Assessing Decision Inputs in Drug Development between Small, Early Stage Companies and Big Pharma: Is There a Difference?

by

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Abstract

The pipeline productivity challenge facing large, publicly traded pharmaceutical companies, collectively referred to as "Big Pharma," is well known. The unprecedented success Big Pharma achieved over the past few decades in commercializing blockbuster products means that it is now faced with near-term patent expirations on such products, representing billions of dollars in lost sales and profits. In order to maintain its economic momentum, Big Pharma is increasingly relying on the universe of smaller, early stage biotechnology and pharmaceutical companies as a source of new products.

Early stage companies may offer Big Pharma something beyond simply more product bets. Several recent consulting studies have shown that economic returns to Big Pharma of products sourced externally are greater than those developed internally, which raises the question: What, if anything, are early stage companies doing differently from Big Pharma in their product development programs?

The goal of this thesis is to evaluate product development programs ("projects") and compare qualitatively and quantitatively the decisions for projects at key decision points between early stage pharmaceutical and biotechnology companies and Big Pharma. Given that much of the critical discovery and R&D work on pharmaceutical products happens both before and during a product's entry into human clinical trials, this thesis focuses on those areas of the development continuum where R&D plays a central role. The key decision points are therefore: lead candidate selection/optimization, moving a project from pre-clinical trials into Phase I human clinical trials, and moving a project from Phase I to Phase II clinical trials in humans.

The thesis tests the hypothesis that small, early stage, publicly traded U.S. & Canadian biotech and pharma firms (Small Pharma) focused on 1-2 therapeutic areas who high levels of homogeneity in their decision making process, number of decision inputs, prioritization processes, and metrics for all three key decision points in the product development process irrespective of whether a product originates inside or outside the company. In comparison, Big Pharma companies will show heterogeneity in these variables for their projects. I have obtained data from primary interviews of industry executives within Big Pharma and Small Pharma firms.

The therapeutic areas selected for the early stage company data set are: (1) cancer and autoimmune disease, (2) cardiovascular disease, and (3) infectious disease. The rationale for these therapeutic areas is that there is significant drug development activity taking place in these fields, and there are significant unmet medical needs within them. Additionally, both Big Pharma and Small Pharma companies are developing products in these fields. I compare these data sets statistically using Fisher's exact test and Yates' chi-square test.

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In memory of my father,

David R. Rippy

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I'd like to thank Martha Gray for serving as my academic advisor, and Fiona Murray and Kimberly Thompson for serving as my thesis advisors. I would also like to extend sincere gratitude to HST, Harvard, and MIT faculty members Rox Anderson, Ernie Berndt, Ray Chung, Richard Cohen, Teo Dagi, Howard Golub, Ali Khademhosseini, Stan Lapidus, Rick Mitchell, Bobby Padera, Fred Schoen, Shiladitya Sengupta, Tony Sinskey, and Martin Carey for your passion, inspiration, and support. Thanks also to Traci Anderson and the HST administrative team for all your support as well. Finally, I would like to thank the people who allowed me to interview them and who graciously shared their experiences, insights, and perceptions that provided the much needed data that I rely on in this work.

Thanks also to my classmates in the Biomedical Enterprise Program and HST. You are a great group of people and you will go on to do great things. I have enjoyed studying and working with you immensely. Thanks also to the HST alumni network, which has aided me in this thesis, and which will no doubt continue to help me in the future. The entire HST community exemplifies what W. Edwards Deming called a "yearning for learning." May our learning adventures together last a lifetime.

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Chapter I: Introduction

In recent years, pharmaceutical industry research and development (R&D) productivity has been assessed, discussed, and debated intensively. Faced with patent expirations from 2006-2013 on products that will have generated sales of over $100 billion in the U.S. alone during that time,[1-6] the pharmaceutical industry's leading companies must confront a double challenge: to replace sales and profits lost as the result of product patent expirations, and to grow profits for shareholders. Ostensibly, the most straightforward way for them to address both challenges is to continue to do what they have done historically: commercialize new products that offer improved therapeutic outcomes to patients versus existing therapies. However, the magnitude of the task is unprecedented within the industry, and it begs the question: can an industry maintain such a spectacularly successful run of innovation and productivity?

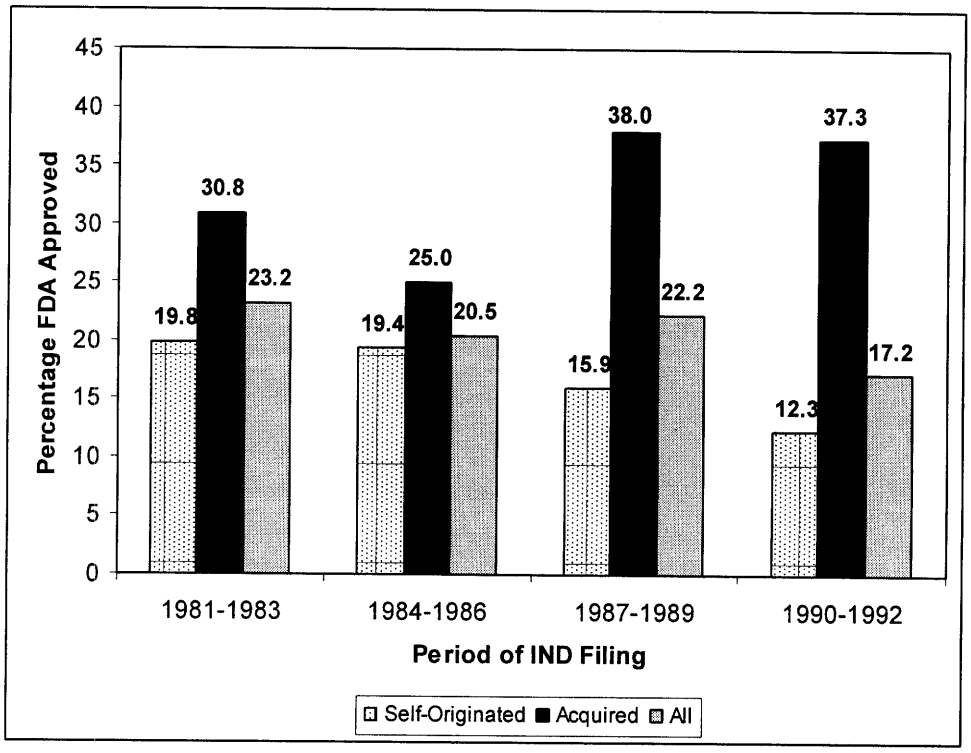
For the past few decades, large pharmaceutical companies ("Big Pharma;" see Exhibit 1 for definition) have licensed and acquired products from outside sources such as smaller, early-stage pharmaceutical and biotechnology firms (as well as universities) to augment product pipelines and enhance prospects for sales and profit growth. While the degree to which companies historically engaged in this activity has varied, virtually all now make it a strategic imperative. Merck exemplifies this trend. In 1999 the company did only 10 licensing deals, whereas it signed 50 in 2004.[7] Going back further, Danzon et al found that the top 20 pharmaceutical firms did an average of 1.4 licensing deals per year with a biotechnology company from 1988-1990, but 5.7 such deals from 1997-1998.[8] PricewaterhouseCoopers found in a 1998 report that the number of alliances per year had more than doubled in the industry from 1989 to 1998, from 248 to 635 per year.[9] Certainly the number of deals does not take into account important parameters such as the potential value of a given deal. However, given the relatively low odds of success of any single early-stage drug development project, the number

of deals has a probabilistic impact on success, and is therefore a metric that is often tracked by industry analysts.

The Benefits of Looking Outside

Recent studies suggest that Big Pharma benefits economically from looking beyond its own walls for new products.[8-11] Studies by McKinsey & Company and Mercer Management Consulting from 2004 and 2003, respectively, have found that products in-licensed by top ten Big Pharma companies have higher rates of success in obtaining marketing approval than internally developed products, and furthermore, in-licensed products generate higher rates of return.[10,11] DiMasi showed that by the end of 1999, the percentage of investigational new drug applications (INDs) of externally acquired new chemical entity (NCE) products filed from 1981 to 1992 that had been approved by the FDA was 33.1%, as compared to 16.9% for all internally developed products.[12] Key findings from the DiMasi study are illustrated in Figure 1.

Figure 1. Clinical Approval Success Rates for NCEs by Origin and Period During Which a First IND Was Filed. [12]



Selected Recent Studies on R&D Productivity and Licensing Activity in the Pharmaceutical Industry

Figure 2 below summarizes selected recent studies on pharmaceutical R&D productivity as well as success rates of externally sourced pharmaceutical products compared to those that were internally developed. Several key themes from these studies include:

- Product licensed by Big Pharma from the outside have higher success rates of approval and higher rates of return on investment compared to internally developed products.
- Licensing deals and strategic alliances between Big Pharmas and Small Pharmas have increased dramatically within the last twenty years.
- Pharmaceutical companies stand to gain economically by licensing programs from other companies – even taking into account failures.

- Regulatory and economic incentives appear to motivate for the expanded development of existing chemical entities (i.e., pursuing approvals of new indications for an already approved drug) in favor of developing new chemical entities (NCEs)
- Increasing organizational bureaucracy and unprecedented Big Pharma firm size appear to adversely impact pharmaceutical R&D success.

These findings have important implications for the ways in which the pharmaceutical industry might manage its R&D efforts to enhance its prospects for success going forward.

Licensing from smaller firms is not the only way in which Big Pharma can augment its pipeline; buying smaller firms outright via mergers & acquisitions is another. Ernst & Young estimates that the top 40 pharmaceutical and biotechnology companies spent $16 billion in 2006 acquiring 20 specialty pharma and biotech companies.[13] While such investment is hardly in the same economic league as the mega-mergers of Pfizer and Warner-Lambert or Glaxo Wellcome and SmithKline Beecham, both in the year 2000, it is notable in that many of these deals are for companies with early stage technologies that will require substantial further investment to commercialize the assets acquired. Mega-mergers historically gave the newly merged companies "breathing room" to grow sales and earnings through organizational synergies that often had little to do with new product development. Commonly, such synergies in Big Pharma mergers have been derived more from cost-cutting measures in administrative and sales force organizations and less from R&D productivity, though rationalizations of R&D pipelines – for the benefit of cost savings – have certainly been pursued.

Figure 2. Selected Recent Studies on R&D Productivity and Licensing Activity in the Pharmaceutical Industry and Findings.[8,9,14 – 25]

Study/Year	Sample	Time Frame	Drug Types	Variables Evaluated	Findings
U.S. Congressional Budget Office (CBO): Research & Development in the Pharmaceutical Industry / 2006	Various	Various	Both new chemical entities (NCEs) and new indications for existing drugs Both new chemical entities (NCEs) and new indications for existing drugs	Various Effect of Mergers	In 2002 the largest 10 pharmaceutical firms accounted for 48% of pharmaceutical sales worldwide, up from 20% in 1985 As of date of report, 8 of 10 the top pharma companies were the products of mergers between two or more drug companies R&D expenditures of merged companies grew slower than those of non-merged companies, though their rate did not change from those of the merging companies; thus, mergers may initially divert resources away from R&D.
U.S. Government Accountability Office (GAO) / 2006	1,264 new drug applications (NDAs)	1993-2004	Both NCEs and new indications for existing drugs	NCEs versus new indications for existing drugs	68% of NDAs submitted during the period were for non-new chemical entities (NCEs) (e.g., new indications for existing drugs)
Georgia State University & Emory University: "The outsourcing of R&D through acquisitions in the pharmaceutical industry" / 2005	180 transactions in 15 countries	1994-2001	Both NCEs and new indications for existing drugs	Motivations for merging or acquiring Degree of success in leveraging R&D from acquisition Degree of access to information in pre-acquisition period on the part of the acquirer prior to doing the acquisition Can acquirers avoid over-paying (as evidenced by stock market returns post acquisition)?	Deterioration of internal R&D pipeline correlates with likelihood of acquiring another company; firms experiencing the greatest deterioration in R&D pipelines were found to be most likely to pursue an acquisition of a research intensive firm 71% of acquirers were found to improve or maintain their product pipelines or portfolios post-acquisition; abnormally high stock market returns for post-announcement period was found to be +3.91% (1) Alliances with target firm prior to acquisition; (2) alliances with other firms in same therapeutic category as target firm; and (3) internal research and prior sales within same therapeutic category as target firm all correlate with higher acquirer returns Yes. Through information gathering (see above), acquirers realize higher returns than firms who do not engage in information gathering activities.

Study/Year	Sample	Time Frame	Drug Types	Variables Evaluated	Findings
Boston Consulting Group / 2004	- Top 10 pharmaceutical companies - Top 10 biotech companies - All but top 10 biotech companies	Various depending on parameter: 1980s, 1990s, 2004	Both NCEs and new indications for existing drugs	- Dollar productivity - Capitalization - Products in Pipeline	From 1991-2001, most revenue growth for top biotechnology & pharmaceutical companies came from an increase in the number of blockbusters The number of blockbusters is approaching "equilibrium" – i.e., the number of blockbusters going off patent will soon equal or exceed the number of new blockbusters being launched in a given year Increasing complexity in terms of larger organization and size of R&D budget may bring economies of scale but also results in less organizational knowledge about each project Scale disadvantages larger firms relative to the "intimate... dialogue and partnering enjoyed by academia and small biotechs," and thus impedes progress in highly insight-driven elements of the value chain, such as medicinal chemistry or protocol design Small biotechnology companies were found to have less than 10% of the biopharmaceutical industry's cash yet 67% of the industry's pipeline in 2003 External sources (i.e., licensing partnerships) are cited as one of the key "remedies" to the biopharmaceutical industry's R&D product pipeline challenges.
Boston Consulting Group: "The Gentle Art of Licensing" / 2004	2500 compounds ("Worldwide Clinical Pipeline") within small biopharmaceutical companies	Point in time: 2004	Both NCEs and new indications for existing drugs Both NCEs and new indications for existing drugs	Status: licensed or not	1,000 of the available compounds were licensed at time of study Compounds were being licensed at rate of 10% per year Supply (e.g., new compounds available) were growing at 2% per year Only 30% of remaining compounds would be "suitable" for licensing Thus, a shortage in available compounds for licensing was predicted.

Study/Year	Sample	Time Frame	Drug Types	Variables Evaluated	Findings
McKinsey & Company / 2004	- Top 10 pharmaceutical companies' preclinical compounds and 77 in-licensed preclinical compounds - 71 internal and 73 in-licensed compounds - 1,448 compounds	1995-2001 1997- 2001 1998-2000	Both NCEs and new indications for existing drugs Both NCEs and new indications for existing drugs Both NCEs and new indications for existing drugs	Cost of development Average cumulative four year revenues Success in progressing to commercialization	Pre-clinical development costs range from $21 to $29 million for internally developed compounds versus $14 - $19 million those that are in-licensed Internal compounds fail more often in Phase 2 than in-licensed ones Virtually no difference in average cumulative revenues was found for first four years of commercialization between internal and externally sourced compounds. Licensed compounds were successful in 27% of cases (Phases 1-3) while internal candidates were successful only 14% in these stages.
McKinsey & Company Trends in R&D Productivity and Implications for Japan / 2004	Top 10 Pharma & Other Companies R&D Costs	1997 – 2002 1991-2001	Both NCEs and new indications for existing drugs	Compounds in Development Compounds in development	Total number of compounds in development in all phases grew from 5,015 in 1997 to 5,604 in 2002; during that time, Top 10 Pharma's share of these programs declined as a percentage of total from 25% to 15% and also declined in total number R&D costs for Top 10 pharma companies and other companies were $7B and $5B, respectively in 1991 and $12B and $19B in 2001; CAGRs for R&D were 6% and 14% respectively during the time period, with development costs far exceeding research costs. Japanese firms were found to be producing more than twice (2x) as many compounds per dollar of R&D spend; however, they were not as successful as global leaders in terms of commercial sales or in return on R&D spend; partnerships and alliances were cited as two ways for Japanese companies to close the gap.
Long Island University / Koenig & Mezick / 2004	Two mergers in 1989 ("first wave"); Five mergers from 1994-1996 ("second wave"); Eight comparator non-merged companies	1981-1989 1994-1996 1990-2000	NCEs only	Cost per NME of merged versus non-merged companies	First wave: Cost per NME in constant dollars increased by 65% compared to an increase of 101% for non-merged companies Second wave: Cost per NME in constant dollars increased by 17% compared to an increase of 93% for non-merged companies

Study/Year	Sample	Time Frame	Drug Types	Variables Measured	Findings
Danzon, Nicholson, Pereira / 2003	900 firms	1988-2000	Both NCEs and new indications for existing drugs	Phase-specific success rates based on Overall firm experience Firm experience within therapeutic category Diversification of firm experience Firm alliances with large and small firms	Firm experience and experience within therapeutic category do not matter for Phase I but do correlate with success beyond Phase I Development alliances occurs for majority of compounds by Phase 2 or 3 Products developed in alliances have higher probability of success in Phase 2 and 3, especially if licensor is a large firm (a firm with > 25 compounds in development).
Mercer Management Consulting / 2003	68 compounds across 10 leading pharmaceutical companies	1995-1999	Both NCEs and new indications for existing drugs	Success in clinical development	In-licensed products had higher rates of clinical development success at all stages (47%, 14%, and 38% at pre-clinical, Phase 1-2, and Phase 3, respectively) Approved in-licensed compounds attained relatively lower (76%) sales than internally sourced compounds Internal rates of return on in-licensed compounds were higher than internally developed ones (3.1% at Pre-clinical, 4.0% at Phase 1-2, and 8.2% at Phase 3, compared to 2.1% for all internally developed compounds). IRR of in-licensed compounds improved with stage of licensing.
DiMasi, Hansen & Grabowski / 2003	68 NCEs randomly selected from 10 pharmaceutical firms	2000	NCEs	Capitalized out of pocket costs of an NCE to point of marketing approval	Capitalized out of pocket costs for an NCE to the point of marketing approval = $802MM in 2000 dollars.
McKinsey & Company / 2002	Top 12 pharma company licensing deals with biotechnology firms from 1991 – 2002	1991-2002	Both NCEs and new indications for existing drugs Both NCEs and new indications for existing drugs	Simulated Monte Carlo analysis based on industry averages to determine: - optimal time of licensing - value realization by firm type by phase of development.	Pharma companies could dramatically increase the amounts paid for licenses in early development (150% more in most cases at the pre-clinical stage) A pharma company reaped maximum value in 85% of cases by licensing (where a license deal could be negotiated) at the pre-clinical phase Pharma companies capture greatest expected value from pre-clinical licensing virtually 100% of the time because greater risk of failure was more than offset by low deal terms at this early development stage; biotech firms reap maximum value in Phase 2 or 3 If deal terms were economically more attractive to biotech firms, licensing at earlier stages could become more attractive due to incremental upside.

Study/Year	Sample	Time Frame	Drug Types	Variables Evaluated	Findings
DiMasi / Clinical Pharmacology & Therapeutics / 2001	671 NCEs	1981-1992	NCEs only	Time from investigational new drug (IND) filing to abandonment or approval	Out of 508 Self-originated NCEs and 163 acquired NCEs, by end of 1999: 20.9% of NCEs with INDs filed from 1981 to 1992 had been approved for US marketing Success rates for types of NCEs were as follows: NCES that were acquired: 33.1% NCEs that were self-originated: 16.9% NCEs that were self-originated and first tested in humans in the US: 8.6%. Mean residence time (time to either approval or research abandonment) declined from the 1981-1983 interval to the 1990-1992 interval by 30% (1.5 years). Median survival time decreased 12% from 4.9 years to 4.3 years for the 1981-1983 to 1990-1992 filing intervals, respectively.
PriceWaterhouseCoopers: "Pharma 2005" / 1998	Various	1996-1998	Both new chemical entities (NCEs) and new indications for existing drugs	R&D spending of U.S. pharmaceutical and biotech companies Number of pre-clinical candidates in the pharmaceutical industry pipeline Qualitative observations about process of research Number of strategic alliances in the pharmaceutical industry	U.S. pharmaceutical and biotech companies spent $6.5B on R&D in 1988 and an estimated $21.1 billion in 1998 From 1996-1998, the number of compounds in pre-clinical testing were as follows: 1996: 2,853 1997: 3,102 1998: 3,278 "... many research scientists tell us that they do not find working in large organizations conducive to originality, lateral thinking, and innovation." From 1988 to 1998, the number of strategic alliances more than doubled from 248 to 635 per year.

Objective of Thesis

The preponderance of evidence suggests that projects selected by Big Pharma for in-licensing are more successful than those that are developed within the firm. Such evidence raises an important question: what is it about these externally initiated projects that renders them more successful? On the surface, if Big Pharma firms were rational, we would expect that on the margin internal and external projects would be equally successful. There are several possible explanations for the differences observed. First, it may be that Big Pharma gives more attention to in-licensed products and they must therefore meet a higher standard for incorporation into the portfolio. The corollary to this idea is that internal projects are more difficult to "kill" or terminate. Secondly, external projects produced by smaller firms may indeed be of higher quality, supported by more thorough evidence or evaluated on different (more objective) criteria. IN order to examine this question, this thesis explores differences in decision-making processes in two different organizational settings: Big Pharma and Small Pharma.

The specific objective of this thesis is to evaluate whether there is a difference in the ways in which Big Pharma companies and smaller pharmaceutical and biotechnology companies make decisions around and prioritize drug development projects on the basis of whether a project was sourced internally or externally (see Exhibits 1 and 2 for definitions of "Big Pharma" and "Small Pharma," respectively. Specifically, I seek to evaluate selected decision points at both Big Pharma and Small Pharma companies to see if there are discernible differences - either quantitatively or qualitatively - in how which each approaches the drug development process based on the origination of the project (internal or external). Given the results of numerous studies over the past few years, one would hypothesize that there is something different about the way in which the two types of firms manage drug development based on whether a project originates externally or internally.

The Pharmaceutical Industry's R&D Productivity Challenge

In purely economic terms, the pharmaceutical industry, like any other, is challenged to exceed its past performance in the form of earnings growth. Thus, the industry is tasked by investors and shareholders with the challenge of becoming more productive over time. From an investor perspective, gauging the productivity of a business is fairly straightforward. Return on investment (ROI) should increase over time. Other metrics, such as return on capital employed (ROCE) and return on equity (ROE), also help gauge economic productivity. In the pharmaceutical industry, though, where a drug typically takes twelve years or more to be developed, capital can be employed for extended periods of time before generating a return, thus adding to the complexity of assessing industry performance. Nonetheless, the economic metrics of the pharmaceutical industry are perhaps the easiest to assess when one can consider a long period of time historically, such as ten years or more. However, in trying to evaluate shorter-term industry performance and productivity through various other metrics, the challenge becomes far greater.

The Challenge of Assessing Pharmaceutical R&D Metrics: NMEs and "Drug Quality"

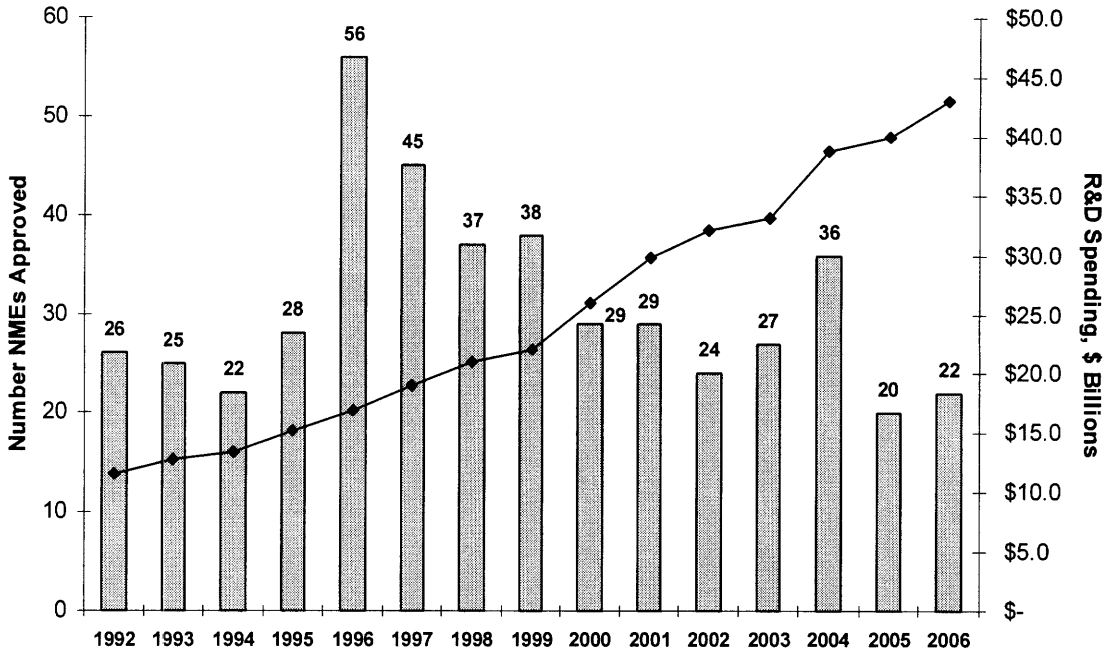
Numerous metrics have been used to assess the productivity of R&D spending within the pharmaceutical industry. The Pharmaceutical Research and Manufacturers of America (PhRMA) tracks annual R&D spending as well as FDA approvals of new medical entities (NMEs) of its member companies, and while PhRMA member firms' R&D spending constitutes only a portion of that for the industry as a whole, it is often used in literature as a barometer for the industry. Sales and total number of new products launched, two other closely monitored metrics, are often measured against R&D spending in a given year. However, it has been noted

that in attempting to assess pharmaceutical R&D productivity, one needs to look ahead in future years to determine the impact of R&D spending in a given year, since the results of such R&D expenditures in terms of products approved, sales, and profits are realized in the future on a rolling basis (i.e., they do not all accrue in one year).

The use of NMEs as a metric of R&D productivity has its challenges and can be misleading. Berndt et al have pointed out that innovation within the pharmaceutical industry can take different forms, such as expanded indications for existing drugs that are supported by new clinical studies, new dosage forms, and new formulations.[26] Such expanded efforts for existing products require significant investment in R&D and often have highly positive economic returns.

Nonetheless, industry observers and participants alike, including the FDA and other government entities, continue to assess pharmaceutical R&D spending and NME approvals as two important industry metrics. In utilizing data from the U.S. Pharmaceutical Research Manufacturer's Association (PhRMA), such metrics generally yield a picture of escalating R&D spend with a concurrent declining trend in the number of NMEs approved since the 1998-1999 time frame, as illustrated by Figure 3.

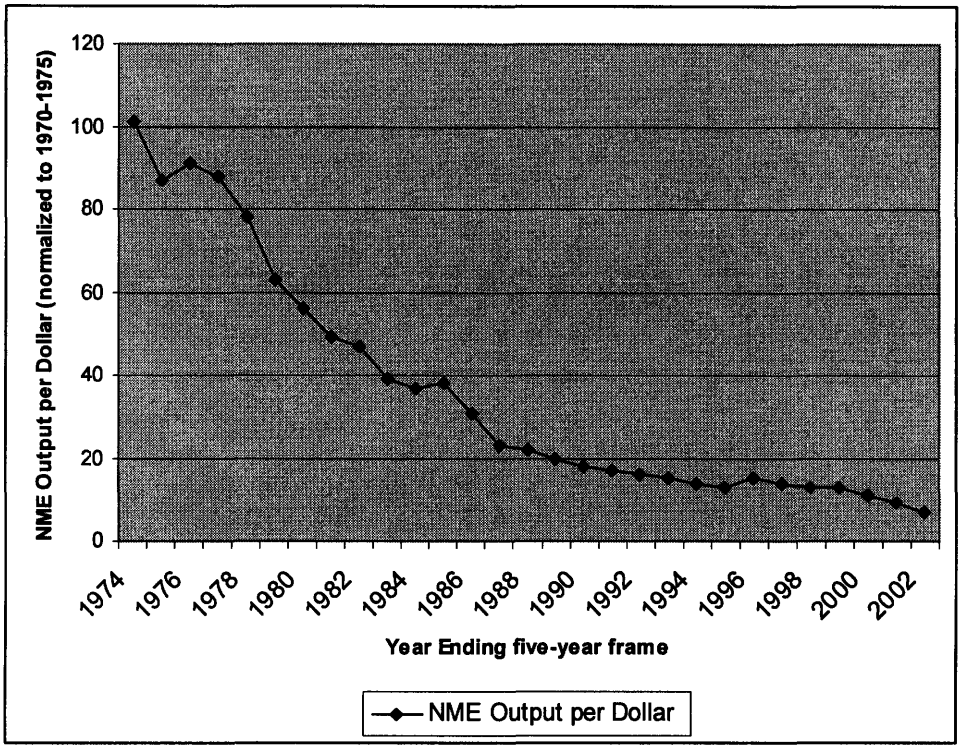
Figure 3. PhRMA Member Firm FDA NME Approvals and R&D Spending by Year, 1992-2006.



Source: Pharmaceutical Research Manufacturers of America (PhRMA). Years 1996-2006 include both FDA Center for Drug Evaluation and Research (CDER) reviewed products as well as those transferred into CDER from the Center for Biologics Evaluation and Research (CBER).

Figure 4 represents another look at the situation. Booth and Zemmel looked at NME output per R&D dollar in 2004.[27] As can be seen, NME output per dollar, normalized to 1970-1975 average dollar values, has declined on a prolonged basis.

Figure 4. The Decline in NME Output per R&D Dollar, 1974-2002.



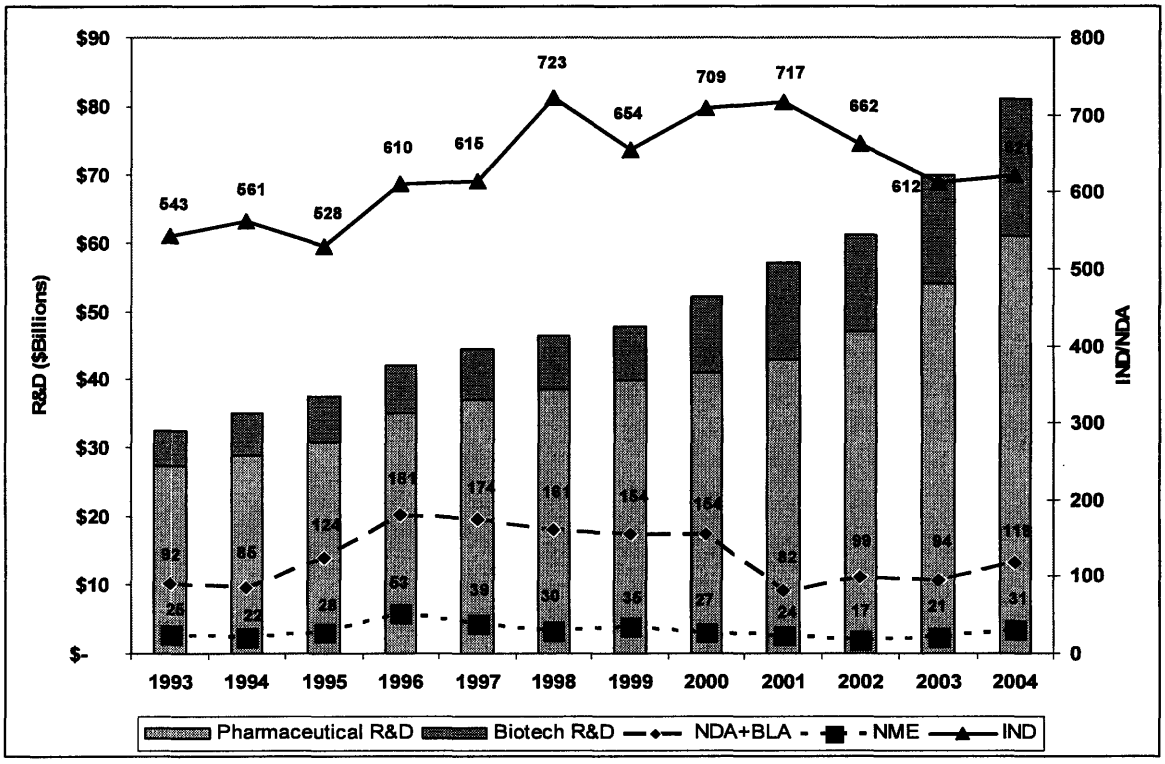
Sources: PhRMA, Parexel Pharmaceutical R&D Statistical Sourcebook, McKinsey & Company.

The rationale for using NME output as a metric to evaluate the industry is that an NME is essentially by definition a newly-patented product and is therefore the purest form of product innovation. While companies can extend market exclusivity on existing products by developing new indications (in the U.S., for example, three-year extended exclusivity is permitted through new use/new clinical studies by an applicant for new indications for an already approved drug), doing so does not provide the same period of market exclusivity that might be realized by a newly issued patent on an approved NME.

However, as a 2006 U.S. Congressional Budget Office (CBO) report observes, the metric of NME approvals does not take into account "drug quality," which can have also have a significant

impact upon productivity.[14] Unfortunately, defining and measuring quality can be difficult. Few studies have attempted to define drug quality, and it remains a debated term.

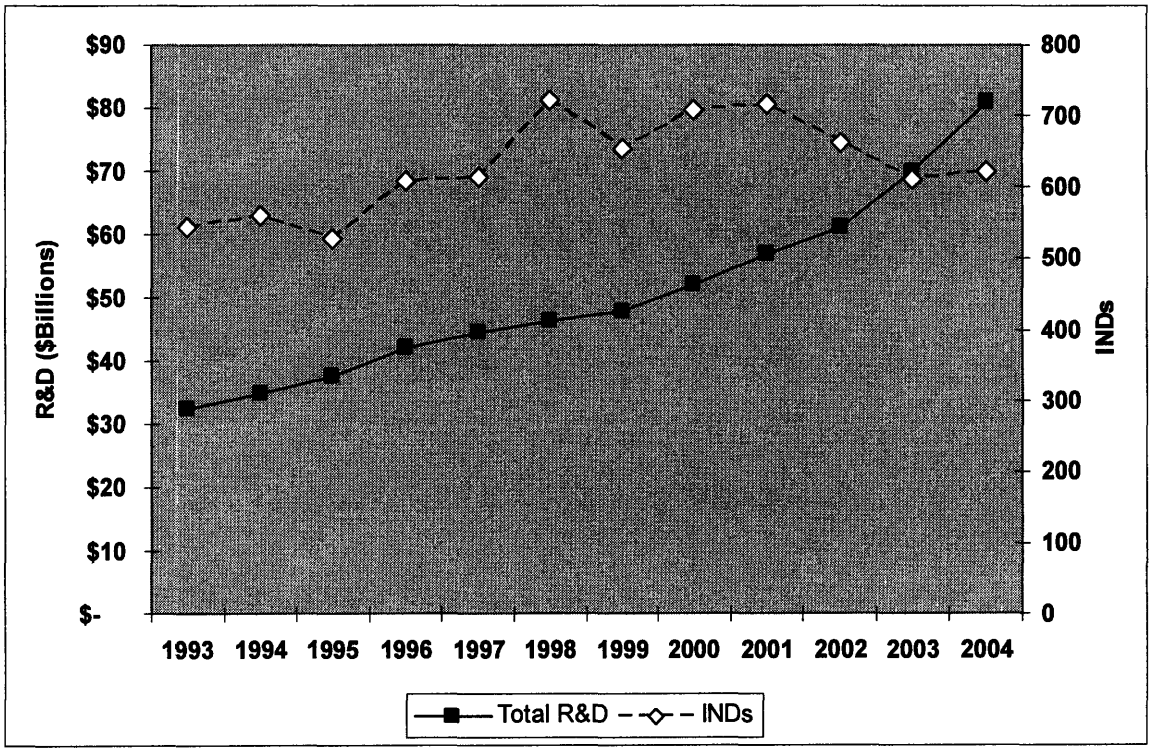
Figure 5. Global Pharmaceutical & Biotech R&D Spending Compared to Commercial Investigational New Drugs.



Sources: CDER, CMR, Ernst & Young, Goldman Sachs, Pharmaceutical Product Development (PPDI).

When taking into account not only NMEs but also new drug applications (NDAs) on a global level, the picture is similar in terms of flat to declining numbers of NDAs and NMEs in the pipeline compared to growing R&D spending both within pharmaceutical and biotechnology companies (Note: please refer to Chapter . Figure 5 shows industry output compared to R&D expenditure from 1993-2004. A look at the trend lines shows that global R&D spending has increased at the rate of 7.9% per year since 1993, whereas the number of INDs filed has grown at 1.1% per year since that time. These figures, as well as their trend lines, are plotted against each other in Figure 6 below.

Figure 6. Global Pharma & Biotech R&D Spend and IND Filings and Trends, 1993-2004.



Sources: CDER, CMR, Ernst & Yong, Goldman Sachs, Pharmaceutical Product Development (PPDI).

Costs of Drug Development

On a pure cost basis, costs of drug development per NDA have risen steadily over time. Cost estimates for developing an NDA drug candidate range from $802 million[23] from DiMasi et al to a Bain & Company estimate of $1.7 billion.[28] While in the past, increases in R&D costs could be absorbed due to top line sales growth in Big Pharma firms, the question of whether such expenditures can be sustained in the wake of declining sales and fewer NDA/BLA filings per R&D dollar becomes relevant due to future patent expirations on large-selling Big Pharma products. We will look at this question in more detail later.

The Perception of an Industry R&D Productivity Decline

While various metrics pose challenges in assessing whether there is a productivity decline in pharmaceutical R&D, a cursory view of industry and academic literature reveals a broadly held perception that a productivity gap exists. Indeed, the CBO 2006 report states that:

"In the absence of comprehensive, statistical measures, the drug industry's performance can be considered qualitatively. Even if drug quality has been increasing, the industry's performance may still have declined, for several reasons."[14]

The CBO report cites several factors that suggest pharmaceutical R&D productivity has declined, such as a decline in number of drugs approved per dollar of R&D and a growing share of industry R&D investment expended on "incremental" improvements to drugs.[14] The report cites several possible causes for a decline in pharmaceutical industry R&D productivity. They include: the ebb and flow of scientific innovations and discoveries (as opposed to linear progression); increasing technological complexity; rising real wages without an accompanying increase in R&D output; and increased current R&D spending as investment in higher future productivity.[14] To these factors, we can add several proposed by Cuatrecasas, such as: the sheer mass and complexity of today's large pharmaceutical organizations (e.g., Big Pharma) which perpetuate bureaucracy and discourage innovation; the lack of understanding among Big Pharma management, Wall Street, and investors regarding the drug development process and timeline; and the decline of the role of the "champion" in drug development.[29] We explore these factors and how they may be impacting pharmaceutical R&D in the next section.

The Pharmaceutical R&D Environment

Significant debate has ensued recently as to whether the "blockbuster" model of Big Pharma, that of commercializing products that realize a billion dollars (often multiple billions of dollars) in sales, is viable or sustainable.[30] Rather than targeting cost saving synergies from blockbuster selling organizations, the smaller acquisitions described above have focused more on specific types of technology and expertise than on cost savings synergies. While creating big-selling, blockbuster products will likely always be a consideration in Big Pharma's strategic approach to drug development, a number of questions arise as to the ways in which it might seek to produce new products going forward – blockbuster or not. How should Big Pharma develop new products? What strategies should it employ to produce products that can enjoy longer life cycles? How can licensing products from the outside augment the process? An examination of the pharmaceutical R&D environment in general may explain some of the strategies by which both Big Pharma and Small Pharma are approaching the development of next-generation therapies and why they are evolving. Factors that may impede productivity could be driving changes in the way the pharmaceutical industry performs R&D as it attempts to become more efficient.

How Did We Get Here? A Look at the Changing Dynamics of Pharma R&D

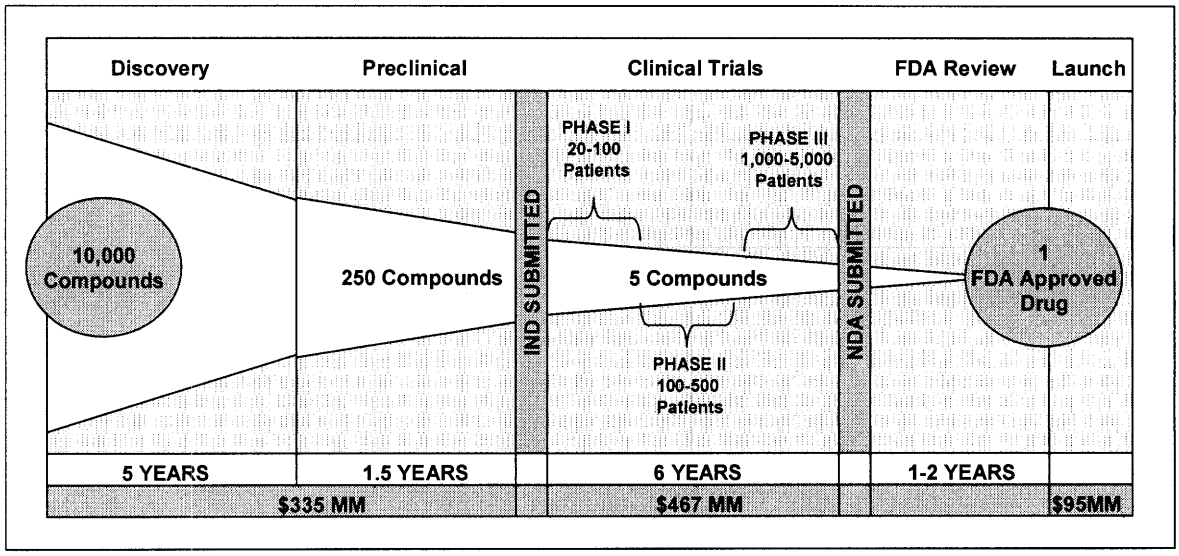
To gain some appreciation for the pharmaceutical R&D environment as it exists today, it is worth elaborating upon the factors cited above as possible contributors to a decline in pharmaceutical R&D productivity. There are no doubt other potential factors to be explored, although Cuatrecasas notes that some of these, such as inadequate staffing and budgetary allocation of regulatory bodies such as the FDA, are merely symptomatic of more fundamental

challenges relating to factors such as pharmaceutical company corporate culture, understanding of science, management, and organizational structure, to name a few.[29] Certain key trends within the industry, such as the explosive growth of partnerships, as well as unprecedented levels of venture capital going into the life sciences, are being driven by, and in response to, these factors. (Note: $2.58 billion of venture capital was invested in U.S. based biotechnology and medical device start-up companies in the first quarter of 2007, all time highs for both categories.[31] In this context, the term "biotechnology" is all encompassing for companies focused on any type of drug development research, including that of traditional pharmaceuticals).

The Ebb and Flow of Scientific Discoveries. With respect to ebb and flow of scientific discoveries, a new scientific finding may lead to a series of quick, new innovations – the "easy" discoveries.[16] Following these, the next discoveries or innovations may be much harder to achieve, require greater R&D expense, and could actually result in lower returns. In essence, the process of discovery is not straightforward or linear. I propose that the dynamic of the ebb and flow of scientific drug discovery, inclusive of both the "easy" and "harder" discoveries, hasn't really changed over time; rather, the expectations of investors and the commitments of management teams of publicly traded Big Pharmas have ratcheted up in recent years, to the point that they have surpassed what is possible in terms of discovery output and capabilities.

Drug discovery has always been a costly, highly risky process. As Figure 7 illustrates, historic experience within the industry has shown that 10,000 compounds must be assessed at the discovery stage, the earliest stage of drug development, for every one drug that is approved. Moreover, the time line for commercializing a drug can often run from 10-14 years in length.

Figure 7. The Drug Development "Funnel" of Candidates Tested by Phase, Timing, and Costs.



Source: PhRMA, 2006.

Increasing Technological Complexity. There is little doubt that technological complexity within drug discovery and development is increasing dramatically. While on the one hand the mapping of the human genome has brought about new scientific tools, such as DNA microarrays and other technologies that theoretically should enhance our understanding of life and disease, it has not translated into an anticipated plethora of new drug filings.[32] Complexity creates enormous challenges in a genomic era of drug discovery in that the vast majority of biological functions occur through the interaction of multiple genes. Furthermore, most biological interactions are non-linear. So, while we have more data than ever before, at the genomic, proteomic, and imaging levels (both systems and anatomical), we are actually now "awash" in it.[33] Figure 8 illustrates the complex feedback loop that exists in drug development programs which requires mastery in the genomic era. Figure 9 illustrates the various levels of organism for which knowledge of each must be integrated in developing and targeting therapeutics in this new age.

Figure 8. Selected Knowledge Driven Components of Drug Development in the Genomic Age.[33]

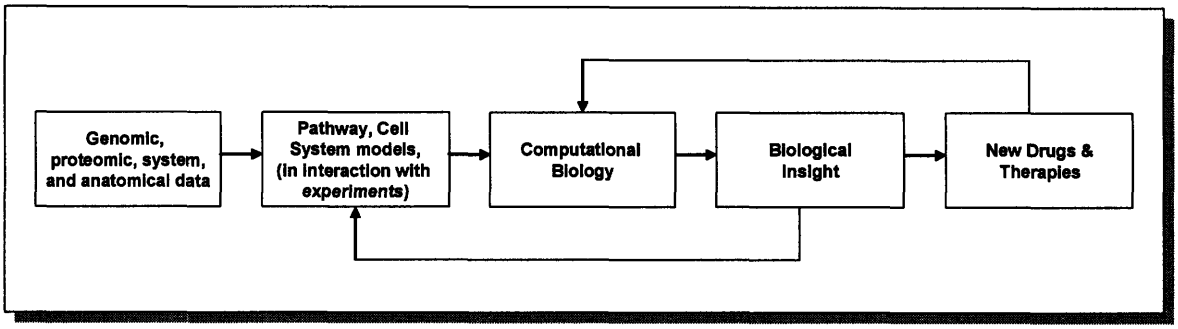
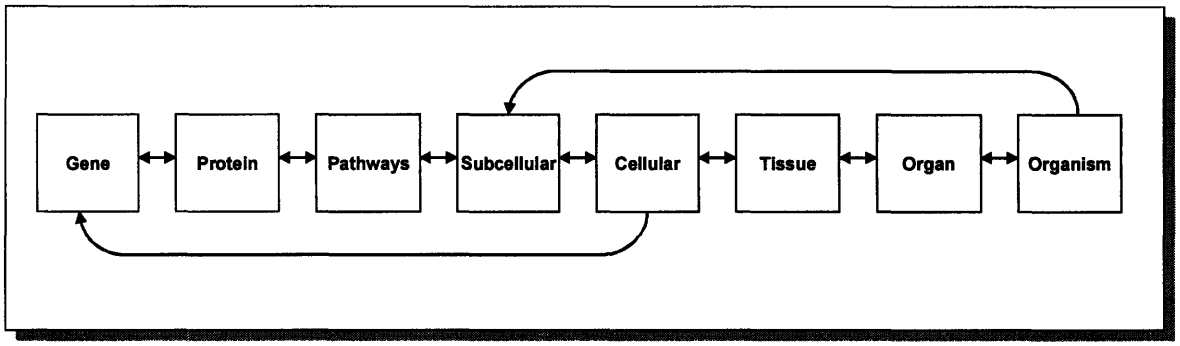


Figure 9. Levels of Organism in Which Knowledge Must be Integrated in the Genomic Age.[33]



Pisano points out that the theoretical promise that biotechnology would revolutionize pharmaceutical R&D productivity has not occurred. Indeed, echoing the point made above about data, he argues that biotechnology has actually increased the uncertainties in pharmaceutical R&D.[34] Considering the complexity illustrated in Figures 8 and 9 above, one can appreciate how it has proliferated in the genomic age.

Rising R&D Costs. The U.S. CBO report cites the possibility of rising real R&D wages without an accompanying increase in R&D output as a possible contributor to a productivity gap. However, it appears that a greater potential contributor to pharmaceutical R&D labor costs may be the growth in R&D staffing within the industry. In the U.S., the number of R&D scientists and

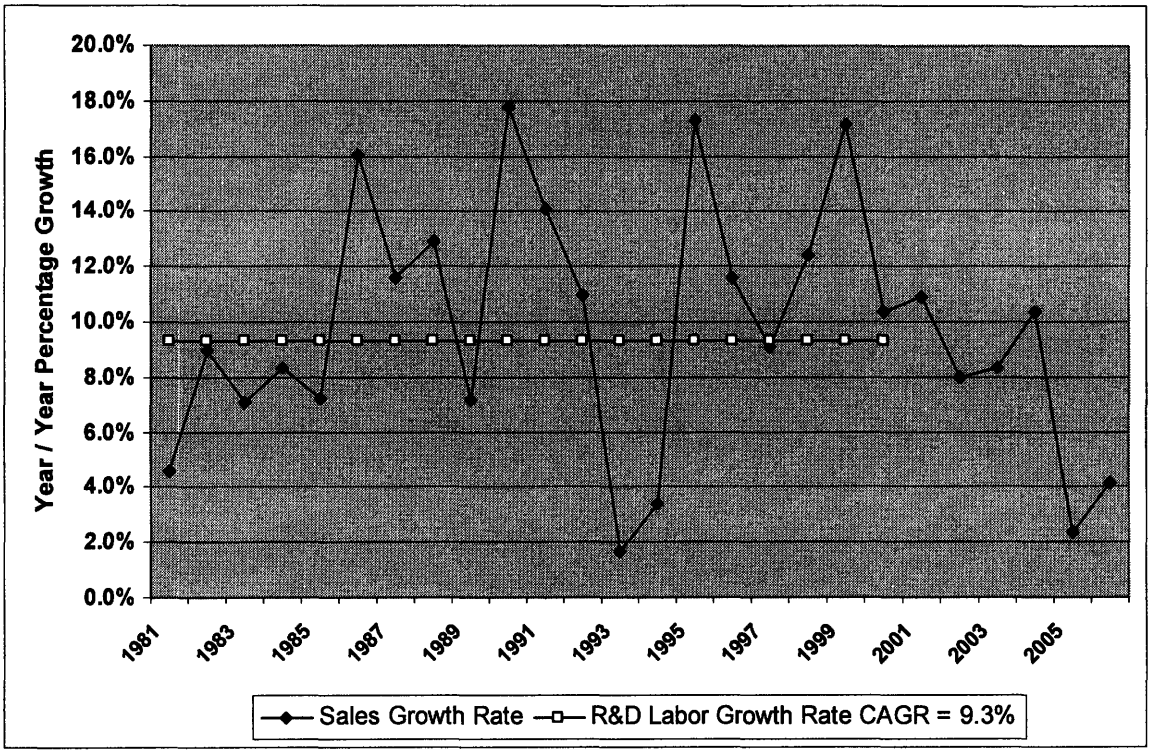
engineers in the pharmaceutical industry grew from an estimated 34,300 in 1990 to roughly 50,000 in 1999, an increase of 45.8%.[35] On an annualized basis, then, staffing levels of R&D scientists and engineers in the U.S. grew over 3.8% per year. If this growing labor pool has realized real wage growth for the past twenty years, which it has, then there is a compounding effect on R&D labor expense based on the expansion of the labor pool.

However, Big Pharma company sales and profits increased steadily over that time period, and thus have grown despite increases in R&D scientist headcount and wages and other increasing costs, such as selling, general, and administrative expenses. PhRMA member R&D spending as a percentage of sales nearly doubled from 9.3% in 1970 to 17.5% in 2006.[36] R&D expense for PhRMA members has grown at 12.5% per year from 1970 to 2006, whereas member firm sales growth has increased at 10.6% per year since 1970. So while overall R&D expenses have risen faster than sales, they have not risen so rapidly as to cause profits to decline.

DiMasi et al evaluated growth in industry R&D employment costs and reached similar conclusions.[23] They found a 7.4% annual growth rate in total R&D employment from 1980 to 2000. They found a 1.75% increase in real wages for full-time employed biological scientists from 1993 to 1999 using median annual salary data from the National Science Foundation (NSF) and adjusting for inflation (using the GDP Implicit Price Deflator). Salary data for every two years from the U.S. Office of Technology Assessment (OTA) showed similar growth in real wages; from 1981 to 1989 for biological scientists with doctorates employed business or industry was 1.77%. Thus, DiMasi et al applied the average of the two real wage growth figures, 1.76%, across the 7.4% total R&D employment growth, the result of which is a 9.3% annual increase in R&D labor costs for the period 1980 to 2000.[23] They conclude, as I have, that most of the growth in labor costs has come from labor force expansion within R&D as opposed to real wage increases. PhRMA member firm sales varied greatly over the time period but grew at a

rate exceeding 9.3% annually in eleven years and less than 9.3% annually for nine years (See Figure 10).

Figure 10. Growth Rates in Top Line Sales of PhRMA Member Firms, 1981-2006, Plotted against 9.3% Annualized Growth Rate in R&D Labor Costs, 1981-2000.



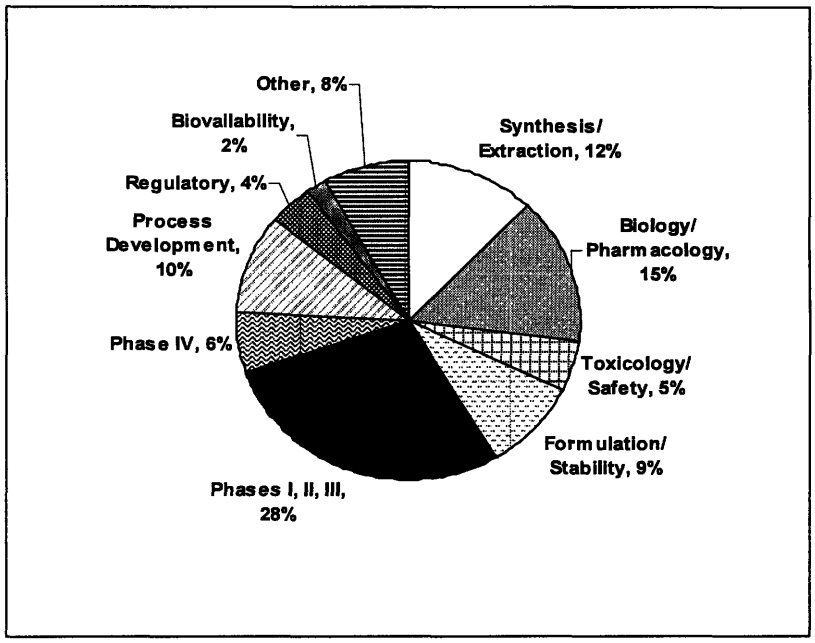
Sources: PhRMA Industry Profile 2007, DiMasi et al.[23]

Rising Clinical Costs. Clinical costs certainly warrant assessment as a driver of pharmaceutical R&D costs, since, at 28% of global pharmaceutical R&D spending (Phases I, II, and III), they represent the single biggest cost factor, as Figure 11 illustrates. While R&D labor costs have contributed to the increasing costs of drug development, clinical trial costs have been growing more rapidly. DiMasi et al found that for the period from 1984 to 1997, clinical trial costs grew at a compound annual growth rate of 11.4%.[23] Furthermore, DiMasi et al cite data that indicate a 4.8% increase in complexity of clinical trials for Phases I through III from 1992 to

2000.[23] (Complexity in this case is an index based on the mean number of medical procedures to be conducted on patients per the protocol of the clinical trial.) This added complexity translates directly into higher costs.

The costs of clinical trials have escalated over time for various reasons. Many of them pertain to inclusion of larger populations in clinical studies. In the U.S., the FDA has pushed for larger safety subject databases, a broader range of dosing studies during phase 3, more diverse populations in phase 3, inclusion of comparative safety trials, and large simple safety studies (LSSS) as an element of pre-market development.[37] The number of patients required by the FDA for clinical studies nearly doubled from 1995-2005.[37] While there has been some question as to whether longer regulatory approval times have contributed to higher clinical costs, evidence from Booth and Zemmel and others does not appear to support this hypothesis.[27]

Figure 11. Breakdown of Global Pharmaceutical R&D Costs, 2006.



Sources: PhRMA; Pharmaceutical Product Development (PPDI), 2006.

Increased R&D Spending as an Investment in Higher Future Productivity. Investment is made in R&D by businesses routinely when there is an anticipated opportunity for higher productivity at a future point in time. As we have already seen, increasing technological complexity and the advent of biotechnology have not demonstrably led to reduced R&D costs in drug development. Certain technologies, such as high throughput screening and biomarkers, offer the potential to reduce costs by enabling earlier stage, more precise identification of desired targets, thus preventing expenditures of large sums of money downstream in clinical development on candidates that may ultimately fail in clinical trials. Drug companies are buying and using these technologies aggressively. However, they have yet to demonstrate benefit in simplifying or reducing costs in the drug development process.

In the case of biomarkers, which are in the early stages of development as a technology, they are viewed currently as somewhat unreliable. The initial investment for a biomarker program is substantial, and additional challenges with biomarker technology include: the lack of standardized methods, equipment evaluation, appropriate sensitivity and specificity for selected markers, and qualification of the markers themselves. It is clear that until the pharmaceutical industry and its constituents overcome these obstacles, such technologies cannot provide maximum value to the drug development process.

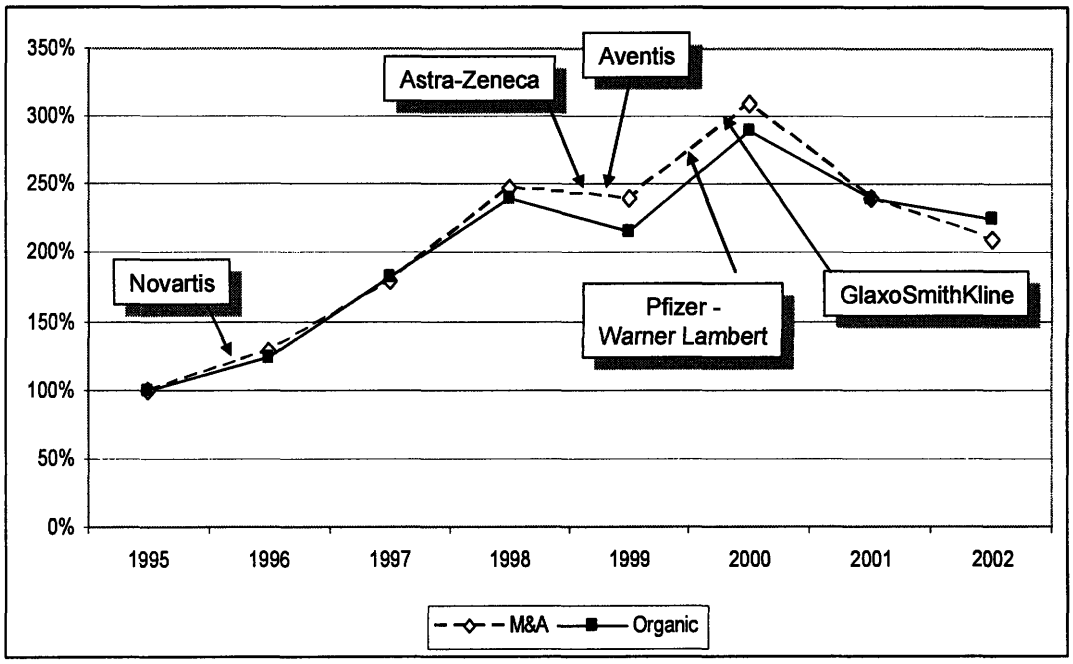
Unprecedented Big Pharma Firm Size. Big Pharma has never been bigger in terms of firm sales. Indeed, many of the Big Pharma companies, Aventis, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Pfizer, and Wyeth, are the products of mega-mergers. For a time period, it is certainly possible to wring profits out of combining organizations. Eliminating duplicative functions or organizations, rationalizing drug development portfolios, and consolidating manufacturing operations are a few of the ways in which merging companies seek to reduce operating costs of a newly merged entity. While the costs savings can climb into the billions of dollars per year, the downside of large mergers is that the new, larger company must find even more products and generate even more sales to deliver long-term profit growth to investors.

The blockbuster model, commercializing products with sales in excess of $1 billion annually, has become necessary for such enormous firms to sustain sales and profit growth and satisfy investors. Thus, products with smaller market potential are often ignored by Big Pharma firms, a development which has given rise to a class of mid-sized pharmaceutical companies. Cuatrescasas, with over twenty-five years of R&D operational and company board level experience at Glaxo Wellcome (and predecessor firm Burroughs Wellcome) and Warner-

Lambert, refers to the merger and blockbuster phenomena of Big Pharma as "merger mania" and "blockbuster mania" respectively.[29]

As to whether mergers of large pharmaceutical firms actually provide long-term benefits over companies who seek to grow organically, the consulting firm Wood Mackenzie has done some work in the area to evaluate this question. The firm looked at a basket of selected merger events as compared to companies that have grown without doing a "megamerger" (e.g., merger with a company approximately equivalent in size). The merger events were Novartis (a merger between Ciba-Geigy and Sandoz) in 1996, the Astra AB merger with Zeneca in 1998 to create AstraZeneca (the deal closed in 1999), the merger of Sanofi and Rhone Poulenc to create Aventis in 1998 (the deal closed in 1999), the Pfizer merger with Warner Lambert in 2000, and the merger of Glaxo Wellcome and SmithKline Beecham to create GlaxoSmithKline in 2000. The organic growth companies used in the comparison set were Johnson & Johnson, Eli Lilly, and Merck. Figure 12 depicts the experiences of both sets of companies.

Figure 12. Comparison of Share Price Performance of Selected Merged Big Pharma Pharmaceutical Firms and Organic Growth Big Pharma Firms, 1995-2002.



Source: Wood Mackenzie. M& A companies: Novartis, AstraZeneca, Aventis, Pfizer/Warner Lambert, and GlaxoSmithKline. Organic companies: Eli Lilly, Johnson & Johnson, and Merck.

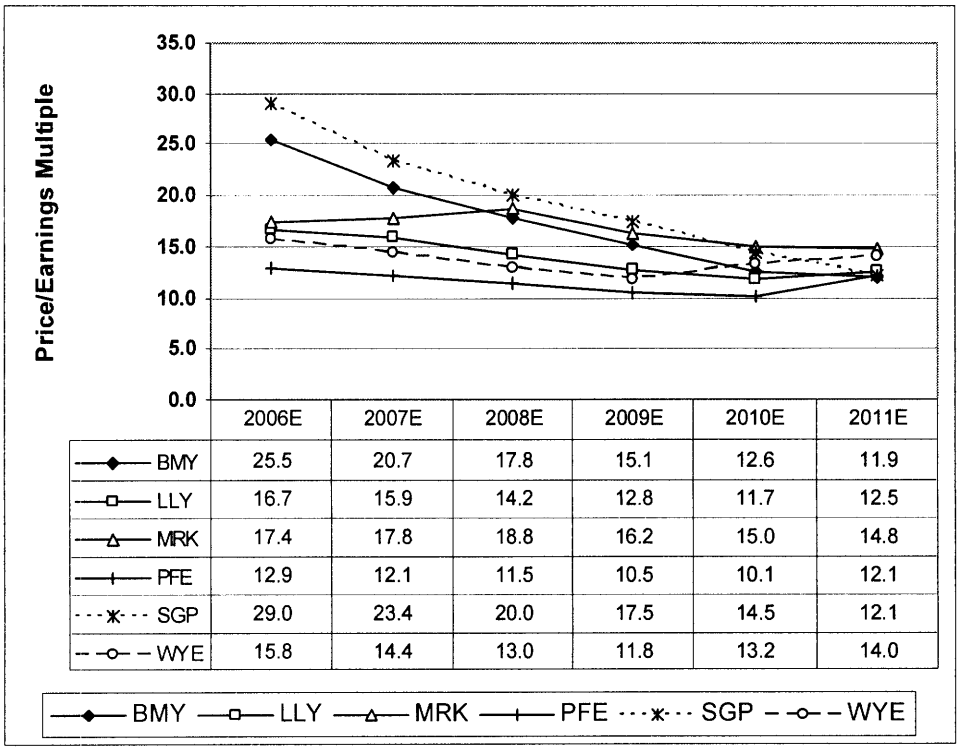
The same analysis by Wood Mackenzie found that the combined worldwide market shares of companies heading into a merger were actually higher before the merger, and declined in the two years following a merger event. This finding suggests that mergers were undertaken to "solve a growth problem."[39] While investors may have come out ahead in the near-term with respect to cost savings and organizational synergies, the merged company lost market share and was actually positioned for longer-term challenges of having to develop more blockbuster products to sustain sales and profit growth once the initial cost savings were realized.

Priorities around drug development programs within a Big Pharma firm can change every few years, often to the detriment of the firm. For example, given the fairly typical career progression of pharmaceutical executives, who may be in a role for three years before being promoted or moved elsewhere, there can be a continuous re-shifting of priorities, such that a program that

was attractive to one executive may be unattractive or undesirable to another, and the new executive in charge decides to cut the program. In a merger integration environment, pharmaceutical business leaders may seek to eliminate programs of either entity – the target firm or the acquiring firm - for a variety of reasons. Anecdotally, numerous executives I interviewed with Big Pharma backgrounds and who had worked at numerous different Big Pharma firms suggested that this dynamic of shifting priorities exists within Big Pharma. Changing priorities every three years or so obviously can have disruptive effects on drug development activities, especially given that a drug can easily require ten to twelve years of R&D effort prior to commercialization.

The Investor Outlook on Pharmaceutical Discovery and Drug Development. Investors have become painfully aware of the challenges facing Big Pharma as well. Indeed, the price-earnings trading multiples of many Big Pharma firms have declined in recent years and currently reflect relatively flat to declining expected earnings growth over the next several years, as Figure 13 illustrates. A convergence in price-earnings (PE) multiples in roughly 2011 suggests that expected growth rates of these Big Pharma firms will converge as well. PEs of the following firms are charted: Bristol-Myers Squibb (BMY), Eli Lilly (LLY), Merck (MRK), Pfizer (PFE), Schering-Plough (SGP), and Wyeth (WYE).

Figure 13. Price to Earnings Multiples of Selected Big Pharma Firms based on Projected Earnings, 2006E-2011E.



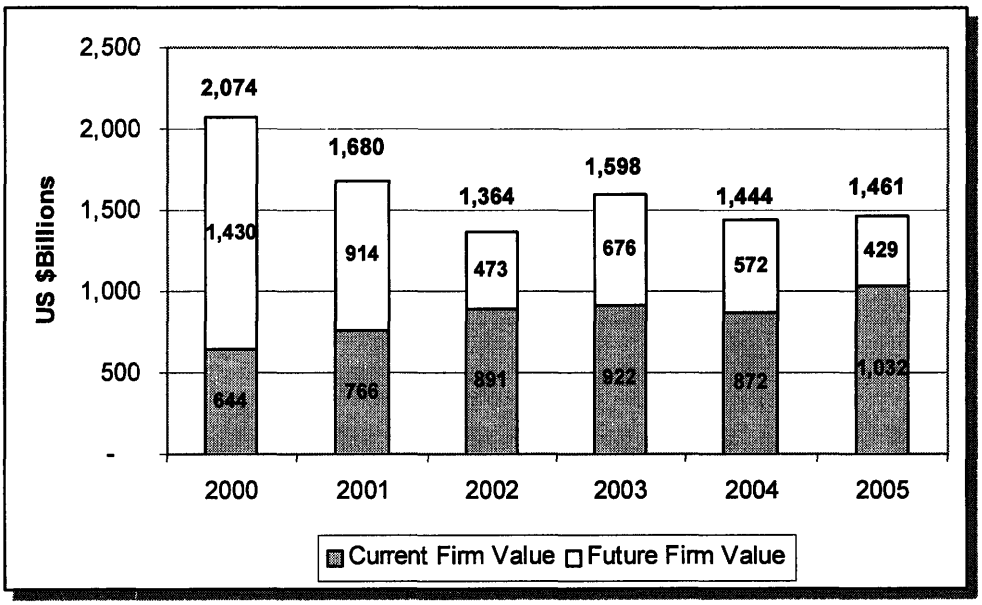
	2006E	2007E	2008E	2009E	2010E	2011E
BMY	25.5	20.7	17.8	15.1	12.6	11.9
LLY	16.7	15.9	14.2	12.8	11.7	12.5
MRK	17.4	17.8	18.8	16.2	15.0	14.8
PFE	12.9	12.1	11.5	10.5	10.1	12.1
SGP	29.0	23.4	20.0	17.5	14.5	12.1
WYE	15.8	14.4	13.0	11.8	13.2	14.0

Source: Goldman Sachs Equity Research.

Historic valuation analysis of fourteen Big Pharma firms by Accenture shows clearly that investors have shifted valuation emphasis to a company's cash flow from ongoing operations and away from its expected future value from operations.[40] As Figure 14 shows, since 2000, investors have become much less risk tolerant as they try to decipher Big Pharma's prospects for growth based on future product launches. Given increasingly less visibility to firms' future earnings, investors voted with their feet. Over $500 billion of market value was lost from 2000-2005 by the fourteen Big Pharma firms in the Accenture study. In addition, we see compound annual growth in firm current value of 9.9% for the 2000-2005 period, but a decline of 21.0% in future firm value for this basket of companies during the period. Recent events unrelated to

product patent expirations, such as Merck's 2004 withdrawal of Vioxx due to increased health risks to patients, have no doubt had some effect on the outlook for Big Pharma as well.

Figure 14. Valuation of Fourteen Big Pharma Firms, 2000-2005.



Current Firm Value CAGR: 9.9%
Future Firm Value CAGR: -21.0%
Expected Firm Value CAGR: -7.0%

Firms included:

- Abbott Laboratories
- Amgen
- Astra Zeneca
- Aventis
- Bristol-Myers Squibb
- Eli Lilly
- GlaxoSmithKline
- Johnson & Johnson
- Merck
- Novartis
- Pfizer
- Roche
- Schering-Plough
- Wyeth

Sources: Accenture,[40] S&P 500.

Clearly, then, investors have become attuned to the challenging growth environment facing Big Pharma. As we have seen, investors are clearly expecting that this environment will intensify over the next few years. The recent shifts in market valuations of Big Pharma companies demonstrates that investors have developed greater understanding of the reduced earnings

visibility and commensurately high risks associated with drug development faced by Big Pharma during this time frame. While it is possible that Big Pharma managements have been complicit in keeping Big Pharma valuations high by touting perhaps unrealistic growth expectations to Wall Street, most knowledgeable investors have a full understanding of the drug development process, as well as recognition for the patent expiration environment, which will prove especially challenging in the 2010-2013 time frame.

Though biotechnology may not have made drug development cheaper, as Pisano suggests,[34] and the same could be said of genomic medicine up to this point, Danzon suggests that biotechnology (the term "biotechnology" here appears to be used as a general reference to smaller biotechnology and pharmaceutical companies) has "transformed the nature of drug discovery and the structure of the industry" in that "increasingly, new drugs originate with in small firms, which often outlicense their products to more experienced firms for later stage drug development, regulatory review, and commercialization."[41]

The Decline of the Role of the Champion. A recent report by Cambridge Healthtech Associates observes that "hierarchical organizations have the advantage of encouraging the emergence of product champions, who (if their views turn out to be correct) can turn the whole company around."[42] Given the size of most Big Pharma firms today, however, "they have moved inexorably towards matrix structures."[43] The implication here is that matrix structures are emblematic of the large, unwieldy, often centralized bureaucracies that exist within many Big Pharma companies. However, I would make a distinction between organizational configuration (e.g., matrix or hierarchy) and centralization or decentralization.

In an era of pharmaceutical mega-mergers, Cuatrecasas notes that people are discouraged by the risk of being wrong.[19] Some Big Pharma firms such as Novartis and Johnson & Johnson

(J&J), are viewed as successful even in an era of ever larger companies, mainly because of their willingness to pursue different, decentralized organizational approaches.[43] In the case of Novartis, it has organized into a series of fairly integrated, standalone, specialty business units, such as oncology, primary care, and more mature brands. J&J has long been known for its decentralized operating structure, which is evidenced by its different pharmaceutical businesses: Alza, Centocor, Janssen, Ortho-McNeil, and Scios, to name a few.

Big Pharma Response to Recent Pressures

It appears that managements of Big Pharma firms clearly understand the pressures they face with respect to new product development and commercialization, as evidenced by stepped up R&D investment activity and a notable increasing trend in partnering activity over the past ten years (I have cited numerous figures that describe the Big Pharma partnering trend previously). The bottom line is that Big Pharma management realize that their firms are economically challenged. While this realization may not prevent future merger activity as a temporary way of addressing this challenge, a review of the recent literature and my interviews suggest that Big Pharma executives understand that new ways of doing business, as opposed to merging with other firms, are required for long-term success.

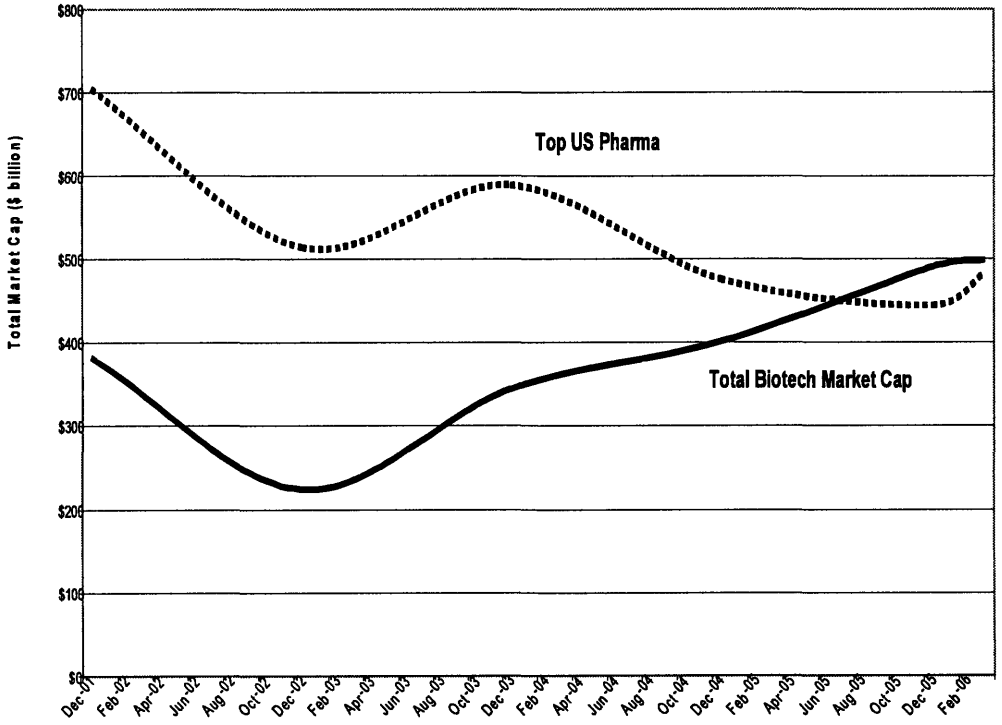
Is Big Pharma's Loss Small Pharma's Gain?

There is some evidence to suggest that Big Pharma's loss in market valuation has translated into gains for Small Pharma. Figure 15 depicts the change in recent market capitalization between leading U.S. pharmaceutical companies (the index consists of Bristol-Myers Squibb, Eli

Lilly, Johnson & Johnson, Merck, and Pfizer) and all biotechnology companies (including Amgen and Genentech). For years 2002 through 2005 there is an appreciable difference in the performance of these indices, particularly starting in the last quarter of 2003. While movement in market capitalization – upward or downward – of a handful of the larger biotechnology companies, such as Amgen and Genentech, can have a pronounced effect on the index, an increase of over $250 billion is nonetheless dramatic.

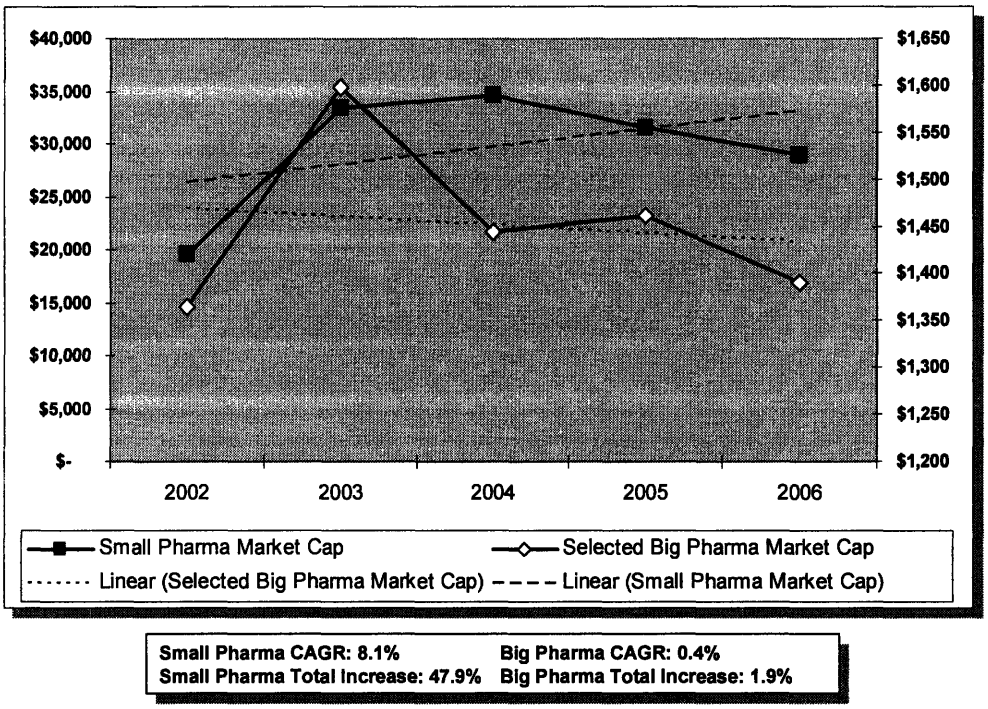
Figure 16 looks at the universe of Small Pharma companies relevant to this thesis and compares their market capitalization to those of the fourteen selected Big Pharma companies whose market capitalizations were illustrated in Figure 14. Market capitalizations of sixty Small Pharma companies in all were used. The companies had to be publicly traded in 2002 and independent for the 2002-2006 time frame for this analysis.

Figure 15. Market Capitalizations of Top U.S. Pharma Companies and All Biotechnology Companies, 2002-2005.



Source: Burrill & Company.

Figure 16. Market Capitalizations of Small Pharma Firms (n=60) (fist Y axis) and Fourteen Big Pharma Firms (second Y axis), 2002-2006. ($Millions)



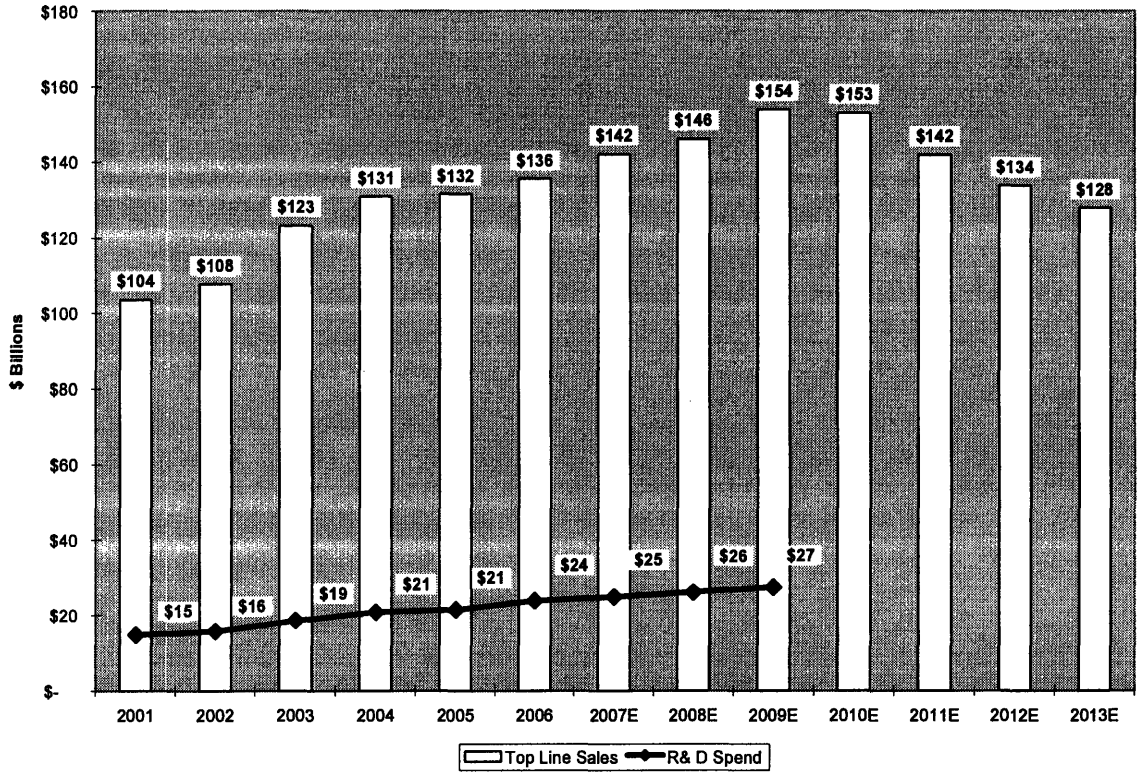
Source: Author analysis of historic stock price data from Hemscott Americas.

The Looming Challenge for Big Pharma in Sustaining R&D

The question of whether R&D investment in all areas can or will be sustained truly becomes relevant in a time frame in which Big Pharma is adversely impacted by patent expirations, as it will be in the years 2010-2013. A look at a basket of the Big Pharma companies is illustrative. Figure 17 shows the aggregate historic and projected sales (2001-2013) and historic and projected R&D expenditures (2001-2009) for six companies that will be significantly impacted by patent expirations in the 2010-2013 time frame: Bristol-Myers Squibb, Eli Lilly, Merck, Pfizer, Schering-Plough, and Wyeth. Will these Big Pharma companies continue to expand their R&D budgets beyond 2009 when their sales will be negatively impacted by patent expirations?

Historically, Big Pharma companies have either spent less in R&D or only slightly more than the prior year in a year of sales decline. Several companies, such as Bristol-Myers Squibb and Pfizer, are at high risk of experiencing several consecutive years of sales declines in the 2010-2013 period.

Figure 17. Historic and Projected Sales (2001-2013) and R&D Expenditure (2001-2009) for Six Big Pharma Companies.
(Bristol-Myers Squibb, Eli Lilly, Merck, Pfizer, Schering-Plough, Wyeth)

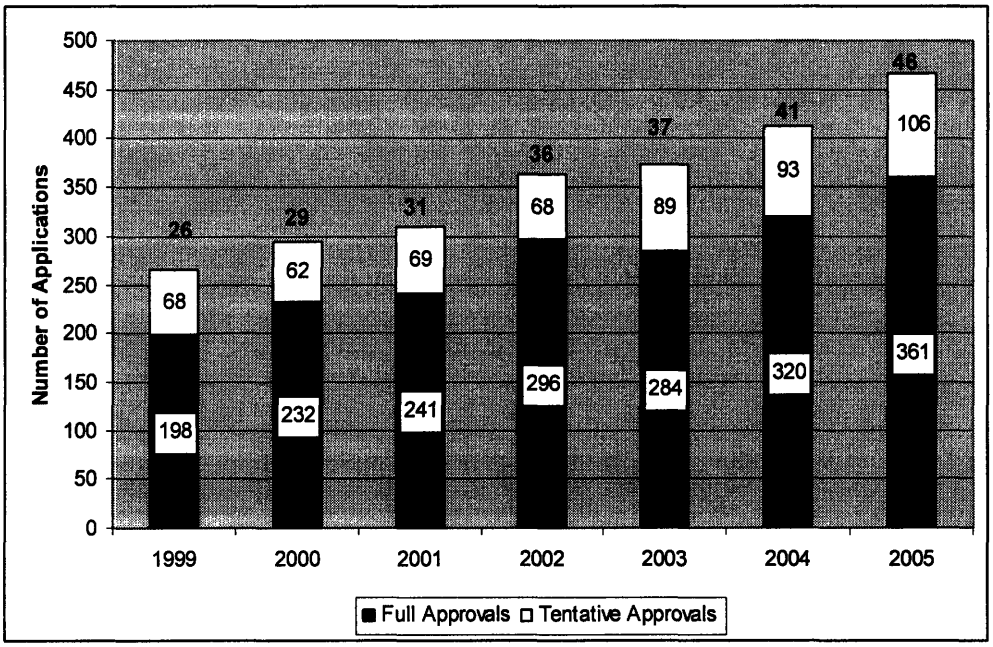


Sources: Company 10-K Filings, 2001-2006; Goldman Sachs equity research; author projections.

Welcome to Niagara Falls: The Impending Wave of Drug Patent Expirations

Clearly the wave of patent expirations on Big Pharma drug products is affecting Big Pharma economically, and generic drug companies have been the beneficiaries. As illustrated in Figure 18, the number of generic approvals in the U.S. has soared in recent years, and is expected to continue to do so as many blockbuster products go off patent. Globally, 74 major drugs are projected to go off patent from 2007-2011.[44]

Figure 18. FDA Generic Drug Approvals, 1999-2005.[33]



Within the U.S., sales of drugs marketed by U.S. companies during the 2006-2013 time frame will total over $75 billion. Figure 19 details the timing and projected prior year sales of these products.

Figure 19. Historic and Estimated Sales of Drug Products Going off Patent in the U.S. by Year of Patent Expiration, 2006-2013E. ($ Millions)

2006		2007E		2008E		2009E	
Drug/Company	Prior Year Sales	Drug/Company	Prior Year Sales	Drug/Company	Prior Year Sales	Drug/Company	Prior Year Sales
Pravachol/BMY	$ 2,300	Norvasc/PFE	$ 4,700	Zerit/BMY	$ 150	Clarinex/SGP	$ 650
Zocor/MRK	$ 4,400	Zyrtec/PFE	$ 1,600	Fosamax/MRK	$ 2,800		
Proscar/MRK	$ 750	Elocon/SGP	$ 150	Trusopt/Cosopt/MRK	$ 800		
Zoloft/PFE	$ 3,300			Camptosar/PFE	$ 900		
				Altace/ WYE/KG	$ 500		
Total	**$ 10,750**		**$ 6,450**		**$ 5,150**		**$ 650**

2010E		2011E		21012E		2013E	
Drug/Company	Prior Year Sales	Drug/Company	Prior Year Sales	Drug/Company	Prior Year Sales	Drug/Company	Prior Year Sales
Baraclude/BMY	$ 170	Zyprexa/LLY	$ 4,100	Avapro/Avalide/BMY	$ 1,700	Sustiva/BMY	$ 1,100
Cozaar/Hyzaar/MRK	$ 3,200	Zolinza/MRK	$ 200	Plavix/BMY	$ 5,600	Humalog/LLY	$ 1,500
Aricept/PFE	$ 400	Lipitor/PFE	$ 11,000	Singulair/MRK	$ 5,100	Gemzar/LLY	$ 1,600
Effexor XR/WYE	$ 2,900	Xalatan/PFE	$ 1,700	Viagra/PFE	$ 2,100	Emend/MRK	$ 350
Protnoix/WYE	$ 2,100	Caduet/PFE	$ 1,000	Detrol/PFE	$ 800	Propecia/MRK	$ 450
				Geodon/PFE	$ 400	Celebrex/PFE	$ 2,600
						Lyrica/PFE	$ 3,400
						Rapamune/WYE	$ 550
						Tygacil/WYE	$ 400
Total	**$ 8,770**		**$ 18,000**		**$ 15,700**		**$ 11,950**

Total 2006-2013E	**$ 77,420**

Sources: Company Data, Orange Book, Goldman Sachs Research estimates.

Ticker Symbols listed in this chart:
BMY: Bristol-Myers Squibb
MRK: Merck
PFE: Pfizer
SGP: Schering-Plough
WYE: Wyeth
KG: King Pharmaceuticals
LLY: Eli Lilly.

What Has Changed and What Hasn't in Global Pharmaceutical R&D

Clearly, some dynamics of drug development have changed within the past few years. Investment capital has shifted away from Big Pharma and into smaller companies – a signal from the market that investors view their product prospects as more compelling. Nonetheless, on the whole, Big Pharma continues to plow more capital into R&D than ever before. More tools are available to aid in numerous aspects of drug discovery and drug development, although, as we have discussed, their availability has not necessarily made the process more efficient or easier. The reliance of Big Pharma on startup pharmaceutical and biotechnology companies as new sources of products and technologies has become more pronounced and will likely accelerate. The challenge of product patent expirations faced by Big Pharma over the next decade is unprecedented in its magnitude.

Moving or establishing certain functions or operations overseas has become commonplace as Big Pharma firms seek to outsource certain activities of their businesses. Conducting of clinical trials is one example of this growing trend. Cockburn found that from 2002-2006, the share of "traditional" countries where clinical trials are conducted (including Australia, the United States, countries in Western Europe, and New Zealand) declined from 92.4% to 82.0%.[45] Another example is the exporting of contract research services to locations such as India, eastern Europe, and elsewhere. Certain economies, specifically those of India and China, are seeing higher levels of in-house product oriented R&D investment than in the past.

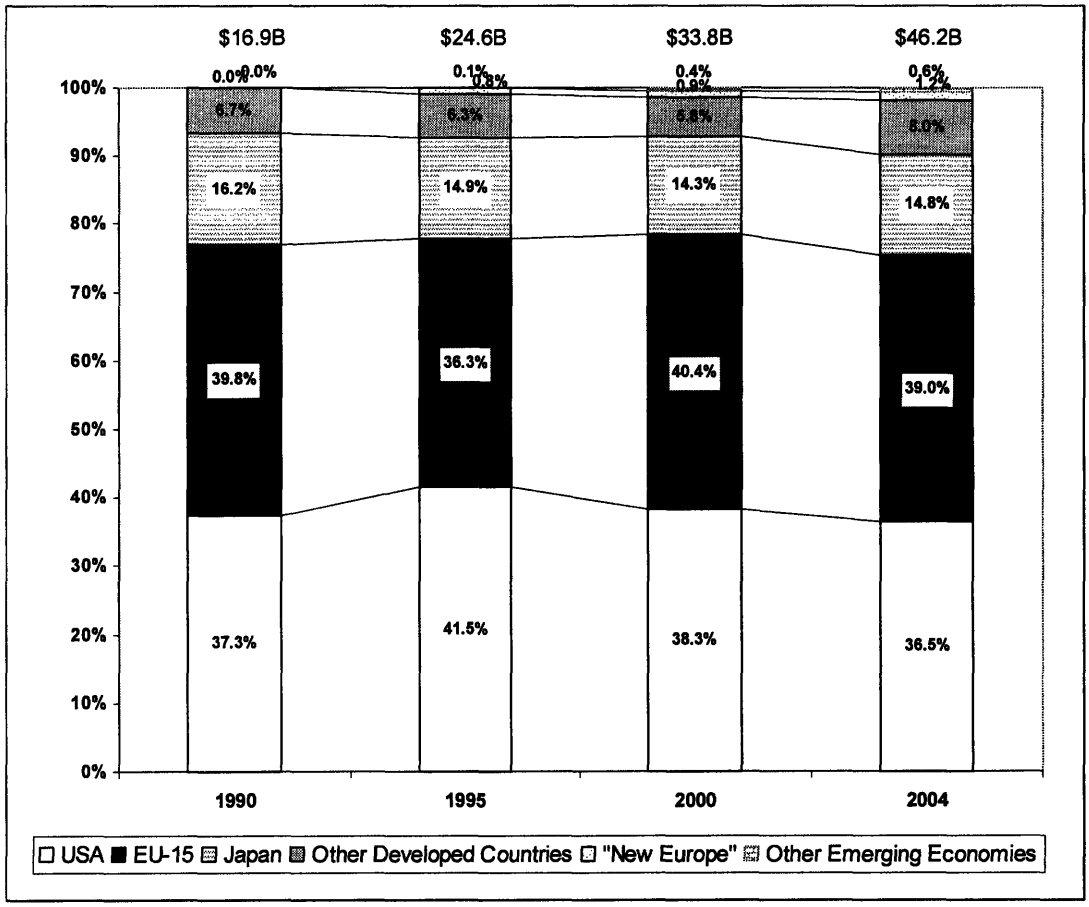
So what hasn't changed? Despite recent efforts of governments and municipalities around the world to compete in establishing life science knowledge centers, those that have supported pharmaceutical innovation in the past ten to twenty years remain largely the same. Cockburn's findings suggest that the landscape of "innovative activity," in which R&D is the most essential

component, is highly concentrated geographically, wherein localized "knowledge spillovers," robust patent protection systems, and favorable governmental policies - both national and regional (ranging from drug price regulation to tax incentives for companies to locate in a given geography) – have significant influence.[45] "Clusters" where pharmaceutical R&D activity is aggregated seem to be confined to a relatively few geographic metropolitan statistical areas: Boston; New York/New Jersey/Connecticut; Philadelphia; Research Triangle in North Carolina; San Diego; the San Francisco Bay Area; the Rhine Valley; suburban London; Stockholm, Sweden; and Tokyo/Kansei. Other such clusters are certainly emerging around the world and are vying to attract investment, but historically the few listed above have been the generally recognized pharmaceutical R&D centers.

Spending by geography has also remained largely consistent. The trend in overall pharmaceutical global R&D investment across geography, in line with that observed in the PhRMA data, shows a substantial increase in the total amount of capital invested in R&D since 1990. Indeed, from 1990 to 2004, according to the Organization for Economic Cooperation and Development (OECD), the amount of business expenditure in R&D (BERD) in pharmaceuticals nearly tripled from roughly $17 billion to over $46 billion.[45]

However, the shares of that investment by geography have remained fairly constant over time. Figure 20 illustrates this consistency in terms of percentage of global pharmaceutical R&D spending that each major geographic region represents. Pharmaceutical R&D spending in the U.S. and the EU-15 nations has consistently stayed at around the 40% level during the time frame, while spending in Japan has also remained consistent at roughly 15%. Emerging economies and formerly Soviet bloc countries represent a small but increasing fraction of total pharmaceutical R&D spending.

Figure 20. Business Expenditure in R&D (BERD) by Geographic Region, 1990-2004.[45]



Note: All figures determined on the basis of purchasing power parity (PPP) exchange rates.

Towards Increased Licensing Activity and Collaboration

Given the complexities of new drug discovery and development, as well as the patent expiry landscape, it is not surprising that Big Pharma has struck more licensing deals recently. Indeed, such deals are often partnerships that can encompass much more than simply the licensing of new products; they involve collaborating in numerous parts of the drug development continuum, including basic science, discovery, drug target validation strategies, genetics, high-throughput

screening, pharmacogenomics, protein characterization, and proteomics. But while the need is great for Big Pharma companies in particular to identify new products outside of their own R&D groups, they remain keenly aware of their own competencies and capabilities. Such awareness most likely has some influence on Big Pharma firms' licensing decisions, one of the considerations that gave rise to the hypothesis for this thesis.

Chapter 2. Hypothesis Development and Methods

Given the findings of studies summarized earlier in Figure 2, which suggest that Big Pharma realizes better rates of clinical and financial success on projects that are in-licensed compared to those developed internally, this thesis seeks to explore the hypothesis that there is something different in the way decisions are made in drug development projects in Small Pharma companies compared to those in Big Pharma on the basis of whether projects are developed internally or are in-licensed from outside the firm. Are there differences in the perceptions between executives at Big Pharma and Small Pharma firms about how their firms make project decisions on the basis of whether a program is developed internally or is licensed in from outside the firm? Obtaining a comparison of how executives perceived the drug development decision making process within their firms for each type of project (internally developed versus in-licensed from outside the firm) was desirable, then, for purposes of this thesis.

The Survey

I developed a survey with the intent of capturing various attributes about interviewees' perceptions about the decision making process and inputs in the drug development decisions of their companies for specific projects (See Exhibit 3 for the interview questionnaire). The survey was designed for two types of interviewees: (1) those with experience working for Big Pharma companies and (2) those with experience working for Small Pharma companies. Interviewee perception of their firm's project management based on specific type of project is the unit of analysis. Thus, the questionnaire asked a series of questions based on these executives' perceptions about how projects were or are managed in their organizations.

I wanted to understand how prioritization happens within each type of firm and identify the major functional players engaged in the process. I also sought to capture the resources, tools, and inputs that interviewees identified as important contributors to the drug development decision making process within their firms. I hoped to understand from the perception of interviewees who they perceived as the most influential people (in terms of title) within the organization and the most important inputs into the drug development decision making process. Moving from the project level of analysis to the organizational level, I also asked interviewees questions about their entire project portfolio to provide more insights into the decision making context. Specifically, I asked interviewees how many projects their companies are currently developing or were developing at the time they were last with the firm, and the percentage of internally-developed projects versus in-licensed projects.

The critical section of the questionnaire for purposes of statistical analysis related to three key decision points:

- Lead selection/optimization (settling on a lead candidate and choosing to optimize it)
- The decision to move a project from Pre-Clinical testing into Phase I human clinical trials
- The decision to move a project from Phase I human clinical trials into Phase II human clinical trials.

I asked a series of questions around each of these decision points pertaining to: (1) the decision making process, (2) the number or types of decision inputs, (3) prioritization, and (4) the metrics used to evaluate a drug development project. Each of these questions was asked with respect to whether there were qualitative or quantitative differences on the basis of whether the program originated inside or outside the company. Lastly, I asked interviewees about their perceptions about the newness of a technology (e.g., molecule, protein, etc.) and whether its perceived newness has a positive, negative, or neutral influence on the company's interest level in pursuing its development.

A few interviewees made the observation that a decision to move a project into Phase I is a decision to move it into Phase II. Since a Phase I study is conducted simply to establish a drug's safety, one really cannot learn anything about efficacy until and unless assessing it in a Phase II trial. For a drug whose safety is established in a Phase I clinical trial, it is indeed true that the next step is to take it into Phase II clinical trials. However, not all drugs make it through Phase I. Furthermore, especially in an era of sophisticated tools, such as high-throughput screening and combinatorial chemistry, firms must often grapple with the question of which candidates to take into Phase II, and at what dose(s) and formulation, etc.

Testing the Hypothesis

I conducted interviews with 20 people who had worked at 26 different Big Pharma companies. I considered each Big Pharma experience to be discreet for purposes of data collection (n=25). I conducted interviews with 17 people who had worked at 12 different Small Pharma companies. I considered each Small Pharma experience to be discreet for purposes of data collection (n=19). These people worked in a wide variety of roles within their respective firms. Figure 21 lists the different roles interviewees have or had within these organizations. Figure 22 lists the numbers of interviewees from each function within Big Pharma and Small Pharma companies. Collectively, Big Pharma interviewees had 233 years of experience with their firms, and Small Pharma interviewees had 84 years of experience in total. Since not all interviewees were able to answer every question, the total number of responses is given in the results section.

There were five and two interviewees, respectively, in the Big Pharma and Small Pharma data sets who had experience at two firms within the company data set (e.g., Big Pharma or Small Pharma). Thus, I conducted two interviews with these people. To assess for possible biasing

effects from such people in the data, in addition to running statistical analysis on all interviewee data, I ran all statistical analyses on interviewee data sets including data from these individuals based only on their most recent company experience, thus eliminating one of their interviews. In doing so, all of the results presented below remain consistent and statistically significant ($p<0.05$), albeit at slightly lower p-values and chi-square values.

Figure 21. Functional Roles of Big and Small Pharma Interviewees in Their Organizations.

Business Development	Regulatory Affairs
Executive Management (Chairman, CEO*, CFO**, COO***)	Research & Development (R&D)****
	Sales
Finance	Strategic Planning
Legal	Supply Chain Management
Market Research	Technical Operations (Manufacturing)
Marketing	

Notes:
* CEO: chief executive officer
** CFO: chief financial officer
*** COO: chief operating officer
**** R&D included a variety of roles: bench chemistry, chief scientific officer (CSO), discovery, head (vice president) of R&D, and lead development & optimization.

Figure 22. Number of Big and Small Pharma Interviewees by Function.

Functional Role	Big Pharma	Small Pharma
Business Development	4	6
Executive Management	2	4
Finance	0	2
Legal	0	1
Market Research	1	0
Marketing	5	1
Regulatory Affairs	0	1
Research & Development	8	4
Sales	1	0
Strategic Planning	1	0
Supply Chain Management	1	0
Technical Operations	2	0
Total	25	19

I used the Fisher's exact test as well as the Yates' chi-square (X^2) test to test the null versus the alternative hypothesis for a series of questions in my interview survey. The rationale for using these two tests is that the sample size was not always large enough (e.g., $n<10$) with respect to certain responses to the surveys to perform the standard chi-square test. When this situation occurs, a chi-square test may not be appropriate, since the normal approximation to the binomial distribution may not be valid. Such is the case especially for small samples. Interviewee responses to questions about programs on the basis of whether they were developed internally or were licensed in from outside the firm were the variables measured. Additional information on Fisher's exact test and Yates' chi-square test is included in Exhibit 6 in Chapter 5.

Methods

For the Big Pharma data set, I used those pharmaceutical firms whose R&D budgets placed them in the top 100 companies worldwide in terms of R&D spend for the years 2000-2004 as identified by Institute of Electrical and Electronics Engineers (IEEE). This set of companies is listed in Exhibit 1 in Chapter 5. For Small Pharma, I identified those publicly traded U.S. and Canadian firms with market capitalizations of less than $5 billion as of December 29, 2006, that are focused in cancer and autoimmune, cardiovascular, and infectious diseases based on number of projects in development. I identified people who either had worked or were working at these firms. Interviewees came from a variety of functional areas, as has been described. I conducted interviews 25 and 19 interviews with individuals with experience at Big Pharma and Small Pharma firms, respectively. I conducted interviews in person when possible or via telephone.

The Hypothesis

For purposes of statistical analysis, the hypotheses are as follows:

Null hypothesis (H_o): There is no difference qualitatively or quantitatively in the way the company treats drug development projects on the basis of whether the project originated inside or outside the company [$p_1 = p_2$].

Alternative hypothesis (H_1): There is a difference qualitatively or quantitatively in the way the company treats drug development projects on the basis of whether the project originated inside or outside the company [$p_1 \neq p_2$].

Interviewee perception of its treatment of drug development projects is the variable tested. For questions pertaining to in-licensing, Small Pharma interviewees were instructed to consider initial programs that may have been in-licensed as the basis for company formation as internally developed projects, since these projects constituted the basis for company formation. In cases where Small Pharma firms had not in-licensed products, interviewees were asked to consider how the assessment process of external candidates worked, or how they believed it would work. Only 1 of 19 Small Pharma interviewees indicated that their firm had not at least evaluated external opportunities with the possible intent of in-licensing them.

Results

Exhibits 6 and 7 summarize the data collected in the interviews for Big Pharma and Small Pharma respectively.

Years of Experience with Firm. With respect to Big Pharma interviewees, the mean experience time with a Big Pharma firm was 9 years (range 1-26, median 7). The mean experience time for Small Pharma interviewees was 5 years (rage 0.5-13, median 3). Figure 23 summarizes the results. A high proportion of all interviewees (both Big Pharma and Small Pharma, n = 45), 42 out of 45, or 93%, reported that they had exposure to the decision making process for drug development projects at the highest possible levels within their organizations. Such exposure helped because it provided a basis for comparison for individuals who may have had responsibility for a given project to compare to the way in which other projects were managed. Additionally, for those who did not necessarily have project management responsibility, such exposure provided them with insight into how decision making across projects was managed.

Figure 23. Interviewee Length of Experience with Big Pharma Firms (n=25) and Small Pharma Firms (n=19).

	Big Pharma (n=25)	Small Pharma (n=19)
High	26	13
Low	1	0.5
Mean	9	5.0
Median	7	3

Estimated Number of Projects in Development. I asked interviewees to estimate the number of projects in development within their firms either currently or when they were last with the firm. The mean estimated number of drug development projects by interviewees (n=25) within Big Pharma firms was 63 (range, 28-170, median 55). In contrast, for Small Pharma interviewees (n=19), the mean estimated number of projects in development was 6 (range 1-16, median 4). These data are summarized in Figure 27 below.

Figure 24. Estimated Number of Drug Development Projects by Firm Type [Big Pharma (n=25), Small Pharma (n=19)].

	Big Pharma (n=25)	Small Pharma (n=19)
High	170	16
Low	28	1
Mean	63	6
Median	55	4

Estimated Percentages of Projects Developed Internally versus Externally. Within the Big Pharma interviewee set (n=25), the mean estimated percentage of projects internally developed was 60% (range 30-90%, median 58%). The mean estimated percentage of projects sourced externally (i.e., in-licensed from outside the firm) was 40% (range 10-70%, median 42%). These data are illustrated in Figure 25 below.

Within the Small Pharma interviewee set (n=19), the mean estimated percentage of projects internally developed was 100.0% (range 0-100%, median 80%). The mean estimated percentage of projects sourced externally was 20% (range 0-100%, median 20%).

Figure 25. Big Pharma (n=25) and Small Pharma (n=19) Interviewee Estimated Percentages of Company Projects Sourced Internally and Externally.

	Big Pharma		Small Pharma	
	Internally Developed	Externally Sourced	Internally Developed	Externally Sourced
High	90%	70%	100%	100%
Low	30%	10%	0%	0%
Mean	60%	40%	80%	20%
Median	58%	42%	100%	0%

With respect to testing the hypothesis at the three drug development decision points discussed previously, figures 26 -31 present the results with responses of "Don't Know" or "Not Applicable" omitted. Figure 26 presents the interviewee results related to lead optimization/selection for the

interview question: "For each of the three decision points above (Lead Optimization/Selection), does the decision making process for a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company? Based on these results, I rejected the null hypothesis that Big Pharma and Small Pharma use the same decision making process in lead selection/optimization with respect to whether it originated inside or outside the company ($p<0.05$).

Figure 26. Assessing the Decision Making Process – Lead Optimization/Selection.[46, 47]

	Big Pharma Executives	Small Pharma Executives	Total
Yes	21	7	28
No	2	11	13
Total	23	18	41

Fisher's exact test: $p = 0.0005$.

Yates' chi-square value: $X^2 = 10.5$ with p value: $p = 0.001$.

Using $p = 0.05$ as the cutoff point, reject H_o ($p_1 = p_2$) in favor of H_1 ($p_1 \neq p_2$).

Figure 27 presents the interviewee results about transitioning from pre-clinical to Phase I for the interview question: "For each of the three decision points above (transitioning a project from pre-clinical animal studies to phase 1 human clinical studies), does the decision making process for a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company?" Based on these results, I rejected the null hypothesis that Big Pharma and Small Pharma use the same decision making process in transitioning a project from pre-clinical to Phase I development with respect to whether it originated inside or outside the company ($p<0.05$).

Figure 27. Assessing the Decision Making Process – Transitioning a Project from Pre-Clinical to Phase I.[46, 47]

	Big Pharma Executives	Small Pharma Executives	Total
Yes	20	6	26
No	3	12	15
Total	23	18	41

Fisher's exact test: p = 0.0006.

Yates' chi-square value: $X^2 = 10.3$ with p value: p = 0.001.

Using p = 0.05 as the cutoff point, reject H_o ($p_1 = p_2$) in favor of H_1 ($p_1 \neq p_2$).

Figure 28 presents the interviewee results about transitioning a project from Phase I to Phase II for the interview question: "For each of the three decision points above (the decision to move a project from phase I human clinical trials into phase II human clinical trials), does the decision making process for a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company?" Based on these results, I rejected the null hypothesis that Big Pharma and Small Pharma use the same decision making process in transitioning a project from pre-clinical to Phase I development with respect to whether it originated inside or outside the company ($p < 0.05$).

Figure 28. Assessing the Decision Making Process – Transitioning a Project from Phase I to Phase II.[46, 47]

	Big Pharma Executives	Small Pharma Executives	Total
Yes	21	6	27
No	2	10	12
Total	23	16	39

Fisher's exact test: $p = 0.0005$.

Yates' chi-square value: $X^2 = 10.4$ with p value: $p = 0.001$.

Using $p = 0.05$ as the cutoff point, reject H_0 ($p_1 = p_2$) in favor of H_1 ($p_1 \neq p_2$).

Interviewee responses to the questions behind Figures 26 through 28 reveal perspective on how executives from both Big Pharma and Small Pharma view decision making around drug development projects. A Big Pharma executive summarized the Big Pharma's productivity challenge in much the same way that industry analysts view it: "For (Big Pharma) companies, their discovery efforts are not as successful as they have been in the past." Others affirmed that some Big Pharma companies set a higher bar for making a decision to in-license projects than they do for internally developed projects. According to a long-time Big Pharma executive: "(The Big Pharma company) was much more conservative in bringing products in from the outside." Said another: "I know the bar was much higher for bringing projects in from the outside."

As the data from Figures 26 through 28 shows, a majority of Small Pharma executives see no qualitative or quantitative difference in the ways in which their firms make decisions around three key drug development decision points. One Small Pharma executive spoke for many in saying: "The decision making process is no different. It is transparent." Many Small Pharma interviewees also expressed a desire for more market information on any project – whether

internal or external. Said one Small Pharma executive: "There is always more hunger for data around the market opportunity."

Big Pharma executives cited a preference to develop a project within their firms as opposed to going outside to in-license it. According to one Big Pharma executive: "It's harder to decide to pursue early stage (in-licensing) programs if we haven't convinced ourselves we can't do it." In contrast, a Small Pharma company executive described the opportunistic nature of going outside to in-license products: "For us, it was opportunistically driven to a large extent."

Figure 29 presents the interviewee results about number or types of decision inputs on the basis of internal or external development for the interview question: "For each of the three decision points above, does the number or types of decision inputs the company uses differ qualitatively or quantitatively based on whether the product or program was developed internally or externally?" Based on these results, I rejected the null hypothesis that Big Pharma and Small Pharma use the same number or types of decision inputs qualitatively or quantitatively based on whether a project was developed internally or externally ($p<0.05$).

Figure 29. Assessing Differences in Numbers or Types of Decision Inputs of a Drug Development Project on the Basis of Whether It Was Developed Internally or Externally.[46, 47]

	Big Pharma Executives	Small Pharma Executives	Total
Yes	19	7	26
No	2	12	14
Total	21	19	40

Fisher's exact test: $p = 0.0007$.

Yates' chi-square value: $X^2 = 10.4$ with p value: $p = 0.001$.

Using $p = 0.05$ as the cutoff point, reject H_o ($p_1 = p_2$) in favor of H_1 ($p_1 \neq p_2$).

A Big Pharma executive observed: "There are many more people involved in product acquisitions and licensing deals. They consume more resources in terms of cost, organizational effort, and impact." In contrast, a majority of Small Pharma executives did not see a qualitative or quantitative difference in the numbers or types of decision inputs.

Figure 30 presents the interviewee results of firm prioritization for the interview question: "For each of the three decision points above, does the prioritization of a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company? Based on these results, I rejected the null hypothesis that there is no difference qualitatively or quantitatively between Big Pharma and Small Pharma in prioritization of projects based on whether a project was developed internally or externally ($p<0.05$).

Figure 30. Assessing Prioritization of a Drug Development Project on the Basis of Whether It Originated Inside or Outside the Company.[46, 47]

	Big Pharma Executives	Small Pharma Executives	Total
Yes	22	5	27
No	2	14	16
Total	24	19	43

Fisher's exact test: $p = 0.0005$.

Yates' chi-square value: $X^2 = 10.6$ with p value: $p = 0.001$.

Using $p = 0.05$ as the cutoff point, reject H_o ($p_1 = p_2$) in favor of H_1 ($p_1 \neq p_2$).

An overwhelming majority of Big Pharma executives saw a qualitative or quantitative difference in prioritization within their firms based on whether the project originated inside or outside the company. Financial considerations were cited by several Big Pharma executives as one of the ways in which they observed a difference. "There is more preferential treatment for compounds

for which the company has paid a lot of money," stated one. Said another: "If senior management backs an outside product or program and spends a lot of money to get it, then they will be watching the program more closely" compared to an internally developed program. Another Big Pharma executive observed: "People felt the cost more acutely as a result of having spent money" on an outside program.

Big Pharma executives also cited organizational and personal biases as well as politics as ways in which they saw differences in decision making treatment. "An inside development project's content was always suspect," observed a Big Pharma executive. "Personal bias was huge," observed another. "It (the decision making process) could and did vary at all three stages. It was very often politically driven," another remarked.

A majority of Small Pharma executives observed that their firms did not have the financial latitude of being able to prioritize one program over another. One Small Pharma executive put it this way: "We don't have the luxury of looking at fifty candidates. There is one decision making group, an 'n' of one." Another cited science as the key driver of decisions for projects regardless of whether they originated inside or outside the company: "Science would always drive the process."

Figure 31 presents the interviewee results of firm metrics for the interview question: "For each of the three decision points above, do the metrics used to evaluate a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company?" Based on these results, I rejected the null hypothesis that the metrics used do not differ qualitatively or quantitatively between Big Pharma and Small Pharma based on whether a project originated inside or outside the company ($p<0.5$).

Figure 31. Assessing the Metrics Used to Evaluate a Drug Development Project on the Basis of Whether It Originated Inside or Outside the Company.[46, 47]

	Big Pharma Executives	Small Pharma Executives	Total
Yes	17	5	22
No	6	14	20
Total	23	19	42

Fisher's exact test: $p = 0.003$.

Yates' chi-square value: $X^2 = 7.6$ with p value: $p = 0.006$.

Using $p = 0.05$ as the cutoff point, reject H_o ($p_1 = p_2$) in favor of H_1 ($p_1 \neq p_2$).

While not as overwhelming as the previous result, a solid majority of Big Pharma executives nonetheless also reported that the metrics their firms used differed qualitatively or quantitatively on the basis of whether a program originated inside or outside the company. Observed one Big Pharma executive: "For an inbound project from the outside, the company may want higher numbers (hurdle rates, etc.)." Another suggested that "there was much more flexibility around internal programs, and that can be good and bad."

In contrast, a majority of Small Pharma executives found no difference in the metrics their firms used to evaluate a project on the basis of whether it originated inside or outside the company. Said one: "We had to be non-parochial in our approach to build value. We had to be unemotionally involved." Many Small Pharma executives also described using fewer metrics than their Big Pharma counterparts.

Newness of Technology. I also asked interviewees whether the newness of a given technology was viewed as positive, negative, or neutral in terms of its impact on the company's

interest level in pursuing the project. Within Big Pharma interviewees (n=26), 77% (20 out of 26) viewed newness of technology as having a positive impact on the company's interest level, 15% (4 out of 26) responded they did not know, and 8% (2 out of 26) viewed the impact as neutral. By contrast, within Small Pharma interviewees (n=19), only 52% (10 out of 19) viewed newness of technology as having a positive impact on the company's interest level, 37% (7 out of 19) viewed it as neutral, and 11% (2 out of 19) viewed it as negative. It is noteworthy that not one Big Pharma interviewee viewed a new technology as having a negative impact on his or her firm's interest level in pursuing it.

Chapter 3: Findings

Discussion of Results

Based on my interviews of executives from Big Pharma and Small Pharma, these results suggest some pronounced differences in the ways in which the two types of companies manage drug development projects on the basis of whether a program originated inside or outside the company. At high levels of statistical significance, on the basis of both the Fisher's exact test and the Yates' chi-square test, my analysis finds statistically significant differences in decision making between Big Pharma and Small Pharma across four variables, noted in Chapter 2. These data indicate that decision making around drug development projects is managed differently by the two classes of firms, whether intentionally or not. Figures 25-30 show that a consistently strong majority of Small Pharma interviewees responded that their firms' approach to decision making with respect to a project essentially did not or would not differ on the basis of whether the project originated internally or externally. Conversely, an overwhelming majority of Big Pharma executives generally perceived a difference in the ways their firms approached project decision making on the basis or project origination.

From my interviews, it appears that there are a variety of factors that may contribute to this difference. These factors come out of interviewee responses to various questions that I asked. While this discussion will be more qualitative in nature (e.g., it was not my intention within the context of this thesis to evaluate such factors on a statistical basis), these factors emerged as themes from the same interviewees whose responses showed a statistical difference between the Big Pharma and Small Pharma approaches to drug development project decision making. Thus, these factors appear important in potentially explaining the differences observed.

Small Pharma Firms are Able to Focus. Small Pharma executives identified focus as a key factor in why their firms treat drug development projects the same way. Usually operating under significant capital constraints, especially compared to their Big Pharma counterparts, Small Pharma executives are forced to consider decisions carefully and make the best possible decisions with the information they have at the time. While Big Pharma seeks to operate in the same manner, a number of Big Pharma executives suggested that Big Pharma is more willing to wait to have more complete information before making decisions regarding drug development programs. It can be argued that the risks to a Big Pharma firm with respect to making a wrong decision are greater in terms of total dollars. Generally speaking, Big Pharma's opportunity cost is far higher than that of a Small Pharma firm. In other words, if a Big Pharma firm elects to go through with Phase 2 (and subsequent Phase 3) trials for a given drug, its opportunity cost is far higher if the project fails, since presumably it could have invested that capital in an alternative program with a more favorable and profitable outcome. By contrast, Small Pharma executives did not talk about alternative projects to the few their firms were actively pursuing or considering, since because they were cash and resource constrained, such trade-offs came into play much less frequently than in Big Pharma firms.

Whereas Big Pharma firms are more likely to have plenty of cash to invest in programs, and thus have the luxury of selecting a portfolio of projects to pursue out of a much larger potential universe, Small Pharma executives generally described an environment in which they were challenged to find creative, resourceful, and inexpensive ways to pursue even the one or small handful of projects they were developing. I do not mean to suggest that Big Pharma has more cash than it needs, since Big Pharma firms still have to choose those projects they wish to pursue among many alternatives. However, having so many more choices than their Smaller Pharma counterparts suggests that Big Pharma firms have a greater challenge in determining which projects are the best alternatives and offer the best returns. This challenge faced by Big

Pharma associated with selecting projects from a wide range of alternatives may be one of the reasons that Big Pharma and Small Pharma interviewees alike described the slow pace with which Big Pharma makes decisions about projects. It may also help explain why Big Pharma is willing to wait longer to get a slightly higher level of confidence around a given project before making a decision to pursue it or not.

Clearly, the numbers of projects each class of companies is developing at any given time is vastly different. As Figure 23 illustrates, Big Pharma firms on average are developing an estimated 63 projects compared to an estimated 6 projects within their Small Pharma counterparts, and many of the Big Pharma projects are at later stages of development, so the expenditures associated with them are greater. The sheer mass of project content that must be managed is orders of magnitude larger in Big Pharma firms compared to Small Pharma firms.

Not All Small Pharma Firms In-License Products. From my Small Pharma interviewee set, only 8 of 19 interviewees, or 42%, indicated that their companies had in-licensed products. However, of the 8 that did, a majority in all cases indicated that there was no difference in the way their firms managed the decision making process while a minority indicated that there were differences. Figure 31 provides the p values for such results shown in Figures 25-20 using only the responses from those interviewees whose firms had in-licensed a product. The values remain statistically significant for a cut-off of $p < 0.05$. It could be argued that Small Pharma executives whose firms have not in-licensed products might hypothesize that their firms would not treat decision making around drug development projects (internally developed versus sourced externally) differently, but such an argument appears inconsistent with these data.

Figure 32. Summary of p Values Using Fisher's Exact Test and Yates' Chi-Square Test Comparing Big Pharma to Small Pharma Interview Responses Using Only Small Pharma Data from Those Executives Whose Firms Had In-Licensed Products.

	p-values	
Variable	**Fisher's Exact Test**	**Yates' Chi-Square Test**
Decision Making Process		
Lead Selection/Optimization	**P = 0.005**	**p = 0.007**
Pre-Clinical Trials to Phase I Human Clinical Trials	**P = 0.002**	**p = 0.003**
Phase 1 to Phase 2 Human Clinical Trials	**P = 0.002**	**p = 0.003**
Number or Types of Decision Inputs	**p = 0.001**	**p = 0.002**
Prioritization	**p = 0.00006**	**p = 0.00008**
Metrics	**p = 0.003**	**p = 0.007**

Every Decision is Important to the Small Pharma Firm. Boards of Small Pharma firms appear to be more involved in project-specific decisions compared to boards of Big Pharma firms. The total dollar value of such Small Pharma decisions may be smaller than for a Big Pharma firm, but to the Small Pharma firm, those decisions are viewed as critically important. While on the one hand this may lead to increased oversight from the board or executive levels, better decisions may result due to such involvement. It is easy to make the case that in such settings, with more hands-on involvement, projects teams are more accountable, and are therefore less likely to slip on or miss deliverables and deadlines. By contrast, within the Big Pharma environment, several Big Pharma interviewees commented that they saw programs (projects) get killed that they believed should not have, while programs that should not have been taken all the way through the development process were. Given the sheer mass of Big Pharma firms, the same level of corporate scrutiny that seems to exist within Small Pharma firms is not possible, and, indeed, not every decision within Big Pharma is as important on a relative basis. Considering Pfizer, for example, with an R&D budget projected at over $7.5 billion in 2007, the degree of focus on any given project, particularly at the board of directors

level, is simply impossible. By comparison, boards of Small Pharma firms enjoy an ability to get into much more detail with their firms' projects than those of Big Pharma.

Politics Is Less of a Factor within Small Pharma. Small Pharma executives did not mention organizational politics with the same frequency as Big Pharma interviewees as having a role in drug development decision making. 19 out of 23, or 83% of Big Pharma interviewees cited organizational politics as a factor in drug development decision making, whereas only 2 out of 20, or 10% of Small Pharma interviewees cited it as a factor. I did not specifically seek to measure the degree of influence politics had, and, indeed, for nearly all interviewees, 44 out of 46, or 96%, politics was cited as having less than 50% of the overall influence in drug development project decisions. Given the information provided, it is difficult to determine exactly what impact of influence organizational politics may have in decision making, although clear differences exist.

Career Considerations Come into Play, Especially within Big Pharma. Numerous interviewees touched on various aspects of career considerations in decision making around drug development projects. A few Big Pharma interviewees noted the challenges Big Pharma has with killing projects because certain science staff members have long histories – up to 10 to 12 years in some cases. The idea of killing a project that is the basis for a scientist's life work certainly presents a challenge. Big Pharma interviewee responses raised questions around incentives and compensation of those involved with drug development projects – as to whether the goal was to get a project approved or to achieve targeted profitability of projects launched. The other career aspect that several Big Pharma interviewees touched upon was the desire of high level executives to avoid making bad decisions based on the perceptions of their peers and superiors. Risk taking on the whole does not seem to be widely encouraged within Big Pharma firms. This risk-averse mindset may in part play a role in Big Pharma setting "a higher bar" for

projects they seek to in-license from the outside (see below) compared to those they develop internally. An implication for Big Pharma firms is that if their senior executives feel they cannot take risks because of a belief that failures may lead to career derailment, then these firms may miss new, innovative scientific advances and opportunities. Or they may pay more later to license or acquire them from a smaller, early stage company that was willing to take such risk.

The Decision Point is Less Meaningful than the General Approach to Decision Making. If a respondent gave a certain answer to one decision point of the three I assessed, he or she was virtually certain (n = 46 out of 48 respondents, or 96% of all interviewees) to answer the same way with respect to the other two decision points. This suggests that the framework of decision making and approach to it within a firm is more important than the specific decision point itself in influencing whether programs are treated differently on the basis of originating inside or outside the firm. Based on Big Pharma interviews, it appears that the Big Pharma operating environment is much more deliberative about getting even slightly more information – even if it requires waiting a few more weeks or even months for that information. This willingness to wait may be in part a result of the risk averse dynamic that several Big Pharma interviewees described.

Big Pharma Sets a Higher Bar for In-licensing Projects. Several Big Pharma interviewees (3 out of 26, or 12%) indicated that their firms have higher standards of acceptability when assessing products as potential in-licensing candidates compared to internally developed projects. Several others indicated that there would be a greater comfort organizational level with technologies or fields with which their R&D organizations had familiarity or expertise. Big Pharma executives gave several reasons for applying a different set of standards. The potential licensor firm's people do not generally have as much familiarity or experience with the program, so there is inherently more skepticism about whether the work that has been done is

acceptable. A few Big Pharma executives also suggested that Small Pharma firms tend to do less rigorous work on their drug development projects. Another cause for giving higher scrutiny to outside projects is the fact that Big Pharma firm executives knew substantial milestone payments would be required up front, and that the partnering firm would hold their firm more accountable through a contract than would otherwise occur within their own firm in developing the project.

At Some Point, Small Pharma Starts to Act Like Big Pharma. For Small Pharma firms, the stage of a firm seems to affect perception of decision making in that firm. For example, if the firm was relatively established with late stage or commercial products, its people might start behaving more like those in a Big Pharma firm, in which emotional attachment to internally developed programs was cited with greater frequency. Also, in some cases, Small Pharma interviewees indicated their firms would set a higher bar for bringing in programs from the outside, just as some Big Pharma executives had stated. For Small Pharma executives whose firms had a market capitalization of less than $100 million, this was less the case than for those whose firms had market capitalizations of $500 million or more.

Within Small Pharma, Project Quality Can be Sacrificed in the Name of Speed or Financial Discipline. Several Big Pharma interviewees indicated that they believe Small Pharma firms sometimes do less work or less rigorous work for a given project than their Big Pharma counterparts. Obviously, financial constraints are far greater in Small Pharma firms than in Big Pharma. Secondly, if the Small Pharma firm's goal is ultimately to out-license or sell a project (or the firm itself) to Big Pharma, then the clinical milestone that the Small Pharma firm seeks to achieve may very well be short of product regulatory approval and launch. For Big Pharma, the end goal is nearly always regulatory approval and product launch. In a market of

constrained supply and unprecedented demand on the part of Big Pharma, it is unclear how much "cutting of corners" on projects truly impacts Small Pharma firms.

Planning is Highly Fluid for Small Pharma Firms. Within Small Pharma firms, decisions around project prioritization appear to happen with much greater fluidity and much more rapidly than within Big Pharma firms. Small Pharma firms were much more wiling to make strategic shifts with respect to the business than Big Pharma firms. Some of the reasons for this flexibility are obvious. For Big Pharma, with massive deployed marketing and sales organizations focused on specific therapeutic areas or physician call points, selling a portfolio of products, the fate of one project does not dictate the firm's future or have anywhere near the same degree of impact on the firm's viability as it might within Small Pharma. Several Small Pharma executives noted that being public certainly exerts constraints on their firms – in terms of funding "skunk works" projects, as an example. For a small market capitalization company, funding of such projects may attract the scrutiny of outside investors. Nonetheless, Small Pharma firms must be positioned to take full advantage of flexibility. A poor clinical result may force a Small Pharma firm to change its strategy dramatically or close its doors.

The Time Frame within a Firm Can Impact One's Perspective Significantly. For both sets of firms, Big Pharma and Small Pharma, impressions of how the firm made or makes decisions could be impacted by the time frame in which the interviewee worked with the firm. As an example, Pfizer in the 1970's operated much differently from the way it does so today. Similarly, the Small Pharma firm that had high hopes for a certain technology in the early 1990's only to watch it fail in late stage clinical trials has moved on to other projects with a different strategic focus – and management team – today.

Functional Role Can Also Impact Perspective Significantly. The functional role one plays in a firm and level within the organization also impact one's perceptions about how project decisions are made. In a couple of cases, I interviewed executives within the same firm who had totally different perceptions about the firm's strategies or core competencies. Despite such differences, they answered my interview questions the same way, meaning that while their perceptions of certain organizational attributes could vary widely, they did not vary with respect to firm treatment of drug development programs on the basis of internal development or in-licensing from the outside.

Newness of Technology: A Conundrum. As mentioned previously, 77% of Big Pharma executives and 52% of their Small Pharma counterparts viewed newness of technology (e.g., first in therapeutic class, new molecule, biologic, etc.) as having a positive influence on their firm's interest in pursuing it. 8% and 37%, respectively, viewed it as having a neutral impact. From my interviews with Small Pharma executives, it seemed that more of their ambivalence about a technology's newness related to an appreciation for the work – scientifically, clinically, and financially – that had to be done relative to the new technology. Invariably, regulatory agencies have more questions regarding technologies that they haven't seen before. The overwhelming Big Pharma view of new technology as having a positive impact on firm interest level raises the question of whether such new technologies are worth the risk or not for smaller, early stage firms to develop. In doing so, they could license or partner such projects with Big Pharma firms at a later stage, presumably for substantial financial terms. However, while the regulatory environment always represents uncertainty for novel technology, it may be even more the case in the current environment due to recent findings of health issues with marketed drugs, such as Vioxx from Merck, or possible health concerns over Avandia from GlaxoSmithKline.

Chapter 4: Limitations and Insights

In any survey of people, different individuals will perceive questions and definitions differently. Organizational definitions can often be challenging, especially given the complex composition of businesses. For example, Bristol-Myers Squibb (BMS), while mainly a pharmaceutical company, maintains a medical device division, ConvaTec. Yet BMS is routinely referred to as a Big Pharma company, which makes sense because BMS' medical device revenues, at roughly $1 billion per year, are clearly a minority of the firm's $18 billion annual sales. The definition of Big Pharma becomes more complicated with Johnson & Johnson (J&J). It can be argued that J&J is not truly a "Big Pharma" company. After all, J&J has very significant businesses in medical devices and diagnostics (MD&D), as well as consumer products. J&J earns a very substantial portion of its revenues and profits from these "non-pharmaceutical" businesses. J&J is sometimes discussed in the literature as a Big Pharma firm, and sometimes is conspicuously absent for the reason previously given.

In addition, other definitions in my survey required occasional clarification. Specifically, the concept of "difference in metrics" required clarification in five (5/46 = 11%) interviews. The need for clarification arose because the phrase could be interpreted to mean different "metrics" or measures of some aspect of a project (e.g., pharmacokinetic profile, pharmacodynamic profile, market opportunity, extent of unmet medical need, etc.) in which different metrics could be applied (e.g., a firm could use metrics a, b, and c for an internally developed program, while using metrics c, d, and e for an externally developed program) whereas the term "difference" could be interpreted by the interviewee as requiring emphasis (e.g., using the same metric – market opportunity – a firm might require a market opportunity of $500 million for an internally

developed program and a market opportunity of $1 billion for an in-licensed program that originated externally).

While different interviewees may have focused on different aspects of certain interview questions, the benefit of having a large sample size is to be able to identify the perceptual patterns that exist. The findings in this thesis are certainly suggestive that there are differences in the ways different firms manage drug development projects on the basis of whether they originated inside or outside the firm. They also raise questions about how we may seek to better understand these dynamics in the future.

What Happens in Mid-Sized Pharma Firms?

In this thesis, I explicitly undertook to assess whether there were differences between Small Pharma firms, publicly traded companies with market capitalizations of less than $5 billion, and Big Pharma firms, which have market capitalizations in the tens and hundreds of billions of dollars. A question my findings raise is: What happens in mid-sized pharma firms? For companies with market capitalizations of $10 to $20 billion, are there differences in the way these firms manage drug development projects on the basis of project origination (internal or external to the firm). Genzyme is a company that would qualify as a mid-sized firm based on the market capitalization range posited above. What might we learn about how Genzyme treats decision making for these two types of drug development projects? Or is the "mid-sized firm" for purposes of this analysis much smaller in size? It may be. It is well worth knowing at what point the small, early stage pharmaceutical company starts to morph into the bigger pharmaceutical company with respect to project decision making.

The Market's Quest for Efficiency

While the current state of R&D productivity in the pharmaceutical industry has its critics, it seems reasonable to consider that the current drug development landscape may, in fact, be the result of the market seeking optimal efficiency. With numerous startup and early stage life science companies being established, funded by abundant venture financing, clearly investors are willing to take on the risks associated with drug development for the prospect of making spectacularly high returns. Moreover, the current trend in which the exit event for venture backed firm via merger or acquisition by a larger Big Pharma is virtually de rigeur in today's market environment suggests that investors are not necessarily betting on an initial public offering (IPO), and believe that it is necessary only to get products through to proof of principle before a Big Pharma company will decide to acquire the small firm in question.

Implications for Future Study

Thinking ahead to future assessment that may be done in the area of pharmaceutical R&D productivity, it will be important to look at what new business models are evolving to meet the needs for new products in the pharmaceutical marketplace. Will it make sense, as some whom I interviewed suggested, for Big Pharma firms to focus on late stage (i.e., Phase 3) development and commercialization of new therapies? Should Big Pharma firms increasingly let smaller, early stage firms do the high-risk, early assessment and validation work on drug development projects before deciding to pursue them?

Assessing the challenges of managing alliances is a worthwhile endeavor as well. Few would doubt the increasing reliance of Big Pharma firms on licensing deals, partnerships, and the like

with outside firms. Understanding how such collaborations are best managed has enormous implications for the pharmaceutical industry.

Lastly, what are the implications for the Small Pharma firm today that aspires to be the Big Pharma firm of tomorrow? In whose footsteps will they seek to follow - Amgen, Genentech, Johnson & Johnson, Novartis, Pfizer, or a different company? Is it possible to avoid an attack of generics upon patent expiration for a given product? If so, how? Are centralized or decentralized models of firm organization more appropriate for Big Pharma firms? What are the right metrics for bolstering drug development portfolio success? Future studies will need to grapple with these questions.

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Chapter 5: Exhibits

Exhibit 1.

Big Pharma Companies

(Definition: Those pharmaceutical companies whose R&D budgets placed them in the top 100 companies worldwide in terms of R&D spend, 2000-2004.)

Abbott Laboratories
Akzo Nobel
Amgen
Astra Zeneca
Bayer
Bristol-Myers Squibb
Eli Lilly
Glaxo SmithKline
Johnson & Johnson
Merck
Novartis
Pfizer
Roche Holding
Sanofi Aventis
Schering AG
Schering-Plough
Takeda
Wyeth

Source: Institute of Electrical and Electronics Engineers (IEEE): *IEEE Spectrum*: December, 2005.

Exhibit 2.

Small, Publicly Traded U.S. and Canadian Pharma and Biotech Companies with a Majority of Programs in Cancer & Autoimmune, Cardiovascular, and/or Infectious Diseases (n=99)*

Abraxis Bioscience, Inc.	Cerus Corporation	Idenix Pharmaceuticals	Oscient Pharmaceuticals
Accentia Biopharmaceuticals	Coley Pharmaceuticals	Idera Pharmaceuticals	Oxigene, Inc.
Acusphere	CombinatoRx	IDM Pharma	Panacos Pharmaceuticals
Adherex Technologies	Corautus Genetics, Inc. (See Note 2 below.)	ImClone Pharmaceuticals	Peregrine Pharmaceuticals
Advanced Life Science Holdings, Inc.	Cubist Pharmaceuticals	Immunogen	Protalex, Inc.
Advanced Magnetics, Inc.	Curagen Corporation	Immunomedics	Praecis Pharmaceuticals (See Note 3, below)
Adventrx Pharmaceuticals	CV Therapeutics	Incyte	Provectus Pharmaceuticals
Alfacell Corporation	Cyclacel Pharmaceuticals, Inc.	Infinity Pharmaceuticals	Quick-Med Technologies, Inc.
Allos Therapeutics	Dendreon Corporation	Interleukin Genetics	Rigel Pharmaceuticals
Antigenics, Inc.	Dyax Corproration	Javelin Pharmaceuticals	Samaritan Pharmaceuticals
Aphton Corporation	Encysive Pharmaceuticals, Inc.	Keryx Biopharmaceuticals	Seattle Genetics
Ariad Pharmaceuticals	Entremed	Kosan Biosciences	SGX Pharmaceuticals
Arqule	Enzon Pharmaceuticals	LaJolla Pharmaceutical Company	Sunesis Pharmaceuticals
Aspreva	Exact Sciences	Ligand Pharmaceuticals	Tanox, Inc.
Autoimmune, Inc.	Favrille, Inc.	Lorus Therapeutics	Targeted Genetics
Avant Immunotherapeutics	Forbes MediTech	Medarex	The Immune Response Corporation (Orchestra Therapeutics)
Avax Technologies	Genitope	Medicure	Threshold Pharmaceuticals
Bioenvision, Inc.	Genta Pharmaceuticals	Metabasis Therapeutics	Valentis Corporation
Biomira, Inc.	GenVec	MGI Pharma	Vertex Pharmaceuticals
Callisto Pharmaceuticals	GlycoGenesis (See Note 2, below)	Micromet	Vical, Inc.
Cardiovascular BioTherapeutics	GPC Biotech	Neopharm	Vion Pharmaceuticals
Cardium Therapeutics	GTC Biotherapeutics	Novacea	VioQuest
Cell Genesys	GTX, Inc.	Nuvelo, Inc.	Viragen
Cell Therapeutics, Inc.	Hana Biosciences	Oculus Innovative Sciences	Virexx Medical Corporation
Cel-Sci corporation	Hollis-Eden Pharmaceuticals	Onyx Pharmaceuticals	

Small, Publicly Traded U.S. and Canadian Pharma and Biotech Companies with a Majority of Programs in Cancer & Autoimmune, Cardiovascular, and/or Infectious Diseases (n=99)*

* Notes accompanying chart:

(1) For purposes of this thesis, "Small Pharma" companies have a market capitalization of equal to or less than $5 billion U.S. as of December 29, 2006.

(2) Corautus Genetics announced a merger with privately held VIA Pharmaceuticals on June 4, 2007.

(3) It was announced on December 21, 2006, that Praecis Pharmaceuticals was being acquired by GlaxoSmithKline.

(4) Note: GlycoGenesis filed a voluntary petition to restructure under Chapter 11 the U.S. Bankruptcy Code in the Bankruptcy Court for the District of Massachusetts on February 3, 2006. The company is no longer publicly traded.

(5) Bio-Imaging Technologies, Inc. is a publicly traded contract research organization that has served a substantial number of Big Pharma and Small Pharma clients in the cancer & autoimmune, cardiovascular disease therapeutic areas. I interviewed the chief executive officer of this company because of its intimate familiarity with drug development decision making processes at both Big Pharma and Small Pharma companies investigated in this thesis.

Exhibit 3. Questionnaire

Location: _____
Date: _____
Start Time: _____
End Time: _____

Total Length of Interview (Hours, Minutes): _____

Interviewee(s) (First Name, Last Name, Title, if applicable, Other)

_____ Business Card ☐
_____ Business Card ☐
_____ Business Card ☐

Interviewer: Rippy ☐

Other Contact Information: _____

Materials Received (e.g., documents, files, etc.) Yes ☐ No ☐

Other Comments on Setting, Interviewee Demeanor & Attitude

_____
_____
_____
_____
_____

☐ **Introduce Investigator:**

☐ **Informed Consent and Confidentiality Statement**

- Your participation in this interview is voluntary
- You may decline to answer any question
- You may withdraw from the interview at any time
- All answers are confidential in that no identifying information (your name, company name, organization names, drug name, type) will be presented in any written or oral report.

☐ **Purpose and Procedure Statement**

- Conducting semi-structured interviews with large pharmaceutical companies ("Big Pharma") and small, publicly traded biotechnology and pharmaceutical companies in the U.S. and Canada with a majority of drug development programs in cancer & autoimmune diseases and cardiovascular disease ("Small Pharma").
    - The interview should not take longer than one hour.
    - The purpose of this research is to explore the ways in which different companies manage decision making and prioritization of their drug development projects.
    - Specifically, I am interested in understanding if you perceive(d) any differences in the decision making and/or prioritization around drug development programs based on whether they were sourced internally or externally (e.g., were in-licensed from the outside).
    - Your specific function or role within the organization is less important than whether you had exposure to the company's decision making and prioritization processes around drug development programs at some level (e.g., project specific, therapeutic category or division, or corporate).
    - We will first start with a few questions about your background at the company and the roles you have played within it. This should take about five minutes or so.
- Your candid responses are important.
- All of this information is strictly confidential and any data presented in journals will be scrubbed of your company name, individuals, product names, or any other labels that could identify you or your company.

☐ **General Definitions Given**

- Lead Selection/Optimization, Pre-Clinical, Phase I, Phase II.

Individual Background and Role

1. For purposes of this interview, is the company you work(ed) for a Big Pharma or Small Pharma?

2. How long have you worked at or did you work at this company? If you are no longer at the company, when you did last work there?

3. What is / was your role in the company? What other roles have you or did you work in?

4. At what level(s) could you observe your company's activities relating to program decision making and prioritization? Select all that apply.

   Project Level ☐ Therapeutic Category or Division Level ☐ Corporate Level ☐

Drug Development Projects at Your Company

5. How many projects is this company actively developing currently or was it developing when you were last there?

6. How does the company prioritize projects? What is the organizational process by which it does so?

7. Is prioritizing typically done on a cyclical (e.g., once a year, twice a year) basis?

8. Does a meeting usually take place for purposes of prioritization? If so, which corporate functions are usually present?

9. Who typically presents at such meetings?

10. What resources, in terms of information and/or personnel, are essential for the discussion?

11. What information is nice to have but is not always available at such discussions?

12. Are there specific tools or inputs that your company uses to evaluate drug development projects? If so, what are they?

13. If you had to quantify in rough percentages the different inputs into a decision around a particular project, how would you do so?

Political	%
Financial	%
Scientific	%
Strategic	%
Other	%

14. Is this distribution representative for most projects in your organization?

15. How would you say your organization balances these different factors? Are there occasions when one factor weighs more than in others (e.g., significant financial opportunity versus strategic fit for a given program)?

16. Within your organization, who are the most influential people in these decisions?

17. What do you consider to be the most important decision inputs in managing drug development?

18. Can you estimate the percentage of your company's projects that were developed internally? What percentage were licensed or acquired from outside the company?

Decision Points in Drug Development Projects

In answering questions 19-22, please consider with respect to each of the following three decision points:

A. Lead Selection/Optimization
B. The decision to move a project from Pre-Clinical to Phase I
C. The decision to move a project from Phase I to Phase II

19. For each of the three decision points above, does the decision making process for a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company?

20. For each of the three decision points above, does the number or types of decision inputs the company uses differ qualitatively or quantitatively based on whether the product or program was developed internally or externally?

21. For each of the three decision points above, does the prioritization of a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company?

22. For each of the three decision points above, do the metrics used to evaluate a drug development project differ qualitatively or quantitatively based on whether it originated inside or outside the company?

Decision Inputs and Influencers

23. In general, what are the decision inputs the company relies upon to make these decisions?

24. Is there usually a given champion within the organization for a development project?

25. If so, is there a formal or informal process or way by which that individual or group of individuals goes about soliciting internal support for programs? From your perspective, is there a difference in the way that process works based on whether the program was sourced internally or externally?

26. To what extent does the "newness" of a program or molecule (in terms of technology) impact your company's decision making process pertaining to in-licensing of outside programs or developing internal ones?

Exhibit 4. Interviewees.

Big Pharma Executives

Amgen
Stephanie Tozer

Astra Zeneca
Jim Taylor

Bristol-Myers Squibb
John Finnegan
Trent Lu
Lisa Rayder
Jordan Warshafsky

Eli Lilly
Brian Miller

GlaxoSmithKline
Mark Celeste

Johnson & Johnson
Jeffrey Berg
Rich Caligaris
Stan Hall
Rob Mart
Jerry Olderman
Dave Piacquad

Merck
Erica Fogg Boyer
Rich Caligaris
Reed Leonard

Novartis
Abbey Celniker
Jeff Elton
Rehan Khan
Mohit Rawat

Pfizer
Erica Fogg Boyer
Braham Shroot
Jim Taylor

Schering-Plough
Dave Piacquad

Wyeth
Abbie Celniker

Small Pharma Executives

Advanced Magnetics
Brian Pereira

Acusphere
Howard Weinstein

Cardium Therapeutics
Barbara Sosnowski

Cubist Pharmaceuticals
Jennifer LaVin
Aaron Pelta
Scott Rocklage

Dyax Corporation
Max Dawson
Lindsay Johnston

GPC Biotech
Vivian Berlin

Javelin Pharmaceuticals
Michael Sheckler

Momenta Pharmaceuticals
Jennifer Eppig

Oculus Innovative Sciences
Bob Miller
Jim Schutz

Panacos Pharmaceuticals
Peyton Marshall

Quick-Med Technologies
Roy Carr

Vertex Pharmaceuticals
Vivian Berlin
Max Dawson
Andrew Marks

Other
Mark Weinstein, Bio-Imaging Technologies
Maria Grunwald, Audact, Inc.

Exhibit 5. Fisher's Exact Test and Yates' Chi Square Test.

Fisher's Exact Test. Fisher's exact test for 2 x 2 tables applies to members from two independent groups (e.g., Big Pharma, Small Pharma) which can fall into one of two mutually exclusive categories (e.g., Yes or No). It is often used to test statistical significance when sample sizes are small (n < 10 for a given outcome). The calculation for Fisher's exact test for a two by two matrix is given in Figure 33 below.

Figure 33. Hypergeometric Distribution of the Exact Probability of Observing a Table with Cells a, b, c, and d.

$$p = \binom{a+b}{a}\binom{c+d}{c} \Big/ \binom{n}{a+c} = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{n!a!b!c!d!}$$

where p is the probability of a specific set of outcomes within the matrix; a, b, c, and d are the outcomes; and ! is a factorial operator. Fisher's exact test assumes that the numbers are fixed. In other words, using the 2 x 2 table below (Figure 34), the numbers of Yes and No responses are fixed at a + b and c + d, respectively. (Note: n = the sum of a + b + c + d.)

Figure 34. General Layout of Fisher's Exact Test.[48]

	Type of Firm		
Response	Big Pharma	Small Pharma	Total
Yes	a	b	a + b
No	c	d	c + d
Total	a + c	b + d	n

Fisher's exact test is used to calculate the probability, given observed marginal frequencies, of obtaining exactly the same frequencies observed as well as any configuration that is more

extreme (i.e., having a smaller probability of occurrence). For purposes of this thesis, a one-tailed test is applicable as opposed to a two tailed test.

Yates' Chi-Square Test. Yates' chi square test is given by Figure 35.

Figure 35. Yates' Chi-Square Test.[49]

$$\chi^2_{Yates} = \sum_{i=1}^{N} \frac{(|O_i - E_i| - .5)^2}{E_i}$$

Yates' chi-square test is used because when there is one degree of freedom, as in Figure 23 above, small frequencies can create bias in the traditional chi-square test. Therefore, Yates' correction of subtracting 0.5 from observed differences of the observed and expected frequencies has the effect of reducing the chi-square value and increasing the resulting p value, effectively making the result more conservative. Some suggestion has been made that the Yates correction yields an overly conservative test in which one may fail to reject a false null hypothesis, which is one of the reasons I also run the Fisher's exact test on the data. As with Fisher's exact test, Yates' chi-square test may be appropriate when one or more cells have frequencies of less than five.

The Yates' chi-square statistic can be re-written in a slightly more convenient version that does not require full computation of the expected table. The short form of the equation for a 2x2 contingency table such as that in Figure 34 is given by the equation in Figure 36 below.

Figure 36. Short Computational Form for Yates Corrected Chi-Square Test for 2 x 2 Contingency Tables.[49]

$$X^2 = n (|ad - bc| - n/2)^2 / [(a + b) (c + d) (a + c) (b + d)]$$

Both the Fisher's exact test and the Yates' chi-square test were run on responses to selected questions from the interview survey.

Exhibit 6. Big Pharma Executive Interview Data.

Interview Number	Years with Company	Projects in Development	Estimated Percentage of Programs Developed		Decision Making Process Differs			Difference in Number/Types of Decision Inputs	Difference in Prioritization	Difference in Metrics
			Internally	Externally	A	B	C			
1	5.0	100	0.60	0.40	Yes	Yes	Yes	Yes	Yes	Yes
2	3.0	125	0.60	0.40	Yes	Yes	Yes	Yes	Yes	Yes
3	7.0	70	0.58	0.42	Yes	Yes	Yes	Yes	Yes	Yes
4	26.0	125	0.30	0.70	Yes	Yes	Yes	Yes	Yes	Yes
5	3.0	40	0.50	0.50	No	No	Yes	Yes	Yes	Yes
6	7.0	40	0.90	0.10	Yes	Yes	Yes	No	Yes	No
7	3.0	55	0.70	0.30	No	No	No	Don't Know	Yes	Don't Know
8	17.0	-	0.38	0.63	Yes	Yes	Yes	Yes	Yes	Yes
9	18.0	250	0.90	0.10	Yes	No	No	Yes	Yes	No
10	7.0	25	0.30	0.70	Yes	Yes	Yes	Yes	Yes	Yes
11	18.0	73	0.90	0.10	Yes	Yes	Yes	No	Yes	No
12	12.0	50	0.50	0.50	Yes	Yes	Yes	Yes	Yes	No
13	5.0	28	0.50	0.50	Yes	Yes	Yes	Yes	Yes	No
14	22.0	-	0.80	0.20	Yes	Yes	Yes	Yes	Yes	Yes
15	6.0	70	0.40	0.60	Yes	Yes	Yes	Yes	Yes	Yes
16	4.0	68	0.80	0.20	Don't Know	Don't Know	Don't Know	Don't Know	No	No
17	10.0	-	0.50	0.50	Don't Know	Don't Know	Don't Know	Don't Know	No	Yes
18	5.0	28	0.80	0.20	Yes	Yes	Yes	Don't Know	Don't Know	Don't Know
19	5.0	60	0.90	0.10	Yes	Yes	Yes	Yes	Yes	Yes
20	8.0	50	0.33	0.67	Yes	Yes	Yes	Yes	Yes	Yes
21	22.0	60	0.33	0.67	Yes	Yes	Yes	Yes	Yes	Yes
22	1.0	40	0.50	0.50	Yes	Yes	Yes	Yes	Yes	Yes
23	12.0	-	0.50	0.50	Yes	Yes	Yes	Yes	Yes	Yes
24	0.5	170	0.70	0.30	Yes	Yes	Yes	Yes	Yes	Yes
25	6.0	40	0.80	0.20	Yes	Yes	Yes	Yes	Yes	Yes
Median	7.0	55	0.58	0.42	Yes: 21	Yes: 20	Yes: 21	Yes: 19	Yes: 22	Yes: 17
Mean (n=25 for project data)	9.3	62.7	0.6	0.4	No: 2	No: 3	No: 2	No: 2	No: 2	No: 6
High	26.0	170.0	0.9	0.7	Don't Know: 2	Don't Know: 2	Don't Know: 2	Don't Know: 4	Don't Know: 1	Don't Know: 2
Low	1.0	28.0	0.33	0.1						

Exhibit 7. Small Pharma Executive Interview Data.

Interview Number	Years with Company	Projects in Development	Estimated Percentage of Programs Developed		Decision Making Process Differs			Difference in Number/Types of Decision Inputs	Difference in Prioritization	Difference in Metrics
			Internally	Externally	A	B	C			
1	2.0	2	1.00	0.00	No	No	No	No	No	No
2	13.0	4	1.00	0.00	No	No	No	No	No	No
3	2.0	3	0.00	1.00	No	No	No	No	No	No
4	2.0	2	1.00	0.00	Yes	Yes	Yes	Yes	Yes	Yes
5	4.5	4	0.50	0.50	No	No	No	No	No	No
6	6.0	16	1.00	0.00	No	No	No	Yes	No	No
7	4.0	1	1.00	0.00	No	No	N/A	No	No	Yes
8	3.0	1	1.00	0.00	No	No	N/A	No	No	No
9	8.0	4	1.00	0.00	Yes	Yes	Yes	Yes	Yes	No
10	0.5	4	1.00	0.00	Yes	Yes	Yes	Yes	Yes	No
11	9.0	7	1.00	0.00	Yes	Yes	Yes	No	No	Yes
12	10.0	4	0.50	0.50	No	No	No	No	No	No
13	3.0	3	1.00	0.00	No	No	No	No	No	No
14	10.0	4	0.50	0.50	No	No	No	No	No	No
15	1.5	12	0.67	0.33	Yes	No	No	No	No	No
16	1.5	4	1.00	0.00	Don't Know	Don't Know	Don't Know	Yes	Yes	Yes
17	1.0	8	0.71	0.29	Yes	Yes	Yes	Yes	No	No
18	3.0	8	0.75	0.25	Yes	Yes	Yes	Yes	Yes	Yes
19	2.0	15	0.50	0.50	No	No	No	No	No	No
Median	3.0	4	1.0	0.0	Yes: 7	Yes: 6	Yes: 6	Yes: 7	Yes: 5	Yes: 5
Mean (n=19 for project data)	4.4	5.1	0.8	0.19	No: 11	No: 12	No: 10	No: 12	No: 14	No: 14
High	13	16	1.0	1.0	Don't Know: 1	Don't Know: 1	Don't Know: 1			
Low	0.5	1	0.0	0.0			N/A: 2			

Chapter 6: Glossary of Selected Terms

Glossary of Selected Terms

Biologic License Application (BLA):	The document submitted in the U.S. to the U.S. Food and Drug Administration (F.D.A.) for biotherapeutic products, such as proteins and antibodies.
Investigational New Drug (IND) Application:	A request for authorization from the F.D.A. to conduct clinical trials of (e.g., to administer) a new, unapproved drug in humans. Such approval is legally required for interstate shipment or administration of any drug or biologic product not approved under an NDA or BLA.
New Chemical Entity (NCE):	A drug that contains no active moiety that has been approved by the F.D.A. in any other application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.
New Drug Application (NDA):	The document submitted in the U.S. to the F.D.A. for approval of a new pharmaceutical for sale and marketing. In addition to containing new chemical entities (NCEs), which are a fraction of the total of NDAs approved in a given year, NDAs include new salts or esters, new formulations or indications for existing drugs, new combinations (where all active ingredients have been previously approved), a new manufacturer for an existing drug, and old drugs that have been marketed without an approved NDA.
New Molecular Entity (NME):	Synonymous with new chemical entity.