartis, on the other hand, viewed improving inventory and coming more in line with JIT principles as an attainable goal.

All three firms referenced finding ways to maximize capacity or improve yields. In the wake of mergers, both Novartis and Pfizer underwent a process of rationalizing and refocusing their plant network for the sake of improved efficiency and synergy. Novartis' plants were specialized Centers of Excellence, while Pfizer's network of plants could either be characterized by whether they were drug substance or drug production plants. This was an industry in which plant processes could not be changed around or re-designed on a whim because changes could adversely affect the product or patient, and regulatory approval was needed for most changes. Thus, for the most part, plant types limited firms; if drugs could not be manufactured within a pre-existing plant, it was likely that the solution was to build a new plant. It was for this reason that a product supply representative was assigned a few years before production was scheduled to begin; this representative was responsible for determining what must be designed for production.

Plants were primarily responsible for improving quality and cost. In this environment, quality and standards were important, but this was more as a direct result of regulations, GMP standards and the obligation to deliver a product that was safe for patients. Attaining the operational goal of finding and eradicating waste may be difficult in pharma because firms would rather spend the resources on ensuring patient safety than cut costs or processes that could result in (potentially fatal) mistakes later. One particularly critical efficiency that all firms seemed to be working on was scaling products from lab scale to pilot plants, and then ultimately to commercial facilities. For Pfizer and Novo Nordisk, pilot plants were important to keeping products from failing. However, the strategies these plants used to keep a product from ending up in the attrition column varied from project to project. Firms could not consistently apply the same operational solutions to save projects. Oftentimes, new solutions needed to be invented on the spot, or extrapolated from other successful projects. The basic mandate within the industry was that as a product progressed through regulatory phases and got closer to receiving approval for a

commercial product launch, the onus greatly shifted to pilot plant, supply chain, CMC and commercial manufacturing facilities to ensure manufacturability.

8.2.2 Design-level SCM: Balancing Strategy and Operating Reality

The design level of the supply chain framework was about balancing the firm strategies against the operating realities of the industry. Frontloading activities was a much more challenging proposition within this industry. Perhaps firms were attempting to apply their own version of frontloading by re-organizing R&D and moving processes to earlier phases of R&D. Designing processes so that some development steps were moved back into Research let firms consider, evaluate and qualify drugs at an earlier stage. This then helped to generate knowledge that allowed firms to decide about the long-term viability of the project more quickly, thus battling the high attrition rates. While these techniques may not guarantee minimal attrition rates, they could identify projects that were worth the investment and those that were not.

Because a molecule was determined and defined by the conclusion of the research phase, this caused a number of difficulties with pharma's ability to evolve multiple options, remain flexible, and create a one piece flow from product design to launch. Novo Nordisk worked towards evolving parallel development and running parallel processes where possible within the CMC phase. This required that all the organizational pieces fit together; as such, Novo Nordisk's process was highly iterative and allowed for molecules to return to earlier phases to resolve problems. Designing a process that was characterized by a one piece flow from product design to launch within pharma firms was similarly challenging because of the number of organizational silos, academic disciplines, and geographic locations which impeded flows. An example of this challenge included discovery teams needing to achieve the product specifications dictated by marketing. Firms realized, however, that creating more multi-directional flows would positively impact knowledge sharing and time savings.

Most firms developed commercial launch facilities that excelled at leading smooth product transitions, optimizing the manufacturing process, and solving potential problems before moving

the product to a permanent commercial manufacturing location. Thus, launch sites fulfilled a number of strategic functions, one of which included determining a long-term operating strategy for a product. This incorporated development and manufacturing in considering long-term operational goals when choosing to add drug delivery technologies or platforms to a firm's capabilities; ideally, the two units wanted to be able to envision a list of multiple future uses for a new platform to maximize the investment in this area; once-off solutions in this area were usually not cost-effective. Part of the design level at Pfizer included evaluating projects so that those with critical or high technology steps remained within experienced (U.S. or European) facilities; Pfizer only moved simple processes or intermediates to low cost locations. The operating reality included a strict regulatory environment, and therefore, to manage that, Pfizer aimed to keep the more complex products completely within its control and at original manufacturing sites.

8.2.3 Strategic-level SCM: Plan and Execute

The strategic level addressed the overall planning used by an organization to identify and reach its objectives and thus focused on the most fundamental aspects of a firm: who it is and what it does. As such, many SCM strategies adapted to the characteristics of each business (Cigolini, Cozzi et al. 2004). Overall, the strategic level of the supply chain was about planning and execution, which was inherently difficult in this industry. As previously mentioned, pharma did not have the luxury of evolving multiple drug options- they were lucky to get one target molecule that worked on one specific disease mechanism to move forward in the development cycle. While the long timelines involved in this industry would seem conducive to extensive planning, plans could fall apart very quickly if a drug fails within the development cycle. In such an environment, it was valuable for firms to recognize a failure as early as possible and divert resources into a more promising project.

The strategic level heavily relied on development to make decisions regarding investment or divestment in capacity when necessary. Development must also alert other organizational units to anticipated needs regarding processes and investments. Firms relied on standard processes,

technologies, and project management methodologies in order to advance and execute project plans. Novartis implemented the development in 1,000 days initiative as a way of reaching its objective of getting products to patients more quickly. This was one way from keeping projects from stalling and failing to be appropriately resourced. As demonstrated in the Liraglutide case, development preferred to avoid inefficiencies in moving the product forward.

Many of the strategies that kept a product moving towards commercial launch were located within the development, as opposed to SCM, organization. At Novo Nordisk, CMC was the most vigilant in controlling the process and molecule in such a way so that steady progress was achieved. This involved only allowing changes and improvements at particular release intervals, because a change in one part of the process impacted the entire process, supply chain and final product. In order for projects to move forward, processes must be locked at different phases. CMC's time to optimize processes and make improvements was limited; deadlines were designed to get the product to market and force the acceptance and adoption of a process that was reliable, but maybe not perfect, in time for phase III trials. Similarly, since proving comparability was an important part of meeting regulatory requirements, CMC never started their process with a compound that was 100% pure because then the bar was set too high, trials must be re-done, thus delaying project planning and execution.

The existing interdependency between product development and SCM was clear in the pharma example; however, product development remained more of a priority than operations or manufacturing concerns. If pharma could get the R&D side into a more reliable and replicable pattern, a consistent optimization of downstream activities would become possible. This would also require pharma to permanently move away from thinking in terms of individual functional processes and instead think about integrated chains of processes.

8.3 *Industry pressures and structure create SCM challenges.*

The industry was pressured to increase global expansion efforts in Asia, in order to lower costs for the industry's high-priced products, but the industry believed that moving to Asia could compromise the integrity of its supply chain (Shah 2004; Jarvis 2005; Kripalani 2005). Low-cost locations, while attractive for savings, made combating illegal copies difficult, and thus, many firms did not move more quickly into this area. Guaranteeing the safety and authenticity of their products for their patients was a higher priority than rapidly and aggressively moving into low-cost locations. Managing this risk tied to safety, as each firm was ultimately responsible for its marketed products, which meant that they must ensure the safety and quality of each product, even if they did not supply all the product components.

At Pfizer, the supply chain was ultimately a mechanism that allowed PGM to control the quality, safety and efficacy of each product. Essentially, Pfizer did not want to risk using a low cost location that could potentially compromise the integrity of a product. Control extended from controlling shipments to appropriate markets, to controlling materials for manufacture, to control of supply chain design. Supply chain groups had to be sure their activities, and in particular, regulatory issues, were coordinated with headquarters. Coordination and control within this system helped manage the complex process of safely producing drugs and its impact on SCM.

Furthermore, the breadth of experience and knowledge available within the organization made moving operations outside of Pfizer less appealing. Scaling up new products was a particularly complex process that involved dealing with the challenges arising from working with new materials, implementing new technologies, coordinating with multiple regulatory agencies and envisioning product evolution. Thirty years of experience and scale-up capabilities in new product introduction and development made Ireland a key location for Pfizer. It was difficult for the firm to imagine transferring these activities to another Pfizer location, never mind to a non-Pfizer organization.

Regulatory bodies also insisted that maintaining the integrity of the supply chain was ultimately the responsibility of each pharmaceutical firm, as was determining any new, innovative methods to secure the supply chain. This mandate increased pharma's hesitation to outsource or partner in manufacturing. It was easier for firms to focus on outsourcing or partnering in terms of R&D capabilities, because ultimately firms select the most promising potential drugs to develop further. Firms could then bring a potential drug in-house, and coordinate the remaining development activities and manufacturing with their own centers, remaining in complete control of the supply chain network design to accommodate the new product (Shah 2004).

The number of regulatory bodies that the industry was responsible to added more complexity to its process. Pfizer's Irish plants, for example, had to be certified by at least three regulatory bodies, the FDA, EMEA as well as the Irish Medicines Board. Drug product packaging involved such a high level of variation in terms of different markets, languages and regulatory bodies, that managing the leaflets, cartons and packaging literature involved configurations that resulted in "a thousand different SKUs." The regulatory environment also discouraged pharma firms from making product or process changes, because it was prohibitively expensive (Shah 2004). Pfizer explained that making such changes involved doing so sector by sector, seeking approval from each market. This aspect made it easy for processes to become stagnant; firms were unwilling to take the time and effort to update or modernize their manufacturing capabilities. Furthermore, because firms lacked the ability to predict a product's evolution, it was difficult to anticipate or envision future regulatory issues or obligations.

In light of regulatory requirements, the Liraglutide project worked to heighten awareness of regulatory requirements outside of CMC. In particular, Susanne Rugh's role within this the development phase of the project was highly focused on quality and meeting regulatory standards. To facilitate meeting regulatory obligations, Rugh devised a new, collaborative process that shared more responsibility for safety, quality and regulatory concerns between the discovery, development and CMC teams. Rugh believed that more communication,

documentation and anticipation of regulatory filings at earlier stages in the discovery and development process would save time and result in smoother regulatory applications. In spite of a culturally ingrained resistance amongst scientists who preferred focusing on molecule discoveries, Rugh instituted practices requiring increased levels of documentation by discovery. These practices were directly motivated by regulations and would better align lab and commercial scale processes to accelerate production of the first GMP batch. This improved flow of regulatory documentation would conserve time and resources, particularly when CMC attempted to make identical pre-clinical and first GMP batches.

Novartis also took a novel approach to regulations in the Gleevec case; this project reached the market in record-breaking time in part because of an unprecedented collaboration with the FDA (Vasella and Slater 2003). Part of the collaboration was facilitated by Gleevec's life-saving potential, which earned it a fast-track designation from the FDA, but Novartis also was responsive in complying with the FDA's request to change the drug's name as well as providing sufficient and thorough data in order to receive manufacturing process validation. Further, Novartis' supply chain team worked very closely with the FDA in order to make it possible to ship the product within one day of receiving FDA approval. This required an openness, willingness and determination on the part of both organizations for this drug to reach patients as quickly as possible.

Finally, as opposed to thinking about supply chains in terms of months, pharma had to think in terms of years, usually in terms of three to five year timelines and forecasts, which was highly unusual for supply chain planning. For pharma firms, capitalizing on patent life required three to five year planning, building long-term, reliable relationships with suppliers, and maintaining a stable supply chain without any breakdowns or interruptions in service. In terms of research and development, getting the most out of a patent meant developing products as quickly as possible, which included creating efficient hand-offs between different development stages, remaining vigilant about documentation, or improving processes. The industry's consistent and relentless

quest for time savings was directly linked to the constraints imposed by patent expiration timelines.

Jim Edwards at Novartis explained that in terms of supply chain planning, the development unit had the greatest impact on SCM- development must provide a successful drug before decisions regarding capacity investment could be made. Three to four years before filing an application with the FDA, firms began the process of selecting and qualifying a site within their network for manufacturing. If a brand new site needed to be built, the firm required even more time. Inventory levels and lead times were also unusually high compared to other industry supply chains, many of which were driven by lean and JIT principles. Pfizer supply chain managers justified their cycle times and excessive inventory because of quality analytical testing. Edwards at Novartis, on the other hand, believed that lead times could decrease by as much as 80% if product movement inefficiencies and waste were eliminated from planning and execution. Also unusual in terms of supply chain operations were long-term relationships with suppliers because of regulatory requirements and the prohibitive cost of changing supply chains once a product had gained regulatory approval.

8.4 *Piecemeal knowledge management strategies support firm activities.*

The value of knowledge will vary from industry to industry, but pharma is knowledge-intensive (Miles, Miles et al. 1998). R&D, traditionally an upstream activity, relies on knowledge to produce new products and services, and ultimately value (Grant and Baden-Fuller 1995; Grant 1996; Grant 1996; Grant 1999). The high levels of complexity in pharma require knowledge sharing between up and downstream functions, but the case research demonstrates that the industry has yet to master this (Ingelgard, Roth et al. 2002; Kalling 2003; Roth 2003).

Knowledge management strategies presented in the empirical evidence show that firms attempt, on a small scale as opposed to on an organization-wide scale, to bridge identified gaps, manage

interfaces, educate employees on the entire drug development process, and organize work through cross functional teams.

The complexity of the industry's products directly affected the challenges the firms had with managing knowledge within their organizations. Managing knowledge within these organizations was significant, as evinced by an NIBR manger's report that 70% of the company's activities had to do with generating information and data, and only 30% of activities were drug development related. Firms must contend with the knowledge associated with the number of disciplines and skills involved in creating a drug, as well as the unique nature of each project. While these organizations routinely codified explicit knowledge for regulatory filings, and remained intensely focused on capturing and recording their techniques and procedures for regulatory submission documents, they were challenged in capturing the tacit knowledge available within the organization. While all three case firms had similar knowledge management goals, they all lacked a coherent knowledge management strategy, opting instead for a variety of efforts to improve in this area.

8.4.1 KM Strategy 1: Leverage Accumulated Experience and Informal Networks

All of the pharma firms were very conscientious about avoiding re-inventing the wheel from project to project and a main strategy for preventing this relies on leveraging experience within the firm. Experience seemed particularly critical for ensuring that knowledge was recycled within the organization; experience made it possible for existing procedures and techniques to be tried and adjusted on a project-by-project basis. The three firms definitely had a preference for team members with experience and accumulated knowledge, but realized the difficulties that occurred given long timelines and resource demands, which made it difficult to keep people on the same project.

The tacit knowledge created through hands-on experience was particularly important to pharma firms; this was reflected and linked into the supply chain in terms of pilot plants and launch facilities. For Pfizer, Ireland was the primary location for new product scale-up, and as

such, the supply chain teams at Pfizer Ireland were a critical part of the PGM organization and the co-development process. The Irish plants formed a network of experienced manufacturing sites that were not only able to expertly manage the day to day manufacturing operations, but could develop, coordinate, and problem-solve with respect to new products and associated processes. Novartis exclusively relied on three product launch locations: Switzerland, Ireland and France, primarily because these three sites had the experience interacting with development. The CMC team at Novo Nordisk, as opposed to specific geographical launch locations, possessed a body of tacit knowledge and experience with potential scale-up techniques. CMC had the knowledge to choose and adjust different technologies and techniques in conjunction with a drug project; their experience in this area was, at times, critical from keeping projects from dying.

Creating informal networks for tacit knowledge sharing was important in the pharma firms because everyone within the firm had knowledge outside of the project s/he was currently working on. In order to create informal networks for knowledge sharing, Novartis sponsored a Global Research Symposium every year to facilitate research collaborations, but also to create research synergies. Novo Nordisk believed that because their organization was smaller, it was much easier to tap into tacit knowledge; employees generally knew who in the organization possessed the knowledge or information they needed. Electronic brainstorming systems or electronic staff directories were suggested, by the larger firms in the study, as ways for accessing tacit knowledge and human capital within organizations.

8.4.2 KM Strategy 2: Share Knowledge

Pfizer wanted to make sure that employees had the basic skills for knowledge and information transfer. For the most part, this heavily relied on communication skills between PGRD and PGM during the co-development process. Pfizer's most significant mechanism that facilitated knowledge flows was the team-based, cross-disciplinary co-development process facilitated by PGRD and PGM. Using multiple sub-teams drawn from PharmSci, NPD and manufacturing, co-development determined a product strategy and created a production process

that accounted for safety, risk and attained cost-savings. The co-development process was notable for its attempts to account for both knowledge and SCM concerns. The right the first time office worked to make sure that the right people had access to the right knowledge when they needed it throughout co-development. This office eliminated some of the knowledge barriers and complexities by streamlining the multiple languages and standards that resulted from having numerous units participating in the process. The PharmSci unit increased the flow of knowledge by bridging the apparent gap and between PGRD and PGM. This unit, technically located within the people-oriented Research division, looked and acted more like PGM because of its focus on engineering, efficiency and efficacy, thus addressing supply chain and manufacturing concerns earlier in the process. PharmSci's presence within Research broadened PGRD thinking beyond lab science and molecule development, thus making it easier for PGRD to recognize PGM concerns.

On the PGM side of co-development, Pfizer aimed to keep the more complex products within their control and at their original manufacturing sites, which strategically minimized issues related to knowledge and supply chains. Strategic level knowledge and supply chain efficiencies extended to evaluation, implementation, coordination and control of technologies associated with drug development: PGM's technical project managers assisted in evaluating new drug delivery technologies (i.e. technology for extended release tablets), and considering whether it would require Pfizer to contract, partner, or invest internally.

Notably, however, NIBR pursued more people-based knowledge initiatives such as education and storytelling in order to address the lack of knowledge sharing between Research and Development. NIBR viewed its storytelling initiative as a people-based and patient focused way of developing an accumulated knowledge base to help identify problems and share solutions. In so doing, this initiative would closely examine the organization, propose improvements and fill the gap that existed in communicating successes, challenges, solutions and motivation to the

entire organization. Ultimately, storytelling would capture some of the tacit knowledge within the organization and decrease the rate of project failure and attrition.

NIBR seemed particularly adept at identifying gaps in their organization and recognizing the key interfaces within the drug development process. NIBR hoped to achieve a higher degree of integration by working towards a number of knowledge goals (as outlined in figure 6.3). A primary knowledge goal for the Education Office was to provide all employees with a basic understanding of broad pharmaceutical industry concepts, including how a drug gets from target to pill. This would eliminate the barriers to integration created by a staff that came from a variety of scientific disciplines and industry backgrounds. It also was clear to the Education Office that the best science was done at the interface of two disciplines, but barriers between chemists and biologists impaired drug discovery and development efforts. Thus, this office committed to integrating their scientists through promoting knowledge sharing and speaking one language, as opposed to exclusively using discipline-specific languages. With similar integration intentions as the Education Office, the Translational Medicine Group, comprised of physician-scientists, was created because of the in-depth knowledge required to integrate disease pathology and clinical trials. This group was expected to improve the matching between drug targets and disease indications, thereby facilitating the transition from bench and animal studies to human trials.

Like NIBR, Novartis' supply chain unit, CPOSCM, remained aware of organizational interfaces for strategic and design level SCM reasons: it had to interface with every function that had the potential to impact SCM. CPOSCM believed that communicating with any unit or project with the potential for making a long-term impact on SCM was critical. Consulting with these interfaces and sharing knowledge could assist with long range planning that prevented delays later in the process.

8.4.3 KM Strategy 3: Recruit Talented Staff

People were critical to pharma's business; as such, the firms hired talented and well-educated people. Recruiting top talent from universities or industry was a top priority for Novartis: NIBR was counting on the notion that recruiting a talented staff and providing them with a measure of freedom and access to resources would produce innovation in processes and products. Not only that, but PhDs would bring a high degree of specialization in a particular scientific discipline to the organization. CPOSCM recruited the top graduates from specific supply chain programs. While Pfizer was slightly less aggressive than Novartis in terms of talent recruitment tactics, R&D managers recognized the need for M.S. and Ph.D. scientists to ensure competitiveness and enable growth, but recognized that leadership and abilities to work with a team were, at times, equally important as education level. Novo Nordisk did not deviate from these models, desiring employees with levels of education beyond a Bachelor's degree; most Novo managers held advanced degrees but were required to continuously work on professional and personal development plans.

In terms of leadership structure, Pfizer seemed the most hierarchical and centralized of the three firms. For the supply chain aspect of the organization, managers in Ireland were responsible for reporting to headquarters in New York. Keeping headquarters up to date on long term planning was one way to handle the organization's size. Pfizer also believed that experienced managers could conquer some of the organization's current challenges and as such, the firm looked to promote and fill positions from within. For example, the complexity of co-development meant that managers needed extensive prior experience before being invited to join the Co-development Leadership Team. Experienced managers were recruited from either manufacturing or R&D and had the technical skills to develop products, transfer technology and manage a product for 10-20 years.

While Pfizer and Novo Nordisk value strong leadership abilities, Novartis' success was attributed to the direction and vision of a strong CEO (Vasella) and Research Director (Fishman).

Fishman and Vasella elevated the importance of Novartis' corporate culture and aimed to align the global culture with the organization's core strategic objectives, which included innovation, a focus on patients and a strong commitment to external collaborations and partnerships. Vasella introduced American-style capitalism to the company shortly after being appointed CEO; he expanded the bonus pool, created a stock-option plan, and implemented performance-based incentives. When Dr. Mark Fishman joined the firm to lead Research, he directed an organizational culture overhaul, trying to infuse the organization with a blend of entrepreneurial, academic, collaborative and innovative qualities.

8.4.4 KM Strategy 4: Create a team that synthesizes knowledge

While the CMC team technically belonged as its own unit within the pharmaceutical development process, the CMC function essentially bridged the development, manufacturing and drug registration phases (as depicted in Figure 7.2). CMC was located at a critical juncture for synthesizing knowledge: discovery and development impacted CMC decisions during phase I and phase II clinical production that would ultimately affect commercial manufacturing. At the same time, CMC had to keep moving forward from discovery/development by planning and anticipating the transfer of activities in phase II to production and control labs. Here, decisions regarding process and product design were made in consultation with pilot plants so that the drug would be able to attain commercial scale production levels.

CMC was also responsible for coordinating Novo Nordisk's parallel drug development process strategy, so that in the end, all the pieces of the process fit together and complied with control and comparability standards. Para development meant that CMC sub-teams did not wait for one process to finish before beginning work on another process; it also meant that its success was dependent upon the CMC manager as well as communication and exchange of input between sub teams. Product profiling, processes for manufacturing, validation, design and formulation occurred at the same time. For CMC to reach the point at which the process was locked, iteration between different units was necessary. CMC's role on the Liraglutide project demonstrated how

through collaboration with research and development, knowledge was combined to achieve a scaleable production process in line with GMP regulations.

Novo Nordisk's organizational size allowed the Liraglutide team to be aware of new technologies and developments on other Novo projects. The molecule and associated knowledge about the molecule moved back and forth between discovery, development, clinical and CMC without internal organizational obstacles (consider inserting Figure 6.1). However, while Novo Nordisk has glowing instances of knowledge management mechanisms working well, integration does fail at other junctures within the organization. Often, the clinical trial part of the organization fails to consult with CMC regarding product availability for trials, instead, assuming when product will be ready for delivery. Further, it seemed as though more collaboration was needed between research and marketing, especially in terms of developing innovative products.

8.4.5 Challenges in Knowledge Management

The nature of pharma organizations is, for the most part, huge, siloed, and globally dispersed, which presents a number of impediments to managing knowledge. Both Pfizer and Novartis realize that the extensive global scopes of their organizations create significant challenges in terms of cultural, language and time zone issues. In an ideal world, Pfizer and Novartis would be more coordinated on a global scale, collaborating between different locations would happen more often and more easily, and everyone would speak the same scientific and drug development language. As a smaller, more geographically concentrated organization, Novo Nordisk had an advantage here. Teams were co-located at facilities in the greater Copenhagen area, and therefore, interaction between sub-teams did not have to bridge a geographical divide; for example, meetings could be held on short notice or team members from discovery could easily visit the development team.

Gathering tacit knowledge within a pharma organization relied upon overcoming cultural, language and location challenges. The overall concept driving the Education Office at NIBR was to act as a "knowledge interpreter," creating a common language and making messages broadly

understood. This directly linked to Dr. Fishman's overall strategic vision to create a new vocabulary and grammar for drug discovery. Each scientific discipline functioned in a slightly different and nuanced language. NIBR believed harmonizing the language between chemists and biologists would advance drug development. In comparison with NIBR, Pfizer's co-development team was a team-based mechanism for knowledge sharing, but for the most part experienced similar frustrations with lacking a common language. Potentially, each scientific and engineering discipline had its own language; thus, just because team members were placed on a co-development team, it did not mean that they automatically shared the same language. Therefore, it was critical for the team to have a common platform from which to work or obstacles would inevitably arise and opportunities to gain efficiencies would be lost.

8.5 Summary

The Pfizer, Novartis and Novo Nordisk case studies demonstrated that re-thinking the way their firms work is an overwhelming challenge. At the most basic level, the firms cannot avoid the realities of the industry environment in which they operate. While the three case firms made attempts at re-organizing their drug discovery and development processes that ranged from moving chemical processes into earlier discovery phases to a complete overhaul of an entire Research and Development program, this did not automatically result in getting better products out faster. The industry still quoted a drug development timeline of 10-15 years; Wall Street remained frustrated with high attrition rates; and scientists continued to wait for basic science discoveries to jump start their process and mitigate some of the complexity underlying their products (PhRMA 2006; Pisano 2006; Lander March 9, 2007). Further, their best efforts in using cross-functional and multi-disciplinary teams in getting a new product to launch phase did not make a marked difference.

The case research shows a distinct division between up and downstream activities pharma. This yields a theoretical observation regarding these two streams: the orchestration of knowledge

is critical, a dominant concern, in efforts to improve upstream activities; but when looking to improve downstream activities, strategies concentrate on SCM issues. Neither stream has considered an improvement strategy that spans both up and downstream activities, nor is there a strategy that tries to maximize KM or SCM practices to make organization-wide improvements in moving a new product from discovery to launch.

A tighter linkage between KM and SCM could increase the level of cooperation and collaboration between up and downstream activities in branded ethical pharmaceuticals. Knowledge impacts how R&D and SCM components interact; an upstream choice, such as how to conduct R&D for a particular drug, will have implications for downstream manufacturing and supply chain planning. As such, each choice has implications for other choices, and knowledge integration could extend across disciplinary and functional boundaries. This supports the view in the literature that upstream processes are as critical as downstream ones in creating benefits for the entire chain (Balasubramanian 2001; Mangan and Christopher 2005; Tracey, Lim et al. 2005).

To improve the chain of activities between the two streams, manufacturing and supply chains would need to be viewed as more of a priority within an organization that is intensely concentrated on the R&D aspect of the organization. The literature indicates, however, that designing firm activities in such a way can create a firm with considerable upstream capabilities, and consequently, downstream rigidities (Leonard-Barton, Bowen et al. 1994). The state of upstream and downstream activities observed in the pharma case studies supports what has been proposed within the SCM literature: that supply chains, which are fundamentally about flows and the movement of tangibles (i.e. materials) and intangibles (i.e. money and information) must relate to knowledge flows (Fahey and Prusak 1998; Holtshouse 1998). Synergies exist between supply chains and knowledge management: in order to achieve supply chain optimization, all elements of the supply chain must be connected to enable the flow of knowledge (Desouza, Chattaraj et al. 2003).

Forging a tighter link between supply chain units and new product R&D, allowing better access to, and flow of, knowledge, has the potential to improve, or increase efficiencies in, getting a product to the launch phase. Since the path from product design through to product launch in ethical pharmaceuticals is particularly knowledge-intensive, the switchover between up and downstream activities requires managing multidirectional flows. Given that all “managements” (i.e. knowledge management, supply chain management, change management, risk management, etc.) concurrently work in living and breathing companies for the purpose of improving performance, creating tight links between knowledge management and SCM may benefit these case study firms. Thus, firm practices suggest that KM and SCM could be more tightly linked.

Chapter 9: Conclusion

The very beginnings of this project were grounded in a study of the pharmaceutical industry and an extensive review of the supply chain management literature. During the course of gathering information in these two areas, and conducting an SCM-focused pilot study⁸⁴ within the branded ethical pharmaceutical sector, it was observed that there was a disconnection between the literature (or theory) and practice in this sector. Essentially, the operations literature suggested that upstream processes were as critical as downstream processes in creating benefits for the entire supply chain (Balasubramanian 2001; Mangan and Christopher 2005; Tracey, Lim et al. 2005). Further, it suggested that product development was enabled by coordinating upstream and downstream activities, information, and knowledge workers (Hong, Doll et al. 2004). However, the two initial case studies revealed that there were not particularly strong links between R&D and SCM. This was interesting considering that within the branded ethical sector, upstream processes played a critical role, as R&D was the center of control in pharma firms, with the remainder of the firm organizing accordingly (Jassawlla and Sashittal 2000; Becker and Lillemark 2006). It was also important to consider that as a new drug moved towards commercial launch, the R&D team often had the best knowledge of the new product (Garrett 2002), making some interaction between upstream and downstream processes crucial for a successful launch.

Bearing this in mind, a qualitative study, with a particular emphasis on new product R&D and SCM was designed to investigate to what extent SCM was considered by R&D within the branded ethical pharmaceutical industry. Two additional top-25 pharma firms (Novartis and Novo Nordisk) were successfully recruited to participate in the research, making the number of total participants three firms⁸⁵. These firms provided extensive evidence describing how firm activities worked within the context of the pharma firm's central activity: drug development and production. Conducting three in-depth case studies provided detailed insight into firm practices

⁸⁴ This refers Fujisawa Ireland, which was a pilot case study, and Pfizer Ireland, which was used as one of the three cases for this dissertation.

⁸⁵ This refers to the three firms used as case studies in this dissertation (Pfizer, Novartis and Novo Nordisk) and does not include Fujisawa, which was used as a pilot case study.

in three successful organizations. By exploring how R&D worked in each firm and how SCM worked, a picture regarding the considerations each unit gave to the other began to emerge. In line with recommendations made by case study methodology literature, the evidence was compiled and written as descriptive narratives which appear as Chapters 5-7 (Eisenhardt 1989; Bryman and Burgess 1994; Stake 1995; Remenyi, Williams et al. 1998).

The final phase involved synthesizing the case study findings with the literature and each other. Primarily, this analysis was in terms of considering R&D activities in each firm, SCM activities in each firm, as well as what was similar or different between the cases. The analysis also had to account for industry-specific characteristics and company background. By taking an open approach to analysis themes were allowed to emerge in reviewing the data; it was also possible to determine instances in which pieces from the literature review resonated, or did not resonate, with what was observed at the case study firms.

9.1 Conclusions and Contributions

The results of this exploratory research provide an answer to the research question, make a contribution to both management theory and practice, and delineate several potential avenues for further research. Additionally, the research was conducted on a topic on which there was very little available literature. While both supply chain management and the pharmaceutical industry have established literature bases, there was very little published literature on supply chain management in the branded ethical pharmaceutical industry. Further, the use of case research for this study contributes to methodological approaches in management research. The qualitative data collection at the case firms generated extensive and descriptive case write-ups for analysis, thus supporting the value of this approach in unexplored areas.

The majority of the conclusions from this work concurrently contribute to both theory and practice; this is because the research was deeply rooted in fieldwork at three branded ethical

pharmaceutical firms. Perhaps the only contribution exclusively focused on theory stems from the literature review phase in which a set of common industry characteristics emerged:

- The industry is more affected by the health of the world population than by changes in the global economy.
- Economic opportunities in pharmaceuticals is inextricably linked to the progress of science.
- A branded ethical pharmaceutical company typically does not possess internally all the capabilities necessary to produce a new product.
- The pharmaceutical industry is characterized by exceedingly long timelines, high attrition rates, and high degrees of uncertainty in product development.
- The industry's existence depends upon patents.
- Pharmaceuticals is one of the most regulated industries in the world.

The case research further supported both the presence and significance of these qualities.

Additionally, these characteristics, which were identified during the literature review stage, were supported in Pisano's book, "Science Business," which was published two months after the literature review had been drafted.

It is worth noting that some of the commonalities that exist in branded ethical pharmaceuticals would be difficult to identify in a number of other industries. Pharma's product development cycle and markets are impacted by conditions that are non-existent in many other industries. Electronics or automotive, for example, have a very steady stream of development and production which operates in cycles that can range from a few weeks to 24 months; pharma's development and production is not only unpredictable and uncertain, but takes an unusually long time: 10-15 years. While in many industries, firms can reliably forecast market demand for new products from year to year, pharma's market demand varies depending upon the health of the world population and which therapeutic classes are fashionable. Other industries can also more easily fulfill promises for x number of new products per year. In pharma, projects suddenly die in late stage development, and while this clearly indicates that the industry needs to fix its pipeline, not a single firm has created a "reliable" stream of blockbuster drugs. Pharma is still looking for a way to efficiently fill the pipeline and guarantee x number of product approvals per year.

Through an iterative, emergent and inductive process that relied upon moving back and forth between case data, the constructed case narratives and the literature review, a number of conclusions were developed which contribute to both management theory and practice.

1. The branded ethical pharmaceutical sector maintains a strong focus on upstream activities, namely R&D.

While this conclusion is rooted in well-documented pharmaceutical industry practice, it is worth noting because it demonstrates that in spite of industry pressures to cut costs and increase efficiency, the industry has not made any fundamental changes or upgraded the status of downstream activities to respond to these pressures. In fact, the number of changes the case study firms have made in terms of R&D practices and processes greatly exceeds the number of changes made within the set of downstream activities. R&D remains unpredictable; in an environment in which each drug is unique, R&D adjusts on a case-by-case basis, however, downstream activities remain markedly stable by comparison.

The industry's firms justify this narrow focus because, quite simply, without successful R&D, a firm will lack products to fill its pipeline. R&D completes most of the knowledge intensive new product development phases (Garrett 2002); this keeps the upstream side of the firm focused on the business of developing products for commercialization. In particular, a pharma firm's organization of its disease area portfolio and its quest to benefit from new scientific knowledge or progress re-inforce this focus on upstream activities.

2. The priorities for the pharma supply chain are not to attain operational efficiencies, but rather strategic or design-level efficiencies.

The development of an evaluative SCM framework (see Figure 3.1), contributes to the SCM literature by helping to define the nature and function of supply chains (Burgess, Singh et al. 2006; Cousins, Lawson et al. 2006; Harland, Lamming et al. 2006; Storey, Emberson et al. 2006; Vachon and Klassen 2006). The case study firms' were considered in light of this SCM

framework and as such, supported a broader, more holistic approach to SCM, particularly in terms of advancing the development of the strategic and design level of SCM (Beamon 1998). The case research suggests that pharma is focusing on strategic and design level changes, more than strictly operational ones, grounded in effective management of knowledge and supply chains, to result in reduced levels of uncertainty, decreased cycle times, lower cost, improved quality and better management of complexity.

The SCM literature proposes that firms will benefit from considering supply chain issues at a very early stage of the design, so that all parties are aware of requirements and constraints, and how decisions made upstream can impact management and design of the supply chain (Haque 2003). The case research illustrates that in an industry like pharma, where making operational-level SCM improvements is markedly constrained by regulatory approvals and the need to guarantee product safety, the attempted SCM efficiencies exhibited by the case study firms focus instead on improving strategic or design-level efficiencies. To better achieve the strategic objectives of their organization, firms have re-designed processes; a primary example is the re-design of the R&D process so that it is more reliable and can predictably feed the downstream functions. Additionally, firms have tried to coordinate R&D and SCM as soon as possible to predict product evolution in order to facilitate the regulatory process.

3. Industry pressures and structure create SCM challenges.

The branded ethical firms for this study articulated their reluctance to revolutionize or significantly change SCM practices. Part of the hesitation to make SCM changes is a direct result of regulatory requirements and the associated costs to obtain regulatory approvals for new process steps or materials. Further, while cost-savings could be realized in moving to lower cost locations, the firms have not aggressively pursued this strategy because the responsibility for the final product is theirs and theirs alone. Taking advantage of a lower cost location or outsourcing part of the manufacturing process means sacrificing a degree of control over ensuring the final

product is safe and that the integrity of the supply chain remains in tact. Simply stated, the risks and the costs of making any dramatic changes in current manufacturing practices out-weighed the benefits for these case study firms.

In the aggregate, pharma seems to operate in environment that requires it to put out fires, maximize successes, and make small-scale improvements if feasible. The case study firms demonstrated that the branded ethical pharmaceutical sector does not seem as aggressive in improving downstream activities, as say, a company like Dell or Walmart. When a drug is close to success, meaning it has reached phase III clinical trials or the product launch phase, inevitably the project has made it through the extensive (and costly) patenting and regulatory processes as well as overcome incredibly high attrition statistics. Thus, pharma companies, anxious to deliver better products faster, will do what it takes to get products to patients. In these situations, it is possible that entire supply chains or new drug manufacturing facilities must be created in order to accommodate new therapies. In doing so, the firm wants to maintain complete control over these processes.

On a positive note, the degree of control exercised by Novartis in the Gleevec project meant the firm was able to create new optimizations and collaborate in novel ways with both internal and external parties in order to accelerate product launch. However, in spite of the optimizations and efficiencies gained through the Gleevec experience, a similar success story has yet to emerge from Novartis, which could indicate that Gleevec's optimizations either do not translate to other projects, or that the firm has yet to recycle the knowledge gained on this project.

4. Piecemeal knowledge management strategies support firm activities.

The case study firms demonstrate that while their operating environment is particularly dependent on knowledge to produce new products, none of the firms have been able to manage knowledge flows on an organization wide basis. Instead, knowledge seems to be managed within teams or silos, but the firms do not excel at moving knowledge between the firms' units or

activities. The firms do employ, however, a number of strategies for knowledge management, but these do not extend throughout the organization: leverage accumulated experience and informal networks; share knowledge; recruit a talented staff; create a team that synthesized knowledge. Further, firms depend on individual employees' tacit knowledge in coping with the complex and ever-changing body of knowledge that characterizes the sector. Multidisciplinary teams also serve as critical knowledge management points during different segments of the new product process. The rather piecemeal approach, however, contrasts with the suggestion in the literature that successful new products typically are facilitated by the integration of upstream and downstream knowledge workers.

It is interesting to consider the lack of a comprehensive knowledge management strategy in light of the difficult new product decisions that can happen at any time from discovery to launch. These decisions compound pharma's desire for less interruption in production and development. One of the hardest decisions is to decide to abandon an experimental drug that is not working; the further along the product is in development, the more significant the disruption. However, not admitting failure at the appropriate time will lead to inefficiencies. A reluctance to give up on projects is influenced by the amount of time that goes into pharma product development. As such, discovery and development teams will extend themselves in order to achieve success; this includes extensive problem solving to prevent giving up on potential treatments too soon. It is worth noting, as with Novo Nordisk's Liraglutide product, an inability to recognize success is also problematic. Recognizing projects worth pursuing versus admitting failure is tricky, even an industry that claims it is grounded in scientific principles. The knowledge associated with a decision must be collected, disseminated and even recycled; enabling an organization wide knowledge flow would benefit the knowledge-intensive decisions that must be made.

These conclusions help to provide some insight to how the research question, *To what extent is SCM considered by R&D within the branded ethical pharmaceutical industry?*, can be

answered. The literature suggests it is beneficial for up and downstream activities if supply chains coordinate with R&D (Balasubramanian 2001; Singhal and Singhal 2002; Haque 2003; Hult 2003; Fine, Golany et al. 2005; Power 2005). Furthermore, upstream processes are as critical as downstream ones in creating benefits for the entire chain (Balasubramanian 2001; Mangan and Christopher 2005; Tracey, Lim et al. 2005). Because the link between R&D and SCM was not obviously manifest in the pilot case study firms, the research aimed to determine if SCM is considered by R&D within the branded ethical pharmaceutical industry. I believe the answer to this is a qualified “yes”; SCM is considered, but not to the extent suggested as desirable by the SCM literature reviewed in chapters 2 and 3.

The case studies illustrate that the firms continue to prioritize R&D, successfully developing commercialized products is paramount; organizing SCM and manufacturing for a product is secondary- without a viable product, you will not need downstream activities. The firms also do not seem to be seeking the operational benefits of lean or agile supply chains in the same way firms do in other industries. This is partially because the industry faces a number of SCM challenges that make dramatically re-engineering downstream practices (like Dell or Walmart) an unattractive proposition. Further, because the firms are not constantly adjusting and improving their downstream activities, these practices remain somewhat stable, and consequently, there is not the same imperative to connect with the upstream activities that exists in industries where products change more quickly and more frequently.

The lack of a coherent organization-wide knowledge management strategy is going to pose a problem in R&D being able to comprehensively consider SCM in new product development. This means that forging tighter links between knowledge management and SCM may benefit many firms, particularly those in knowledge-intensive industries; pharma could find that a better connection between knowledge workers in R&D and SCM would facilitate knowledge flows and allow a more thorough consideration of SCM concerns in new product development.

9.2 Limitations

No researcher completes his or her ideal research project. The ideal research project is rarely the version that materializes in the final project; researchers must make compromises in order to keep projects both feasible and viable. This is best summarized by Edmondson and McManus as follows:

The research journey can be messy and inefficient, fraught with logistical hurdles and unexpected events. Researchers manage complex relationships with sites, cope with constraints on sample selection and timing of data collection, and often confront mid-project changes to planned research designs. (Edmondson and McManus 2007)

Further, quite often projects are influenced by conditions outside of the researcher's control: time, funding and accessibility.

The limitations of employing a case study methodology, as opposed to other research methodologies, were addressed in Chapter 4 and will not be repeated here. This research, however, could have benefitted, had time permitted and companies been more cooperative, from a larger sample size to increase replication and extension. With two top ten pharma firms as study participants, it may have been useful to find an additional, smaller top-25 firm that would have complemented Novo Nordisk. The addition of another small firm could have magnified the apparent differences in scale between the firms and allowed for a greater number of conclusions to result from the sample strategy. Furthermore, had time permitted, it would have been appropriate to design and administer a survey to case study firms as an alternate method of triangulation to confirm the observations and conclusions that developed from the semi-structured case interviews and narrative reports.

Finally, defining the scope and appropriate literature bases for this research was a challenge. Confining the literature primarily to topics directly related to ethical branded pharmaceuticals, R&D and SCM was a necessary choice. Given the number of disciplines that currently contribute to the SCM literature (Burgess, Singh et al. 2006), exploring additional literature from a variety of areas in management research would have been feasible, had this research not been limited in

scope by its nature as a doctoral project. For example, the nature of drug development in ethical pharmaceutical companies makes a case for including the innovation and new product development literature; further, considering the way R&D units and manufacturing units interface in the pharmaceutical industry, organizational behavior literature focused on teams could be factored into a larger study.

9.3 Future Work

I conclude, at the end of my particular project, some future directions based on the work I have already done. There are opportunities for expanding on the work and ideas discussed in this dissertation that can be pursued. First and foremost, the original study could well be expanded to investigate a larger sample of the top-25 ethical pharmaceutical firms. With a larger sample population, a longitudinal study, exploring and investigating up and downstream integration within several firms, over a 5-10 year time period, could be pursued. Given the ever-changing nature of the industry, it might be useful as well to examine the increasing pressure (from Wall Street) on cost-cutting and savings measures to see if eventually that has the effect of elevating the status of SCM and consequently the levels of cooperation between the "ivory tower" of R&D and manufacturing (Becker and Lillemark 2006).

Another direction for expanding this work would focus on other industries; those similar to pharma, either in terms of being similarly knowledge-intensive or health care related, could be a good starting point. An entire multi-industry study on how R&D and SCM may, or may not, work together, could provide useful information to an ever-expanding and relevant industry group. It would be interesting to study a number of firms in other industries to compare to this pharma study.

Finally, this project could expand in terms of influencing and expanding concepts in the management literature. Supply chain management is a growing field with plenty of opportunity for future contributions, particularly in terms of moving SCM out of a strictly operational

perspective. Further development of the strategic and design levels of SCM and identification of other industries or firms in which these levels take priority over the operational level issues would be valuable. Additionally, further research that supports and validates an organizational-wide or early involvement of SCM with R&D or product development activities would be an important continuation of some of the recent SCM literature (Beamon 1998; Kotzab and Otto 2004; Mangan and Christopher 2005; Power 2005; Tracey, Lim et al. 2005).

Appendix I. Brief Biographies of Pfizer Interviewees

A. *Teresa Chambers, Supply Chain Team Leader at Little Island API*

Teresa Chambers was the Supply Chain Team Leader at Little Island API, responsible for overseeing purchasing, warehousing and planning. She studied engineering at university because she enjoyed it. After university she worked in engineering for four years. When her project finished at the company she was working for, there were no other engineering projects available, so she applied for a job in supply chain, thinking that it would serve as an interim job.

As Chambers began her job within the supply chain department, she discovered that she enjoyed it much more than her previous technical engineering role, because it was more diverse and dealt with the whole business. She was responsible for looking at the whole business, where the business was going, and what was going to happen next. Because the supply chain role was essentially a coordinating role for the various production stages. Chambers found her new position complemented her engineering background, due to its focus on detail, but the involvement with supply chain added an aspect of having to look at the broader business and industry picture.

At one stage, Chambers wondered if she should return to engineering management, believing that maybe it was more of a “proper career”. However, she thought that supply chain “has evolved in the last five to ten years... whereas possibly prior to that, it may have gotten less attention”. The new leadership team for Pfizer’s Little Island API site, had nine key areas represented, and supply chain was one of them. Chambers believed this reflected a recognition that supply chain was a “definite area, a department in its own right, a definite part of the leadership team.”

B. *Dr. John Cronin, Director of Customer Service at Ringaskiddy API*

John Cronin, a chemist by background, earned his PhD in organic chemistry at University College, Cork in 1986. He then went to work with Merck, Sharp and Dome at the Ballydine facility in Tipperary for about two and a half years. He arrived at Pfizer in May 1988, and was there 17 years in June 2005.

At Pfizer, Cronin started off in production as Plant Supervisor in OSP 1 before moving to Plant Manager for OSP 2, and subsequently plant manager, commissioning manager, and detail design leader for the OSP 3 facility. He ran OSP 3 for the first 18 months of its activity through 1996. In September 1996 he moved to the customer service department. It was originally called

the materials department, but its name was changed to help support one of Pfizer's mission elements, to be customer focused. Cronin had been in the overall supply chain or materials area for nearly nine years. John believed that the evolution of supply chain at Ringaskiddy and in Ireland for Pfizer "has been extraordinary." (When John joined his current department in 1996, Pfizer had only one plant in Ireland: Ringaskiddy.)

C. *Kieran Ruddy, Supply Chain Team Leader at Loughbeg*

Kieran Ruddy, Supply Chain Team Leader at the Loughbeg Drug Product Plant, started his career as an electronics engineer. He worked in R&D for about three and a half years, designing development systems. Kieran then moved to Apple Computer, and became a Supplier Quality Engineer; after a period of time he moved into procurement and materials management. He left Apple Computer in 2000 and began a job as a Supply Chain Manager at Warner Lambert for five months before it became Pfizer.

Appendix II. Organizational Structure at Pfizer's Loughbeg Drug Product Plant

When Kieran Ruddy joined Warner Lambert, construction at the Loughbeg Drug Product plant was just getting underway and his office was located in a portacabin next to the site. This meant that Ruddy witnessed the qualifications of the equipment and the intense pressure on the plant to ramp up quickly and hold a specific amount of API by July 2001. In order to ramp up quickly and successfully, a team of what Ruddy described as “expatriates from the U.S. and Puerto Rico and Germany” some who had management expertise, some who had even made Lipitor before, arrived at Loughbeg to help with the process. Ruddy believed that the other key factor in getting the plant up and running was that, although the plant was very large, Loughbeg kept automation to a minimum in terms of IT systems.

As the plant was getting up and running, the organizational structure at Loughbeg was created in a most unique fashion, turning the typical hierarchical organizational structure upside down. There was still a leadership team and a support team, but then there was everybody else with the job of making tablets. “We bring in the materials, we make tablets, and back out they go. This is the important part of the process, and everyone else supports it. So the organization was designed around getting the tablets made, the raw materials in and the tablets out,” explained Ruddy.

For example, instead of process teams just making tablets, they made the tablets, looked after the equipment, and managed their own team. There were no middle managers; there was a function head in each function. In the warehouse team, there were 12-15 people without a supervisor or warehouse manager. “They work, they know what’s to be done, we supply support in terms of information and what needs to be done; we’ve got support functions but they’re basically self-managed, they manage their own holidays, they manage their own budget, and budget process,” said Ruddy.

The Loughbeg plant was considered a learning organization, which was built on trust. Creating a learning organization particularly affected Pfizer’s recruitment policy. Pfizer ran an assessment center where potential employees spent a day undergoing personality tests and completing a Gallup questionnaire. The assessment center tried to determine preferences in terms of the way individuals liked to work and if individuals were suited to working in the Loughbeg environment. Overall, recruits were generally self-directed, motivated people. Ruddy said that in this process Pfizer looked for “people who take initiative, are able to manage stuff, people who basically are unoffending... they can actually get on as a team as well, they have good relationships with each other.”

The reason extensive pre-employment evaluation was necessary at Loughbeg was linked to the fact that it was a high performance plant; Pfizer compensated employees for high performance. Everyone in the same job was paid the same money at Loughbeg. “So if we recruit one of the people for the process teams (we call them tablet technicians), if they start tomorrow they’d be paid the same salary as someone who’s been at Pfizer five years,” said Ruddy. Everyone at the Loughbeg plant gets paid a salary, no one gets paid overtime; people were compensated based on their role, but the same job means the same salary, the same holidays, and the same benefits.

The plant had a small HR team, which was essentially comprised of team facilitators that worked with the whole team on dynamics. Additionally, Loughbeg did not have a traditional annual appraisal process, but rather had what was called a “360 evaluation,” in which you invite the people you work with every day to give you feedback in certain areas. Essentially, this was a qualitative peer assessment. It was up to the individual who to invite and which questions to ask, but it was a non-negotiable process that happened every year. The quantitative salary increase

was the same across the plant. To do that, Pfizer externally benchmarked each role based on what the market would pay.

This plant model was new for Pfizer as it was created by Warner Lambert in order to get the plant up and running quickly. In developing this organizational structure, Warner Lambert surveyed and benchmarked difficulties within different businesses across the globe. Then, Warner Lambert designed the organization, how it was controlled and operated. The plant called this model “we deliver.”

Ruddy believed this model provided Loughbeg with a certain degree of flexibility. If the machine brakes down, the team that uses that machine will fix it because Loughbeg did not have a maintenance department. Each team had technical or mechanical qualifications and was able to perform the core activities of making the product, fixing the machines and evaluating the products and processes. Each team had core competencies for whatever specific process they’re managing.

This structure also allowed resource movement; if someone was needed in a different part of the organization, either temporarily or permanently, adjustments could be made, perhaps more easily, according to Ruddy because “We have functions, but we don’t have structures that sometimes prevent other organizations from moving.”

These same organizational rules applied to Ruddy’s supply chain team:

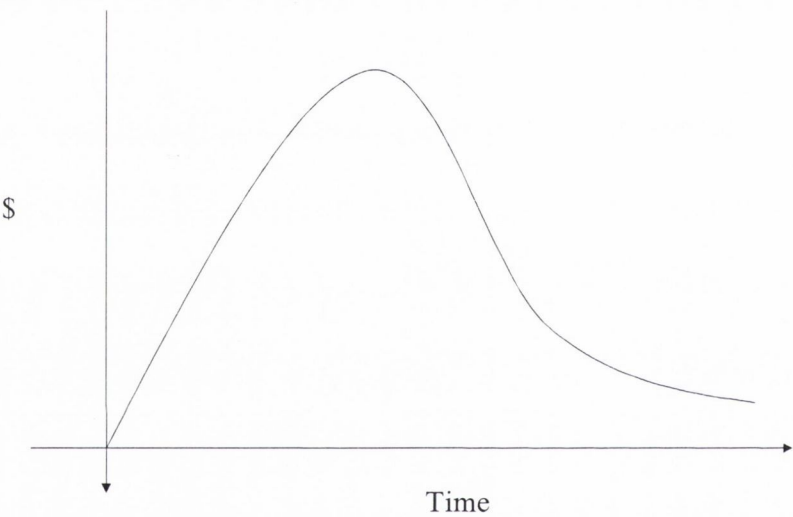
We have a few buyers, we have a planner, we have myself and we have the warehouse team. We would have one raw materials buyer, we’d have one planner, so a customer service person. When the buyer is on holiday, the planner is able to cover that role. We don’t have ten buyers, it’s a kind of give and take, a flexibility. Yes, I’d say it has a lot of organizational sensibility, but I’d also say that it sort of gives the organization here a lot of autonomy.

Appendix III. Pfizer Product Lifecycle, from Interview with John Cronin

Product Life Cycle

The life cycle for a product, from discovery to maturity in the marketplace, including 5 years of planning, is probably on the order of 20 years. From discovery to launch, the product profile looks like this:

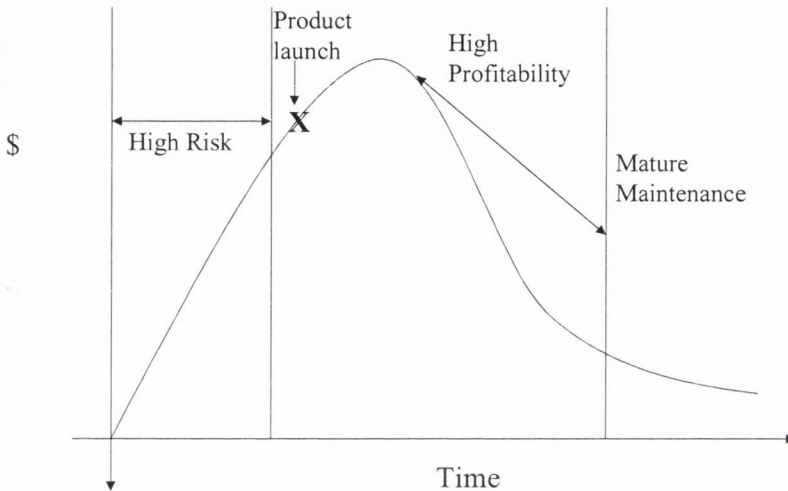
Graph 1. Pharmaceutical Product Lifecycle



The above graph matches the curve of the most successful drug in the world today, Lipitor. This is called the “Lipitor curve.” The Y-Axis is the amount of money Pfizer is spending on the drug: the X axis is time. This product was discovered, assessed, trialed, scaled up, assessed (again), trialed (again) and prepared for launch. Until the time the product is approved, Pfizer essentially does not have a product. “This makes our business high risk,” said Cronin.

If this graph is divided into three sections, it looks like this:

Graph 2. Product Lifecycle detail



1. From the start time to the launch of the product, it's high risk. That risk can be quantified in dollars, and it is a "very, very large amount of money."
2. The X signifies product launch, a significant milestone, and the product continues to grow. For Lipitor, Pfizer is still in the growth stage and the drug is nearing the peak of its life cycle. This second area is "the payback area for Pfizer." This is the area where there is a commercial, high volume, high opportunity product
3. Then third area is the mature/maintenance area for the product. Pfizer's mature maintenance philosophy is as follows:

If people, mostly stakeholders including patients and the medical community, wish Pfizer to provide branded Pfizer versions of our product going forward through its maturity, we will do so. For example, today on this site, we are making a product right now a product that we started the plant up with, in 1972. That product is way off patent, way off. But there are markets in the world that have regard for, and wish to continue to source Pfizer branded. There are many generics available, but some markets continue to seek the Pfizer product for reasons that they hold as important. So that's why Pfizer continues to make this drug. Do we make a lot of money on that drug? No, no way. Do we see an opportunity for any growth on the product? I doubt it. But, our philosophy is that if people out there want Pfizer products, we will give them Pfizer products. Because we have, as well as a commercial, opportunity-oriented focus, we also have a duty of care to assure that people have continuity from therapies that they want. Making a commitment to the marketplace and to people, to supply them with products is in our view a very fundamental thing. Pfizer will do whatever it can to assure the supply of quality products to people who need it. We are not philanthropists, we expect to make money out of doing so, but at

the same time we understand that there is a very serious commitment made by doctors and patients, particularly, to use Pfizer products, and that commitment has to be reciprocated by our approach to assuring quality and the reliable supply of our products (Cronin).

Appendix IV. Diabetes Background Note⁸⁶

Diabetes mellitus is a chronic disease in which insulin production by the pancreas becomes impaired: the pancreas either fails to produce insulin, a hormone that regulates blood glucose (sugar), or the insulin produced is ineffective. Insulin production deficiencies lead to increased amounts of glucose in the blood (hyperglycemia), which can damage many of the body's systems, particularly the blood vessels and nerves. There are two main forms of diabetes, both of which are complex and caused by mutations in more than one gene and by environmental factors.

Type 1 diabetes, in which the pancreas fails to produce the insulin necessary for human survival, accounts for 5% to 10% of all diagnosed cases of diabetes. This form of the disease develops most frequently in children and adolescents, but onset can occur at any age. Type 1 diabetes has been correlated with genetic markers that may increase the risk of developing the disease. Risk factors for Type 1 diabetes may be autoimmune, genetic, or environmental. Type 1 diabetics must take daily insulin injections to keep blood glucose in a normal range.

Type 2 diabetes is more prevalent than Type 1, accounting for approximately 90% of all diabetes cases worldwide. Type 2 diabetes results from the body's inability to respond to the insulin produced by the pancreas; the body's need for insulin outstrips the ability of the pancreas to produce it. Type 2 occurs most frequently in adults, but increasingly affects adolescents. In Type 2 diabetes, symptoms may be less pronounced. Early symptoms may not be apparent and often the disease is diagnosed several years after its onset, too late to avoid some complications.

Type 2 diabetes is strongly familial, but it is only recently that some genes have been linked with increased risk. Ethnicity is an important risk factor with higher rates of Type 2 diabetes reported in people of Asian and African origin, and in indigenous peoples of the Americas and Australasia. There is a strong link between obesity and Type 2 diabetes: 58% of cases worldwide are linked to being overweight. Weight gain may result in insulin resistance in which the body is unable to use the insulin it produces effectively. Physical inactivity, both a cause and consequence of weight gain, also contributes to insulin resistance.

The variety of treatment options for Type 2 diabetes correlates with disease progression. Initially, many patients can keep their blood glucose in a healthy range without medications by effectively managing diet and exercising regularly. Eventually, however, Type 2 diabetics find that exercise and weight control will no longer regulate their blood glucose. This may be due to cells becoming more insulin-resistant over time. Thus, as diabetes progresses, Type 2 patients often switch disease management strategies, from diet and exercise, to oral medications, and, in some cases, to insulin injections.

Complications associated with diabetes mellitus

Diabetes is a leading cause of blindness, limb amputation, and kidney failure. Diabetic neuropathy, injury to vessels that supply blood to nerves, is probably the most common complication of diabetes, affecting up to 50% of diabetics (in varying degrees). Overtime, elevated blood glucose puts diabetics at risk for neuropathy, leading to sensory loss and damage to limbs, which sometimes requires amputation. In particular, diabetic foot disease, caused by changes in blood vessels and nerves, often leads to ulceration and subsequent limb amputation.

⁸⁶ Facts and figures in this section are drawn from the Joslin Diabetes Center (www.joslin.org), the Center for Disease Control and Prevention (www.cdc.gov), the American Diabetes Association (www.diabetes.org) and the World Health Organization (www.who.int).

Diabetes mellitus is also associated with damage to the small blood vessels in the retina, which results in loss of vision. Diabetic retinopathy is a leading cause of blindness and visual disability.

Diabetes has become one of the major causes of premature illness and death in most countries, mainly through the increased risk of cardiovascular disease (CVD). CVD accounts for between 50% and 80% of all deaths among people with diabetes in industrialized countries. Risk factors for heart disease in diabetics include smoking, high blood pressure, high cholesterol and obesity. Many people with diabetes need to take medication to control their cholesterol and blood pressure, both contributing factors for CVD. Studies have shown, however, that complications of diabetes can be prevented or delayed through effective management.

The Insulin Market

In 1985 an estimated 30 million people worldwide had diabetes.⁸⁷ In 2003, the International Diabetes Foundation (IDF) estimated the number of diabetics worldwide at 194 million.⁸⁸ The figure was expected to rise to almost 333 million by the year 2025.⁸⁹

The total market for anti-diabetic drugs in 2004 was estimated to be \$10.5 billion, an increase of 17% over 2003.⁹⁰ Insulin remained the standard treatment for the progressive, chronic disease; worldwide insulin sales in 2004 were \$6.5 billion.⁹¹ The market for diabetes therapies was expected to grow because of demographic changes: increasing life expectancy, earlier onset of Type 2 diabetes, higher rates of obesity, and sedentary lifestyles. The increasing number of diabetics would drive sales of existing products and increase demand for new therapies.

Three companies competed in the global insulin market: Eli Lilly and Novo Nordisk were dominant players; Sanofi-Aventis had made inroads with a long-acting insulin, Lantus[®], which needed to be injected only once a day. There were more than 20 types of insulin products available on the market; they varied along three dimensions: 1) how soon the product started working (onset); 2) when it worked the hardest (peak time); and 3) how long it lasted in the body (duration). Choice of product depended on an individual's lifestyle, the pattern and severity of disease, and the physician's preference and experience.

Insulin products were designed to replicate normal physiological insulin secretion to keep blood glucose levels in a tight, controlled range. This required a mixture of fast acting, intermediate acting and long acting insulin to replicate the two basic modes of insulin secretion in the body: 1) Continuous secretion (basal), and 2) Secretion in response to ingesting food (bolus). Secretion after ingesting food has two phases, a rapid initial release, followed by a longer acting phase that begins 10 minutes after eating and lasts for about one hour.

A patient on insulin therapy might administer one to five injections per day to mimic the normal state of continuous background insulin secretion and meal-associated insulin spikes. The average cost of diabetes therapy in the U.S. ranges from one to eight dollars per day, depending on how insulin is delivered.⁹²

⁸⁷ <http://www.who.int/dietphysicalactivity/publications/facts/diabetes/en/>

⁸⁸ <http://www.idf.org/home/index.cfm?node=1054>.

⁸⁹ <http://www.idf.org/home/index.cfm?node=264>

⁹⁰ "The Diabetes Market 2005: Poised for Growth." Deutsche Bank, May 2, 2005.

⁹¹ Ibid.

⁹² "Novo Nordisk." Bear Stearns, European Equity Research. December 8, 2005.

Appendix V. Glossary of Acronyms

API	Active Pharmaceutical Ingredient
CDLT	Co-development Leadership Team (specific to Pfizer)
CMC	Chemistry, Manufacturing and Control
CPOSCM	Country Pharma Organizations Supply Chain Management (specific to Novartis)
DBF	Dedicated Biotechnology Firm
DCS	Distributed Control System
DFM	Design for Manufacture
EMA	European Medicines Evaluation Agency
ERP	Enterprise Resource Planning
FDA	Food and Drug Administration
GLP-1	Glucagon-like Peptide 1
GMP	Good Manufacturing Practice
JIT	Just-in Time
MDT	Module Development Team
MES	Manufacturing Execution Systems
MGH	Massachusetts General Hospital
MRP	Materials Requirements Planning
NCE	New Chemical Entity
NDA	New Drug Application
NIBR	Novartis' Institutes for Biomedical Research
NPD	New Product Development
OSP	Organic Synthesis Plant (specific to Pfizer)
OTC	Over the counter
PGM	Pfizer Global Manufacturing

PGRD	Pfizer Global Research and Development
PSO	Portfolio Strategy Operations
R&D	Research and Development
SCM	Supply Chain Management

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